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REVIEW

Targeting Skeletal Muscle Melatonin-MT_2 Signaling to Attenuate the Obesity-Cancer Axis: A Metabolic Perspective

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ABSTRACT: Obesity and metabolic syndrome promote malignancies through chronic inflammation and sustained activation of insulin and insulin-like growth factor-1 (IGF-1) signaling. Skeletal muscle is central to this tumor-promoting milieu because it governs insulin-stimulated glucose disposal, lipid oxidation, and endocrine crosstalk. This narrative review explores whether melatonin signaling in skeletal muscle, particularly via melatonin receptor 2 (MT_2), represents a modifiable node within the obesity–cancer axis. Experimental evidence indicates that melatonin activates MT_2-linked Gi/o and calcium-sensitive pathways converging on phosphoinositide 3-kinase–protein kinase B (PI3K–Akt), extracellular signal-regulated kinases (ERK), and calcium/calmodulin-dependent protein kinase II–adenosine monophosphate-activated protein kinase–peroxisome proliferator-activated receptor gamma coactivator 1-alpha (CaMKII–AMPK–PGC-1α) signaling. These pathways enhance insulin sensitivity, mitochondrial function, and lipid partitioning while reducing myosteatosis and cellular stress. By improving muscle quality, melatonin may lower systemic insulin and IGF-1 drive and inflammatory adipokine tone that fuel tumor-promoting PI3K–Akt–mammalian target of rapamycin (mTOR) signaling. However, human evidence remains limited and timing-dependent. Melatonin exposure in the fed state or near carbohydrate intake may worsen glycemia, particularly in carriers of melatonin receptor 1B (MTNR1B) risk alleles. Chronobiology-informed, genotype-guided trials with detailed muscle phenotyping and cancer-relevant endpoints are warranted.

KEYWORDS: Melatonin; melatonin receptor 1; melatonin receptor 2; melatonin receptor 1A gene; melatonin receptor 1B gene; skeletal muscle; insulin resistance; myosteatosis; sarcopenic obesity; myokines; obesity-related cancer

1 Introduction

Obesity and related components of the metabolic syndrome are robustly associated with an increased incidence and mortality of multiple cancer types, including colorectal, postmenopausal breast, endometrial, kidney, pancreatic, and liver cancer [1,2]. Excess adiposity, particularly visceral fat, promotes chronic low-grade inflammation, hyperinsulinemia, and activation of the insulin/insulin-like growth factor-1 (IGF-1) axis, which together enhance mitogenic and anti-apoptotic signaling in preneoplastic and malignant cells [3,4]. These perturbations are tightly coupled to systemic insulin resistance and ectopic lipid deposition in liver and skeletal muscle, thereby embedding cancer risk within a network of metabolic-organ crosstalk rather than adipose tissue alone [3,5].

Skeletal muscle, once viewed predominantly as a contractile organ, is now firmly established as a key metabolic and endocrine tissue. The concept of skeletal muscle as an endocrine organ was first

proposed more than two decades ago, following evidence that skeletal muscle myocytes release a significant amount of anti-inflammatory interleukin-6 (IL-6) into the circulation during exercise [6]. Indeed, myofibers secrete over 600 cytokines and peptide hormones, collectively termed myokines, which act in autocrine, paracrine, and endocrine fashions to regulate substrate metabolism, inflammation, and tissue remodeling in distant organs such as adipose tissue, liver, pancreas, vasculature, bone, and brain [7,8]. For example, IL-6 release from contracting muscle during exercise can increase circulating concentrations up to several hundred-fold, where it acts in a hormone-like manner to stimulate lipolysis, fatty acid oxidation, and hepatic glucose output, and to promote anti-inflammatory mediator production [9,10]. The emerging paradigm of muscle–organ crosstalk thus places skeletal muscle at the center of systemic energy balance, immune modulation, and stress responses [8].

The biological actions of IL-6 exemplify the context dependence of myokine signaling. Transient, muscle-derived IL-6 surges during exercise promote lipid mobilization and oxidation, improve glucose uptake and insulin sensitivity, and induce anti-inflammatory mediators such as IL-1 receptor antagonist and IL-10 [10,11]. In contrast, IL-6, chronically produced by inflamed adipose tissue, participates in "metaflammation" and insulin resistance, acting together with tumor necrosis factor-α (TNF-α) and other cytokines to impair insulin signaling in adipose tissue, liver, and skeletal muscle [4]. Thus, skeletal muscle mass and contractile activity help determine whether IL-6 contributes to an anti-inflammatory, metabolically favorable milieu, or to the chronic pro-inflammatory state that characterizes obesity and promotes tumorigenesis.

Progressive loss of muscle mass and function in sarcopenia is a common clinical condition in older adults and in patients with chronic diseases, including cancer [12]. The revised European Working Group on Sarcopenia in Older People (EWGSOP2) defines sarcopenia as low muscle strength plus low muscle quantity or quality, with poor physical performance indicating severe disease [13]. When sarcopenia coexists with excess adiposity, the condition is termed sarcopenic obesity, now recognized by ESPEN and EASO as a distinct entity in which low muscle mass/function and obesity synergistically worsen cardiometabolic and functional outcomes [14]. Mechanistically, sarcopenic obesity is characterized by intramuscular fat accumulation (myosteatosis), mitochondrial dysfunction, insulin resistance, and amplified low-grade inflammation, which together impair muscle regeneration and contractile efficiency [15,16].

In oncology, low skeletal muscle mass and quality substantially modify prognosis. Skeletal muscle depletion in patients with cancer predicts treatment toxicity, postoperative complications, and reduced overall survival, even in individuals with normal or high body mass index [14]. Sarcopenia is a common condition in cancer patients, occurring at any stage of the disease and across all body mass index (BMI) categories, and is often associated with obesity [17]. Importantly, sarcopenic obesity is also increasingly observed in younger individuals with obesity and cancer, where it correlates with poorer treatment outcomes [18]. Myosteatosis, quantified as low skeletal muscle radiodensity on computed tomography, independently associates with worse overall survival in colorectal cancer, with pooled hazard ratios for mortality of ~1.4–1.6 in recent meta-analyses [19]. These findings underscore that the combination of visceral adiposity, sarcopenia, and myosteatosis produces a particularly adverse metabolic–inflammatory phenotype that fosters cancer progression and compromises treatment tolerance.

Within this metabolic–oncologic framework, skeletal muscle emerges not only as a passive target of catabolic signals but also as a potential therapeutic hub. Interventions that preserve or restore muscle mass, oxidative capacity, and myokine secretion profiles may counteract obesity-driven oncogenic signaling by improving insulin sensitivity, lowering ectopic lipid deposition, and rebalancing systemic cytokine and myokine networks. In support of this concept, a randomized clinical trial in overweight and obese

breast cancer survivors demonstrated that 16 weeks of supervised combined aerobic and resistance training significantly improved sarcopenic obesity, reduced fasting insulin and IGF-1, and favorably modulated the adipokine milieu by decreasing leptin and increasing adiponectin levels [20]. Exercise paradigms that increase muscle mass and myokine release (e.g., IL-6, irisin, secreted protein acidic and rich in cysteine (SPARC)) have been shown to exert systemic anti-inflammatory and antitumor effects in preclinical and clinical settings, supporting the concept of "exercise oncology" as a metabolic and endocrine intervention rather than a purely functional rehabilitation strategy [21,22].

Melatonin, an indoleamine primarily produced by the pineal gland with a well-established role in circadian regulation, also exerts pleiotropic antioxidant and metabolic actions in peripheral tissues, including cardiac and skeletal muscle [23,24]. Preclinical data indicate that melatonin modulates mitochondrial function, glucose and lipid handling, and redox homeostasis in myocytes and may influence muscle regeneration and response to radiotherapy- or chemotherapy-induced damage [25]. These effects are largely mediated through high-affinity G protein–coupled melatonin receptors type 1 (MT_1) and type 2 (MT_2), which are expressed in skeletal muscle and coupled to intracellular pathways that intersect with insulin/IGF-1 signaling, sirtuins, and peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α)-dependent mitochondrial biogenesis. Consistent with this, melatonin receptor signaling in obese diabetic rodent skeletal muscle has been linked to MT_1/MT_2 expression changes and modulation of mitochondrial–stress regulatory nodes, including sirtuin 1/AMP-activated protein kinase/PGC-1α (SIRT1/AMPK/PGC-1α–associated pathways), supporting a receptor-dependent interface between melatonin and muscle metabolic remodeling [26].

Given that obesity-associated cancer risk is deeply rooted in insulin resistance, altered lipid partitioning, and chronic inflammation, and that skeletal muscle is a key determinant of these processes, melatonin–MT_1/MT_2 signaling in muscle represents a plausible, but underexplored, node in the obesity–cancer axis (as schematically shown in Fig. 1). Melatonin has been demonstrated to suppress the growth of various tumors *in vivo* and *in vitro*, as well as having antioxidant and mitochondrial protective activity [27]. The present narrative review will critically examine how melatonin receptor signaling in skeletal muscle modulates the endocrine and metabolic roles of skeletal muscle in obesity and sarcopenic obesity in relation to cancer risk and attenuates obesity-driven oncogenic signaling.

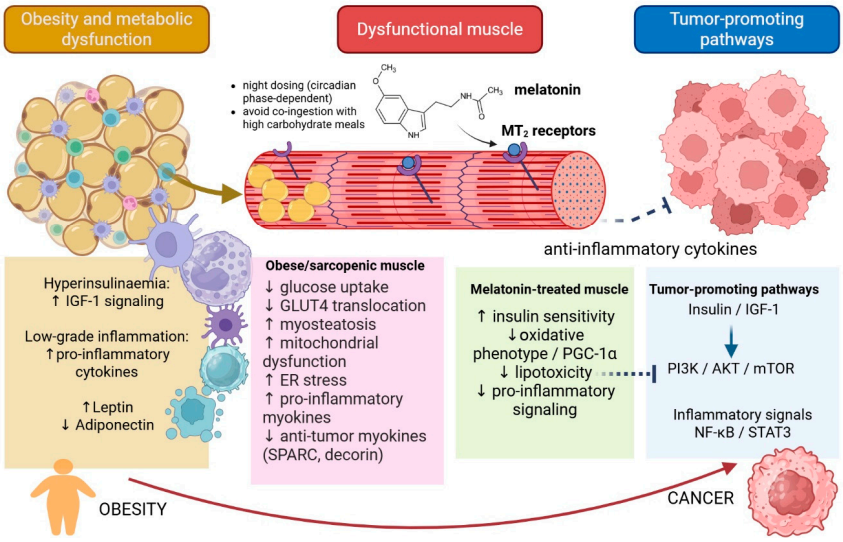

Figure 1: Skeletal muscle as a mechanistic relay in the obesity–cancer axis and a candidate target of melatonin–MT_2 signalling. Obesity is associated with hyperinsulinaemia/IGF-1 axis activation, chronic low-grade inflammation,

and an adverse adipokine profile (higher leptin, lower adiponectin). These systemic drivers promote an obese/sarcopenic muscle phenotype with impaired glucose handling, intramuscular lipid accumulation, mitochondrial dysfunction, and endoplasmic reticulum stress, together with a shift toward a more pro-inflammatory and less anti-tumour myokine output (examples shown: SPARC, decorin). The resulting endocrine–metabolic milieu supports tumour-promoting signalling, including insulin/IGF-1–driven PI3K–AKT–mTOR activation and inflammation-linked NF-κB/STAT3 pathways. Melatonin is proposed to act via skeletal muscle MT_2 receptors to improve insulin sensitivity and oxidative programming (PGC-1α), while reducing lipotoxicity and inflammatory signalling, thereby attenuating tumour-promoting pathway activation. Chronopharmacological considerations (night dosing; avoid co-ingestion with high-carbohydrate meals) are indicated. Symbol key: ↑ and ↓ denote increased or decreased processes/levels, respectively. The curved red arrow indicates the overall directionality of the obesity→cancer axis. Dashed arrow denotes indirect hypothesis-driven link (e.g., endocrine/immune mediation rather than a single direct molecular step). Figure created with BioRender.com (Accessible: https://BioRender.com/sq0dkpw). IGF-1, insulin-like growth factor-1; SPARC, secreted protein acidic and rich in cysteine; PI3K–Akt–mTOR, Phosphoinositide 3-kinase–protein kinase B–mammalian target of rapamycin; NF-κB/STAT3, nuclear factor kappa B/Signal transducer and activator of transcription 3; MT_2, melatonin receptor 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

2 Literature Search Strategy

We conducted this narrative review using a reproducible literature identification strategy centered on PubMed/MEDLINE, because the manuscript's key domains (melatonin receptor pharmacology, skeletal muscle metabolism, obesity-related cancer mechanisms, and chronobiology) are comprehensively indexed and searchable via MeSH terms and structured fields. We searched PubMed from database inception until 31 December 2025, without study-design restrictions at the initial search stage. Our objectives were to identify (i) primary evidence on melatonin–MT_1/MT_2 signaling and downstream metabolic effects in skeletal muscle and myogenic model systems, and (ii) translational evidence linking obesity-associated skeletal muscle dysfunction (insulin resistance, myosteatosis, sarcopenic obesity, altered myokines) with cancer-relevant systemic pathways (insulin/IGF-1 axis; phosphoinositide 3-kinase–protein kinase B–mammalian target of rapamycin PI3K–AKT–mTOR; inflammatory signaling).

We developed PubMed queries by combining receptor/ligand terms with skeletal muscle terms and with pathway/phenotype terms using Boolean operators, field tags (Title/Abstract), truncation, MeSH terms, and we refined searches iteratively by adding or removing concept blocks. Specifically, to capture core literature on melatonin receptors in skeletal muscle and standard myogenic models, we searched: (1) ("melatonin" OR "MT_2" OR "MT_1" OR "MTNR1B" OR "MTNR1A" OR "melatonin receptor") AND ("skeletal muscle" OR myocyte* OR myoblast* OR myotube* OR C2C12 OR L6). To identify mechanistic evidence linking melatonin/MTNR1B to insulin signaling and glucose handling in muscle, we searched: (2) ("melatonin" OR "MTNR1B") AND ("insulin resistance" OR "insulin signaling" OR IRS-1 OR PI3K OR Akt OR GLUT4) AND ("skeletal muscle" OR myotube*). To retrieve studies addressing mitochondrial biology, redox regulation, and energetic remodeling in muscle in response to melatonin, we searched: (3) "melatonin" AND (mitochondria* OR "PGC-1α" OR AMPK OR "oxidative phosphorylation" OR "mitochondrial biogenesis" OR SERCA OR sarcolipin) AND ("skeletal muscle" OR myocyte*). To connect obesity-associated muscle phenotypes (sarcopenia, sarcopenic obesity, myosteatosis) with malignancy-related outcomes and mechanisms, we searched: (4) ("sarcopenia" OR "sarcopenic obesity" OR myosteatosis OR "intramuscular fat") AND (obesity OR "metabolic syndrome") AND (cancer OR neoplasm*). To identify chronobiological and nutrimetabolic studies relevant to melatonin signaling, MTNR1B genetic variation, and glucose tolerance timing effects, we searched: (5) "melatonin" AND (chronobiology OR chronopharmacology OR "meal timing"

OR “dinner timing” OR “postprandial glucose” OR “glucose tolerance”) AND (MTNR1B OR rs10830963 OR polymorphism). When necessary, we complemented these searches with targeted PubMed queries for authoritative receptor/pathway resources (e.g., “IUPHAR melatonin receptor”, “MT_1 MT_2 structure”, “melatonin receptor biased agonism”).

We screened titles and abstracts for relevance to our review questions and then assessed full texts of the most relevant records. We prioritized inclusion of: (i) studies with direct skeletal muscle outcomes (e.g., human biopsy-based signaling/metabolic endpoints, imaging-based muscle composition, or muscle-specific functional/metabolic measures), (ii) mechanistic studies in myogenic cells and rodents delineating MT_1/MT_2-linked pathways relevant to insulin sensitivity, mitochondrial function, calcium handling, oxidative stress, inflammation, and myogenesis, and (iii) higher-level evidence (systematic reviews/meta-analyses, randomized trials, and consensus definitions) addressing sarcopenia/sarcopenic obesity, myosteatosis, and obesity–cancer associations. We also hand-searched reference lists of key primary studies and major reviews to capture additional relevant literature not retrieved by initial keyword combinations. Because this is a narrative review, we did not apply a formal risk-of-bias instrument or PRISMA workflow. Instead, we emphasized consistency across model systems, methodological rigor and recency of human evidence, and mechanistic plausibility linking skeletal muscle alterations in obesity to oncogenic systemic signaling.

3 Melatonin and MT_1/MT_2 Receptors: Signaling Fundamentals

3.1 Biosynthesis, Circadian Rhythms and Pharmacokinetics of Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine synthesized from tryptophan via serotonin through the sequential action of tryptophan hydroxylase, aromatic L-amino acid decarboxylase, arylalkylamine N-acetyltransferase (AANAT), and acetylserotonin O-methyltransferase (ASMT) [28]. Importantly, N-acetylserotonin (NAS) formation is not exclusively AANAT-dependent, as other acetylating enzymes in peripheral tissues can also contribute to serotonin acetylation and NAS generation [29]. In mammals, the pineal gland is the major endocrine source, while numerous extrapineal tissues (gastrointestinal tract, retina, immune cells, skin, bone marrow) generate melatonin for local autocrine and paracrine actions [30]. Extrapineal synthesis can support locally elevated melatonin tone with biological effects that are not directly inferred from circulating concentrations; this is particularly well documented for skin, where local melatoninergic pathways have been linked to barrier function, redox homeostasis, and cytoprotection [31,32].

Pineal synthesis is under strict control of the suprachiasmatic nucleus (SCN) via a multisynaptic sympathetic pathway (SCN $\rightarrow$ paraventricular nucleus $\rightarrow$ intermediolateral cell column $\rightarrow$ superior cervical ganglion $\rightarrow$ pineal gland). Noradrenaline released at night activates β_1- and α_1-adrenergic receptors on pinealocytes, which raises cyclic adenosine monophosphate (cAMP) and Ca^{2+}, and induces AANAT transcription and activity, resulting in a robust nocturnal rise of melatonin secretion [33]. The hormone is released immediately after synthesis, without any significant storage, into the circulation bound predominantly to albumin and, in parallel, into the cerebrospinal fluid [34].

In humans, plasma melatonin concentrations are low during daytime (typically below 10 pg/mL), rise in the evening, peak during the biological night (often 50–80 pg/mL in young adults), and decline in the early morning, whereas the duration of the nocturnal secretory episode encodes night length and thus seasonal information [35]. Age attenuates the amplitude of this rhythm, with nocturnal melatonin production declining to approximately 60 percent of young-adult levels by midlife and further into old age [36].

Endogenous melatonin has a short plasma half-life of around 30–50 min, being mainly metabolized by hepatic cytochrome P4501A2 (CYP1A2) to 6-hydroxymelatonin and excreted as 6-sulfatoxymelatonin in urine [37]. In parallel, extrahepatic enzymatic and non-enzymatic oxidation can generate biologically active metabolites, such as N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) or N^1-acetyl-5-methoxykynuramine (AMK), what is consistent with an antioxidant cascade concept [38]. Oral melatonin shows low and variable bioavailability (often in the 10–20 percent range) because of first-pass metabolism [39,40], while modified-release preparations prolong the terminal half-life and better mimic the physiological nocturnal profile [41]. Circulating melatonin distributes widely into tissues, including metabolic organs such as liver, adipose tissue and skeletal muscle, and crosses both the blood–brain and mitochondrial membranes owing to its amphiphilic character [42].

From the perspective of skeletal muscle and the obesity–cancer axis, melatonin acts as a high-fidelity circadian phase signal and as a lipophilic antioxidant that accumulates within mitochondria, where it modulates respiratory chain activity and limits oxidative damage [43]. Given its rapid metabolism and the biological activity of downstream products, both melatonin and its metabolites should be considered when interpreting mitochondrial and transcriptional effects across experimental systems. These features provide the temporal and redox context for MT_1/MT_2-dependent signaling in myocytes.

3.2 MT_1/MT_2 Receptor Structure, Tissue Distribution and G Protein Coupling

The two canonical mammalian melatonin receptors, MT_1 and MT_2, are class A (rhodopsin-like) G protein-coupled receptors encoded by *MTNR1A* and *MTNR1B*, located on chromosomes 4q35.1 and 11q21–q22, respectively. MT_1 is a 350-amino-acid protein and MT_2 is a 362-amino-acid protein, both displaying the typical seven transmembrane domain architecture with conserved motifs required for G protein–coupled receptor (GPCR) activation and G protein coupling [44].

Recent high-resolution structures of human MT_1 and MT_2 in complex with melatonin or synthetic ligands show compact binding pockets that accommodate the indole ring and side chains of melatonin, with key interactions involving residues in transmembrane segments 3, 5 and 6, including a conserved histidine that coordinates the 5-methoxy group and residues that define MT_2-preferring pockets for ligand selectivity [45].

MT_1 and MT_2 show overlapping but distinct distribution patterns. In the central nervous system, both receptors are expressed in the SCN, thalamus and hippocampus, with region- and cell type-specific predominance that contributes to the regulation of circadian rhythms, sleep–wake architecture and mood [46]. In peripheral tissues, MT_1 and/or MT_2 are found in retina, cardiovascular system, gastrointestinal tract, pancreatic islets, adipose tissue, reproductive organs, immune cells and skin [44,46].

Evidence for melatonin receptors in skeletal muscle is more fragmentary but supports the presence of MT_1/MT_2 transcripts and functional binding sites in rodent limb muscles and myogenic cell lines, including C2C12 myoblasts and myotubes [47]. Importantly, direct human tissue data also demonstrate transcription of genes *MTNR1A* (coding MT_1) and *MTNR1B* (coding MT_2) into corresponding mRNAs and protein expression in paravertebral skeletal muscle biopsies, providing *in vivo* evidence that canonical melatonin receptors are expressed in human skeletal muscle [48]. In human paravertebral skeletal muscle, MT_1 and MT_2 transcripts have been detected by Reverse Transcription Polymerase Chain Reaction (RT-PCR), with side-dependent MT_2 expression reported in adolescent idiopathic scoliosis cohorts [48–50]. Consistent with low, but detectable MT_2 receptor expression in human skeletal muscle transcriptomic resources (e.g., GTEx), *MTNR1B* transcripts are also measurable in cultured primary human myogenic cells, where *MTNR1B* knockdown

abolishes melatonin-induced downstream metabolic/thermogenic signaling, supporting functional MT_2 competence in the muscle lineage [51,52].

Pharmacological and genetic studies demonstrate that both MT_1 and MT_2 predominantly couple to G protein alpha subfamily i/o (Gi/o-type G proteins) and inhibit adenylyl cyclase activity, but cell- and tissue-specific coupling to Gq/11 and, less consistently, to other families is also observed. Receptors can form homo- and heterodimers (for example MT_1/MT_2 and MT_2/5-HT_2C), which modify ligand binding, G protein coupling, and downstream signaling, introducing an additional layer of "system bias" [53].

Beyond membrane receptors, melatonin interacts with additional targets such as nuclear receptors of the retinoic acid receptor-related orphan receptor (ROR/RZR) family and the enzyme quinone reductase 2 (NQO2/QR2), historically termed MT_3, which may contribute to gene regulatory and antioxidant effects. Primary pharmacological work supports MT_3 as a melatonin-sensitive form of QR2 and indicates that MT_3/QR2 binding sites are widely distributed across mammalian tissues, with inter-species and inter-tissue variability [54]. Although their relative importance compared with MT_1/MT_2-mediated signaling remains debated. In addition, melatonin and several of its metabolites have been reported to act as ligands/agonists for ligand-activated transcription factors, including the aryl hydrocarbon receptor (AhR) and peroxisome proliferator-activated receptor-γ (PPARγ), in cell-based reporter and binding assays, providing a plausible mechanism for longer-term phenotypic effects that extend beyond canonical MT_1/MT_2 signaling [55].

3.3 Downstream Signaling Pathways Activated by MT_1/MT_2 Receptors

In most experimental systems, acute activation of MT_1 or MT_2 leads to inhibition of adenylyl cyclase through Gi/o, reduced cAMP formation and decreased protein kinase-A (PKA) activity [56]. Lower cAMP levels alter phosphorylation of cAMP response element binding protein (CREB) and modulate clock gene transcription in the SCN and peripheral oscillators [57]. In many cell types, the receptor-bound Gi/o $\beta\gamma$ subunits activate class I phosphoinositide 3-kinase (PI3K), leading to phosphorylation of protein kinase B (Akt), which integrates survival, metabolic and cytoskeletal signals [58]. Importantly, melatonin is rapidly converted to bioactive metabolites (6-hydroxymelatonin, AFMK, and AMK) that can contribute to antioxidant, immunomodulatory, and transcriptional effects, potentially explaining MT_1/MT_2 receptor–independent actions observed at higher concentrations [59,60]. In heterologous systems and selected native tissues, MT_1 can additionally couple to Gq/11, activating phospholipase C, generating diacylglycerol and inositol trisphosphate and raising cytosolic Ca^{2+} [61]. This mechanism has been demonstrated in the myometrium [62], prostate epithelial cells [63] and pancreatic cells [64]. Both MT_1 and MT_2 stimulate extracellular signal-regulated kinases 1 and 2 (ERK1/2) and, depending on cellular context, can also activate c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38 MAPK) pathways, thereby linking melatonin to proliferation, differentiation and stress responses [65].

MT_2 receptors can additionally, in several preparations, inhibit soluble guanylate cyclase and reduce cyclic guanosine monophosphate (cGMP) levels, thereby providing an additional node for the modulation of vascular tone and synaptic transmission [66]. At the receptor level, signal propagation is strongly linked to desensitization dynamics. Agonist-activated MT_1 and MT_2 efficiently recruit β-arrestins, which promote receptor internalization and endocytic trafficking, as demonstrated in engineered cellular systems showing robust β-arrestin engagement and subsequent endocytosis of both receptor subtypes [67].

Biased agonism is an emerging theme in melatonin pharmacology. Multiparametric profiling of MT_1/MT_2 ligands in HEK293 and CHO cells shows that several synthetic agonists and antagonists display pathway-selective efficacy, with preferential activation of Gi/o-cAMP over ERK or β-arrestin responses at MT_1/MT_2 [67,68]. In parallel, MT_2/5-HT_2C heteromers exhibit a unique signaling pattern in which

melatonin transactivates Gq/PLC signaling via the 5-HT_2C protomer, distinct from MT_2 alone [69]. Natural variants in *MTNR1B* associated with type 2 diabetes alter coupling efficiency to Gi proteins and the balance between cAMP inhibition, ERK activation and β-arrestin recruitment, as demonstrated in large-scale functional profiling of 40 MT_2 variants [70]. These data support the concept that modest, pathway-specific shifts in MT_2 signaling bias can translate into measurable changes in glucose homeostasis.

For skeletal muscle, the most relevant MT_1/MT_2-dependent cascades include Gi/o-mediated suppression of cAMP, activation of phosphoinositide 3-kinase/Protein kinase B (PI3K/Akt) and ERK, and context-dependent modulation of intracellular Ca^{2+}. All of these intersect with pathways governing insulin signaling, mitochondrial biogenesis and myogenesis. In C2C12 myotubes, nanomolar melatonin enhances insulin receptor substrate 1 (IRS-1) tyrosine phosphorylation, increases IRS-1–associated PI3K activity and stimulates insulin-like glucose uptake. Furthermore, these effects are amplified by MT_2 overexpression and abolished by luzindole, indicating that MT_2-biased signaling functionally converges with the canonical IRS-1/PI3K arm of insulin signaling [47]. In palmitate-treated rat skeletal muscle cells and in pinealectomized rats, chronic melatonin restores insulin-stimulated Akt phosphorylation, normalizes mitochondrial respiration and respiratory control ratios, and upregulates cAMP response element-binding protein (CREB–PGC-1α)–driven mitochondrial biogenesis, thereby simultaneously correcting insulin resistance and mitochondrial dysfunction in muscle [71].

Beyond PI3K/Akt, melatonin–MT_2 signaling in muscle engages Ca^{2+}-sensitive pathways that converge on Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), AMPK and PGC-1α. In Wistar rats subjected to endurance exercise, melatonin supplementation potentiates exercise-induced increases in PGC-1α and mitochondrial markers in soleus muscle and improves post-exercise glycogen replenishment and intramuscular lipid handling, consistent with receptor-dependent facilitation of mitochondrial biogenesis and substrate utilization [72]. In Zucker diabetic fatty rats, 12-week oral melatonin increases sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA2) and sarcolipin expression in vastus lateralis, activates the CaMKII/AMPK/PGC-1α axis, enhances mitochondrial biogenesis, promotes SERCA–sarcolipin–driven non-shivering thermogenesis and shifts fiber composition toward a more oxidative phenotype while improving obesity-related metabolic parameters [71,73]. Complementary experiments in primary human skeletal muscle cells show that siRNA-mediated knockdown of MTNR1B abrogates melatonin-induced upregulation of SERCA1/2, sarcolipin, CaMKII, AMPK and PGC-1α, demonstrating that MT_2 is required for activation of this Ca^{2+}-dependent thermogenic and mitochondrial program in human myoblasts [51]. Together, these data indicate that MT_1/MT_2 receptors in skeletal muscle couple to insulin-sensitizing (insulin receptor substrate 1/Phosphoinositide 3-kinase/Protein kinase B (IRS-1/PI3K/Akt) signaling and to Ca^{2+}–CaMKII–AMPK–PGC-1α cascades, integrating glucose transport, mitochondrial biogenesis, fiber-type remodeling and thermogenesis in a manner highly relevant for obesity- and diabesity-related muscle dysfunction.

3.4 Evidence for MT_1/MT_2 Receptor Expression and Function in Skeletal Muscle

Direct characterization of MT_1/MT_2 receptors in skeletal muscle has relied primarily on myogenic cell lines and rodent muscle, with convergent evidence at the mRNA, protein, and functional levels. In C2C12 myotubes, nanomolar melatonin increases glucose uptake approximately twofold, an effect abolished by the non-selective melatonin receptor antagonist luzindole and markedly amplified in cells stably overexpressing MT_2, indicating a receptor-dependent mechanism [47]. In the same model, melatonin enhances IRS-1 tyrosine phosphorylation and PI3K activity without activating AMPK or p38 MAPK, consistent with Gi/o-coupled MT_2 signaling converging on the canonical IRS-1/PI3K/Akt axis that governs muscle glucose transport [47].

Several *in vitro* studies using C2C12, L6 or other skeletal muscle cell models show that melatonin preserves mitochondrial function, limits oxidative stress–induced permeability transition, and prevents cell death, with protective effects attenuated by melatonin receptor antagonists or reproduced by low, receptor-active concentrations of melatonin [71,74]. These studies report improved mitochondrial membrane potential, PI3K–Akt–mTOR, reactive oxygen species (ROS) formation, and maintenance of—adenosine triphosphate (ATP) levels, supporting a role for MT_1/MT_2 in safeguarding myofiber energetics and survival under metabolic or oxidative challenge.

In *in vivo* animal studies, chronic melatonin treatment in high-fat diet or diabetic rodent models improves skeletal muscle insulin sensitivity and normalizes mitochondrial morphology and respiratory chain function, while reducing intramyocellular lipid accumulation and markers of ER and oxidative stress [71,73]. In Zucker diabetic fatty and diet-induced obese rats, melatonin administration enhances the oxidative phenotype of vastus lateralis muscle, upregulates genes involved in oxidative phosphorylation and fatty acid oxidation, and restores calcium handling, changes that are accompanied by improved whole-body glucose tolerance and reduced insulin resistance [75]. In several of these models, pharmacological blockade with luzindole partially blunts the beneficial effects, suggesting that MT_1/MT_2 signaling contributes materially to the observed muscle remodeling.

Human data remains more circumstantial but supports the physiological relevance of melatonin receptor signaling for skeletal muscle metabolism. Genome-wide association and candidate-gene studies demonstrate that common variants in *MTNR1B*, particularly rs10830963, are associated with higher fasting glucose, impaired early insulin secretion, and increased type 2 diabetes risk [76–78]. Although these studies primarily implicate pancreatic β-cell function, altered MTNR1B signaling also modifies systemic glucose excursions and insulin dynamics, which secondarily influence skeletal muscle substrate handling. Additional work in melatonin receptor knockout mice shows that deletion of MT_1 or MT_2 disrupts daily blood glucose rhythms independently of peripheral clock gene disruption and is compatible with a role of melatonin receptors in coordinating temporal aspects of insulin sensitivity in skeletal muscle and other insulin-responsive tissues [79]. Transcriptomic datasets and limited RT-qPCR analyses suggest low but detectable *MTNR1B* expression in human myotubes, but the relative importance of direct receptor signaling in human myofibers versus indirect systemic effects remains to be clarified [51].

Taken together, mechanistic work in myogenic cells and rodent muscle indicates that MT_2, and likely MT_1 to a lesser extent, are expressed in skeletal muscle and signal through Gi/o–PI3K/Akt and mitochondrial protective pathways to enhance glucose uptake, preserve mitochondrial function, and limit lipotoxic and oxidative injury. A key limitation of the current skeletal muscle literature is that many *in vitro* studies use micromolar-to-millimolar melatonin, a range in which receptor-independent redox chemistry and engagement of non-canonical targets (including AhR/PPARγ) become increasingly plausible. Therefore, receptor selectivity should ideally be supported by subtype-selective pharmacology and/or genetic perturbation in each model. Genetic and physiological data in humans reinforce the notion that even modest alterations in melatonin receptor signaling can have measurable metabolic consequences that may extend to skeletal muscle.

3.5 Chronobiology of MT_1/MT_2 Receptor Signaling

Melatonin receptors function in a highly time-structured hormonal milieu. In humans, endogenous melatonin secretion exhibits a robust circadian rhythm with a steep evening rise, nocturnal plateau and daytime nadir, with plasma or salivary concentrations often increasing by more than an order of magnitude during the biological night compared with daytime levels [80]. This nightly surge provides a recurring ligand

pulse that exposes MT_1 and MT_2 to sustained activation during the dark phase and near-complete withdrawal during the light phase. In the suprachiasmatic nucleus (SCN), physiological melatonin concentrations induce phase shifts of neuronal firing rhythms and circadian outputs via MT_2-dependent mechanisms, establishing a feedback loop from the pineal hormone to the central pacemaker [81]. Human phase-response curve studies with exogenous melatonin further confirm that even short courses of daily melatonin can advance or delay the circadian system in a highly time-of-day–dependent manner [82].

MT_1/MT_2 receptor abundance and signaling competence are themselves dynamically regulated over 24 h. In rat SCN2.2 cells and SCN brain slices, pre-exposure to melatonin at physiological night-like concentrations (≈30–300 pM) for durations mimicking the nocturnal peak (up to 8 h) induces internalization and desensitization of MT_2, reducing receptor number and blunting downstream protein kinase C activation and melatonin-induced phase shifts of firing rhythms [81]. Recovery of MT_2 signaling after such nocturnal-like exposure is slow and partially protein-synthesis dependent, implying that the endogenous melatonin rhythm gates subsequent sensitivity of the SCN to melatonin. In contrast, MT_1 appears less prone to functional desensitization at physiological night-time concentrations in these preparations, suggesting subtype-specific chronobiological regulation [81]. In peripheral tissues, deletion of MT_1 or MT_2 in mice abolishes the daily rhythm of blood glucose without grossly disrupting local clock gene oscillations in skeletal muscle, liver or adipose tissue, indicating that melatonin receptor signaling confers temporal structure on metabolic outputs even when peripheral molecular clocks remain intact [79].

Peripheral oscillators in endocrine and metabolic organs interpret melatonin as a rhythmic timing cue. In rodent pituitary cells, the nocturnal melatonin signal acting via MT_1 and heterologous sensitization of adenosine A_2B receptors is required for high-amplitude cycling of the clock gene Per1, and removal of melatonin input suppresses Per1 rhythms and alters prolactin secretion [83]. These data demonstrate that melatonin receptor signaling can reshape both the phase and amplitude of peripheral clock gene expression. In insulin-sensitive tissues, MT_1/MT_2 deletion selectively abolishes the diurnal rhythm in circulating glucose while leaving core clock gene oscillations largely preserved in skeletal muscle, liver and adipose tissue, implying that melatonin signaling modulates metabolic rhythms downstream or parallel to canonical clock machinery [79]. In conclusion, these findings support a model in which melatonin, through MT_1/MT_2 and cAMP-sensitive pathways, acts as a systemic Zeitgeber that couples circadian phase information to metabolic processes.

From a translational standpoint, the chronobiology of MT_1/MT_2 has direct implications for melatonin use in metabolic and oncologic contexts. Human phase-response curves demonstrate that the direction and magnitude of circadian phase shifts depend critically on the timing of melatonin administration relative to endogenous dim-light melatonin onset and habitual sleep–wake cycles [82]. In parallel, mouse studies indicate that loss of melatonin receptor signaling flattens the daily glucose rhythm and elevates mean glycemia, pointing to a diurnal contribution of MT_1/MT_2 to glucose homeostasis [79]. Extrapolated to skeletal muscle, these data suggest that the metabolic and potentially anticancer actions of MT_1/MT_2 signaling in myofibers are likely to depend not only on receptor density and downstream pathway integrity, but also on the circadian phase at which melatonin exposure occurs, and its alignment with feeding–fasting cycles and physical activity. These considerations are highly relevant for the rational design of melatonin supplementation strategies aimed at optimizing muscle metabolism and modulating the obesity–cancer axis.

4 The Dysfunctional Muscle in Obesity-Related Cancer

4.1 Impaired Glucose Uptake and Insulin Signaling in Skeletal Muscle

Overweight and obesity are strongly associated with insulin resistance and the development of type 2 diabetes [84]. Obesity profoundly alters systemic metabolism and contributes to chronic low-grade inflammation, hyperinsulinaemia and increased insulin-like growth factor 1 (IGF-1) activity, dysregulated adipokine secretion, and increased lipid availability [85]. These systemic disturbances directly affect skeletal muscle, leading to impaired insulin signaling, mitochondrial dysfunction, intramuscular lipid accumulation (myosteatosis), and reduced oxidative capacity [86].

Following activation of their respective receptors, insulin and IGFs initiate signaling cascades that elicit tissue-specific cellular responses. In skeletal muscle, these pathways primarily promote glucose uptake and glycogen synthesis, whereas in adipose tissue, insulin predominantly regulates lipid storage and suppresses lipolysis. In healthy skeletal muscle, insulin binds to the insulin receptor and activates insulin receptor substrate 1 and 2 (IRS-1/IRS-2) and phosphoinositide 3-kinase (PI3K), which converts phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3). This signaling cascade activates Akt, which promotes glucose transporter type 4 (GLUT4) translocation to the plasma membrane, enabling glucose uptake for glycogen storage or glycolytic metabolism [87]. Beyond glucose regulation, insulin signaling supports skeletal muscle maintenance by activating (p38 MAPK) and mechanistic target of rapamycin (mTOR)/70-kilodalton ribosomal protein S6 kinase (p70S6K) pathways, thereby inhibiting proteolysis in skeletal muscle [87,88].

In skeletal muscle, insulin resistance is characterized by impaired insulin signaling, which leads to reduced GLUT4 translocation, decreased glucose uptake, diminished glycogen synthesis, and impaired glucose oxidation. This dysfunction contributes to hyperglycemia and systemic metabolic disturbances and is commonly observed in sarcopenic obesity [88] and cancer patients [89]. Compensatory hyperinsulinemia associated with insulin resistance can further exacerbate metabolic dysregulation and may promote cancer development in the context of obesity and type 2 diabetes, may promote cancer development [90]. Mechanistically, chronic hyperinsulinemia and aberrant IGF signaling can drive malignant transformation and tumor progression by sustaining pro-tumorigenic pathways, including PI3K–Akt, Janus kinase—signal transducer and activator of transcription (JAK–STAT), and NF-κB signaling in epithelial and stromal cells, thereby promoting cell survival, proliferation, and pro-inflammatory tumor-supportive microenvironments and highlighting the critical role of skeletal muscle insulin sensitivity and the IGF axis in whole-body metabolic homeostasis and cancer pathogenesis [89,91].

4.2 Mitochondrial Function and Oxidative Metabolism

Obesity intensity disrupted systemic metabolic homeostasis via altered adipokine secretion and elevated lipid availability, thereby exerting detrimental effects on skeletal muscle [92,93], including mitochondrial dysfunction, myosteatosis, and reduced oxidative capacity [94–96].

In sarcopenic obesity, the accumulation of lipid metabolites, including diacylglycerols and ceramides, activates kinases that induce inhibitory serine/threonine phosphorylation of insulin signaling components, leading to reduced GLUT4-mediated glucose uptake in skeletal muscle [94,97]. Insulin resistance is further aggravated by impaired mitochondrial lipid oxidation, as lipid accumulation triggers lipotoxicity, oxidative stress, and inflammation, resulting in mitochondrial dysfunction and activation of stress pathways such as p38 MAPK and JNK, with concurrent suppression of PGC-1α and mitochondrial biogenesis [96,98,99]. In this mechanistic perspective, impaired insulin signaling and chronic inflammation not only exacerbate

metabolic dysfunction but also interfere with anabolic pathways, highlighting the critical role of IGF-1 in skeletal muscle, where IGF-1–PI3K–Akt–mTOR signaling promotes hypertrophy and simultaneously represses forkhead box O transcription factors (FoxO)-driven atrogene expression (MAFbx/atrogin-1, muscle RING-finger protein (MuRF1) [100–102].

4.3 Obesity-Driven Intramuscular Fat Accumulation

Chronic overnutrition and physical inactivity promote sustained hyperglycemia and hyperinsulinemia, leading to the development of myosteatosis, associated with insulin resistance.

The pathogenetic mechanisms underlying obesity-related metabolic dysregulation partially overlap with those driving cancer-associated sarcopenia. Cancer-related inflammation, together with inadequate nutrient intake, may exacerbate fatigue, reduce physical activity, and impair functional mobility, thereby reinforcing dysregulated crosstalk between myocytes and adipocytes [18,103]. This maladaptive interaction contributes to the progression of sarcopenic obesity, with myosteatosis emerging as a key pathological feature in oncology [104].

In cancer-associated myosteatosis, lipid accumulation and inflammation impair insulin/IGF-1 signaling, causing mitochondrial dysfunction, metabolic derangements, and muscle wasting [19]. These muscle-specific metabolic disturbances contribute to systemic hyperinsulinemia, hyperleptinemia and elevated inflammatory mediators IL-6 and TNF-α, which can activate pro-tumorigenic signaling pathways, including PI3K–Akt–mTOR, nuclear factor kappa B (NF-κB), and JAK–STAT, linking skeletal muscle dysfunction directly to tumor progression [105].

In addition, circulating adiponectin, an anti-inflammatory adipokine secreted by adipose tissue, is reduced in obesity and myosteatosis, and this deficiency may remove a key anti-tumor signal. Adiponectin activates AMPK and inhibits PI3K–Akt/mTOR and Wnt/β-catenin signaling, promoting cell cycle arrest, apoptosis, and anti-angiogenic effects in cancer cells [106].

From a clinical perspective, myosteatosis in cancer patients is associated with poorer functional status, increased treatment toxicity, and reduced survival, highlighting its emerging role as a key adverse prognostic factor [19].

4.4 Myokine Secretion and Anti-Tumor Signaling

In addition to circulating growth factors, skeletal muscle and adipose tissue release cytokines that modulate metabolic and inflammatory pathways, as presented in Table 1. Dysregulation of these cytokines during systemic low-grade inflammation contributes to various cancer-related changes in body composition [18]. Muscle-derived (IL-6) enhances glucose uptake in skeletal muscle and exerts anti-inflammatory effects in peripheral tissues via a TNF-α-independent pathway [9]. Circulating IL-6 levels can increase 100-fold during and immediately after physical activity. Consequently, exercise-induced IL-6 release stimulates the production of various anti-inflammatory myokines, including IL-1 receptor antagonist (IL-1ra), IL-10, and IL-15 [9]. Notably, in most exercise-related studies, TNF-α levels, which cause tumor necrosis and growth, remain unchanged or are modestly reduced, likely due to suppression by muscle-derived IL-6.

In contrast, IL-6 from adipose tissue is a key pro-inflammatory mediator in chronic conditions such as obesity, type 2 diabetes, and various cancers [107,108]. Despite being the same molecule, IL-6 exerts context-dependent effects determined by the activation of classical or trans-signaling pathways. Importantly, muscle-derived IL-6 may counteract the deleterious inflammatory actions of chronically elevated IL-6, thereby contributing to the anti-inflammatory benefits of regular physical activity [109].

Another important myokine is irisin, which exerts anti-cancer effects by enhancing cytotoxic immune responses, reducing visceral adiposity and systemic inflammation, activating AMPK, and inhibiting pro-tumorigenic pathways such as PI3K–Akt/mTOR and STAT3, thereby suppressing tumor growth, proliferation, and metastasis [110].

Decorin, a small leucine-rich proteoglycan, exerts anti-cancer effects through multiple mechanisms. It directly interacts with receptor tyrosine kinases (RTKs) such as epidermal growth factor receptor (EGFR), and vascular endothelial growth factor receptor 2 (VEGFR2), inducing their internalization and degradation, which suppresses downstream pro-proliferative and pro-survival signaling (e.g., MAPK/ERK, PI3K/Akt) [111]. Decorin also binds to and antagonizes transforming growth factor beta (TGF-β), inhibiting epithelial–mesenchymal transition (EMT), fibrosis, angiogenesis, and extracellular matrix remodeling, key processes that facilitate tumor progression and metastasis [112]. Furthermore, decorin can modulate the tumor microenvironment by promoting anti-tumor immune responses. Collectively, these actions limit cancer cell proliferation, invasion, and metastasis, making decorin a key tumor-suppressive myokine and potential therapeutic target.

Exercise secreted SPARC (secreted protein acidic and rich in cysteine) exerts anti-tumor effects by modulating extracellular matrix organization, inhibiting angiogenesis, and promoting cancer cell apoptosis [113]. Muscle-derived SPARC has been shown to suppress tumorigenesis, particularly in colorectal cancer models, while reduced SPARC expression in tumors is associated with enhanced proliferation and disease progression [113]. Through its ability to regulate growth factor signaling and vascular remodeling, SPARC contributes to a tumor-suppressive microenvironment, although its effects are context-dependent across cancer types. In addition, SPARC deficiency is associated with increased adiposity and enlarged adipocytes, while elevated SPARC expression limits fat mass expansion, linking SPARC to the regulation of adipose tissue development and metabolic homeostasis [114].

Collectively, these findings support the concept that skeletal muscle mass and force protect against systemic low-grade inflammation through reductions in visceral and total adiposity and the establishment of an anti-inflammatory environment driven by myokine release [115].

By contrast, during physical inactivity, skeletal muscle secretes myostatin, a negative regulator of muscle growth, which promotes inflammation in skeletal muscle and other tissues, highlighting the critical balance between myokines in modulating systemic metabolic and inflammatory homeostasis [116].

Table 1: Pro-tumorigenic factors associated with muscle–adipose tissue dysregulation.

Pro Tumorigenic Factors	Source/Origin	Mechanistic Impact on Tumor Progression
Hyperinsulinemia/IGF-1	Muscle insulin resistance	Activates PI3K-Akt-mTOR signaling → promotes tumor cell proliferation and survival
TNF-α	Adipose tissue & inactive skeletal muscle	Activates NF-κB → supports inflammation
IL-6 (pro-inflammatory)	Adipose tissue	Activates JAK-STAT3 → promotes tumor growth and inflammation.
Leptin	Adipose tissue	Stimulates angiogenesis, proliferation, metastasis
IL-6 (anti-inflammatory) (↓)	Skeletal muscle	Promotes inflammation and hyperinsulinemia
Adiponectin (↓)	Adipose tissue	Loss of anti-tumor signaling → tumor progression
Irisin (↓)	Inactive skeletal muscle	Stimulate tumor growth
Decorin (↓)	Inactive skeletal muscle	Stimulate tumor growth and angiogenesis
SPARC (↓)	Inactive skeletal muscle	Decrease in anti-tumor and anti-angiogenic activity

Table 1: *Cont.*

Pro Tumorigenic Factors	Source/Origin	Mechanistic Impact on Tumor Progression
IL-15 (↓)	Inactive skeletal muscle	Support tumor growth
Free fatty acids/Ceramides	Muscle-adipose crosstalk	Metabolic substrates that enhance tumor growth and alter tumor metabolism
ROS/Oxidative stress	Mitochondrial dysfunction in muscle	DNA damage and activation of pro-tumor signaling pathways
Myostatin	Inactive skeletal muscle	Promotes muscle wasting, systemic inflammation, indirectly supporting tumor growth.

Note: Tumor-promoting systemic mediators associated with skeletal muscle dysfunction and altered muscle–adipose endocrine crosstalk, and their proposed mechanistic contributions to tumor progression. Elevated mediators such as hyperinsulinemia/IGF-1, TNF-α, pro-inflammatory IL-6, leptin, free fatty acids/ceramides, ROS, and myostatin promote inflammation, metabolic dysfunction, angiogenesis, and activation of oncogenic pathways (PI3K-Akt-mTOR, JAK-STAT, NF-κB). Conversely, reduced levels of protective myokines (exercise-induced IL-6, adiponectin, irisin, decorin, SPARC, IL-15) weaken anti-tumor and metabolic regulatory effects, promoting a pro-tumorigenic microenvironment. IGF-1, insulin-like growth factor-1; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; ROS, reactive oxygen species; PI3K–Akt–mTOR, Phosphoinositide 3-kinase–protein kinase B–mammalian target of rapamycin; JAK–STAT, Janus kinase–signal transducer and activator of transcription; NF-κB, nuclear factor kappa B; SPARC, secreted protein acidic and rich in cysteine; IL-15, Interleukin 15. Symbol key ↓ denote decreased levels.

5 Melatonin Actions on Skeletal Muscle Metabolism

5.1 Insulin Sensitization and Glucose Handling via MT_2-Biased IRS-1/PI3K Signaling

Melatonin receptors in skeletal muscle can directly engage canonical insulin signaling. In differentiated C2C12 myotubes, 10^{-9}–10^{-5} mol/L melatonin increases 2-deoxy-D-glucose uptake by 30–60% in a concentration-dependent manner and enhances glycogen synthesis. These effects are accompanied by increased IRS-1 tyrosine phosphorylation, PI3K activity, protein kinase C zeta (PKCζ) activation and GLUT4 translocation to the plasma membrane, and are abolished by the non-selective antagonist luzindole and an MT_2-preferring antagonist, indicating a receptor- and PI3K-dependent mechanism [47]. These data show that melatonin can activate the IRS-1/PI3K axis in myotubes in a way that functionally converges with insulin signaling, with a signaling profile compatible with MT_2-biased activation. Beyond insulin-convergent glucose handling, melatonin has been reported to counteract lipid-driven skeletal muscle insulin resistance by preserving mitochondrial oxidative capacity/biogenesis and improving muscle metabolic flexibility, including reduced intramyocellular lipid accumulation and a shift toward fat utilization under diet- or lipid-induced insulin-resistant conditions [75,117]. In *in vivo* animal experiments, chronic melatonin improves insulin sensitivity and components of the metabolic syndrome in several rodent models. In high-fat diet-fed mice, 8 weeks of melatonin (≈10 mg/kg/day in drinking water) increased glucose infusion rates during hyperinsulinemic–euglycemic clamps, improved glucose tolerance, and restored insulin-induced vasodilation and capillary recruitment in skeletal muscle, in parallel with increased insulin-stimulated Akt and eNOS phosphorylation in the vasculature [118]. In a high-fructose model, male Wistar rats fed a 60% fructose diet for 4–6 weeks developed hyperinsulinemia, dyslipidaemia, visceral adiposity, elevated leptin and TNF-α, reduced adiponectin, and increased homeostatic model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI)-defined insulin resistance. Daily intraperitoneal melatonin (1 or 10 mg/kg) from week 4 to 6 attenuated these changes, particularly at 10 mg/kg, normalizing insulin responses during oral glucose tolerance testing (OGTT) and improving insulin resistance indices [119]. In a related high-fat diet model, melatonin in drinking water (25 μg/mL) for 9–11 weeks reduced body-weight gain, lowered mean insulin, glucose and triglyceride levels, and attenuated

high-fat diet-induced hyperinsulinemia, hyperglycemia, hypertriglyceridemia and hypercholesterolemia, while partially restoring disrupted 24-h profiles of adiponectin, leptin, insulin and cholesterol [120].

Old obese Wistar rats provide a complementary model in which melatonin improves insulin sensitivity in age-related obesity. In these animals, 8–12 weeks of nocturnal melatonin increased insulin sensitivity by about 2.1-fold, as assessed by insulin tolerance tests, and enhanced acute insulin-induced phosphorylation of IR, IRS-1/2 and Akt in liver, skeletal muscle, adipose tissue and hypothalamus, without major early changes in total protein abundance of these signaling elements [121]. In aged rats undergoing aerobic training, 16 weeks of melatonin supplementation further improved glucose tolerance, increased hepatic and muscular glycogen content, reduced body weight and upregulated GLUT4 and AMPK protein expression in skeletal muscle compared with training alone, indicating that adequate melatonin tone is necessary for full exercise-induced metabolic adaptation in muscle [122].

At the cellular stress level, melatonin preserves proximal insulin signaling under endoplasmic reticulum (ER) stress and lipotoxic conditions. In C2C12 myotubes, tunicamycin-induced ER stress activates Protein kinase RNA-like ER kinase/Eukaryotic initiation factor 2 alpha (PERK/eIF2α) and C/EBP homologous protein (CHOP), activates inositol-requiring enzyme 1/c-Jun N-terminal kinase (IRE1/JNK), increases IRS-1 serine phosphorylation, reduces IRS-1 tyrosine phosphorylation and impairs insulin-stimulated Akt activation and glucose uptake. Co-treatment with melatonin reverses these changes, normalizing IRS-1 phosphorylation patterns, restoring Akt phosphorylation and glucose uptake and suppressing PERK/CHOP and JNK signaling in a luzindole-sensitive manner [123]. In high-fat diet-fed rats, chronic melatonin normalizes mitochondrial morphology and respiratory chain function in skeletal muscle, reduces intramyocellular lipid accumulation and oxidative stress and improves insulin-stimulated Akt signaling, linking mitochondrial protection to improved myocytic insulin sensitivity [71]. These findings support the view that melatonin maintains IRS-1/PI3K/Akt integrity by dampening both ER and mitochondrial stress in skeletal muscle.

Pancreatic and systemic actions of melatonin further contribute to insulin sensitization that indirectly benefits the muscle. In senescence-accelerated SAMP8 mice, aging is associated with hyperinsulinemia, elevated HOMA-IR, reduced pancreatic insulin content, decreased pancreatic and duodenal homeobox 1 (Pdx-1), FoxO1, FoxO3a and SIRT1 expression and increased pro-inflammatory mediators. Chronic melatonin treatment reduces plasma insulin, lowers HOMA-IR, increases pancreatic insulin content and restores SIRT1, Pdx-1 and FoxO3a expression, while decreasing glucagon, GLUT2, somatostatin and insulin mRNAs in the pancreas [124,125]. Long-term enteral melatonin in Wistar and Goto-Kakizaki type 2 diabetic rats decreases plasma insulin levels and increases pineal insulin receptor expression, indicating reciprocal adaptation in the insulin–melatonin axis [126]. By reducing chronic hyperinsulinemia and pancreatic inflammation/oxidative stress, melatonin lessens the sustained insulin burden on peripheral tissues, including skeletal muscle, and thereby facilitates improved muscle insulin responsiveness on top of its direct myocytic and microvascular actions.

Human data is more heterogeneous and emphasizes the importance of dose and timing. Acute supraphysiologic melatonin given shortly before a glucose load can transiently impair glucose tolerance: in healthy women, a single 5 mg dose 15 min before a 75 g OGTT increased glucose incremental area under the curve (AUC) by approximately 186% in the morning and 54% in the evening, with parallel changes in insulin secretion and estimated insulin sensitivity [127]. In postmenopausal women, 1 mg melatonin reduced glucose tolerance and insulin sensitivity by intravenous glucose tolerance test (IVGTT) and clamp [128]. In contrast, prolonged-release bedtime melatonin in type 2 diabetic patients with insomnia did not worsen fasting glycemia or lipids and was associated with improved sleep and a modest glycated hemoglobin A1c (HbA1c) reduction in longer-term follow-up [129]. In a 12-week pilot clinical intervention

in obese individuals with acanthosis nigricans, bedtime melatonin (3 mg/day) was associated with significant reductions in fasting insulin and HOMA-IR, alongside improved Matsuda index, supporting a potential insulin-sensitizing signal in selected insulin-resistant phenotypes [130]. More recent randomized data show that evening melatonin over several weeks can reduce insulin sensitivity in individuals carrying MTNR1B risk alleles, highlighting gene–treatment interactions and the importance of circadian phase [131]. In this study, three months of bedtime melatonin (10 mg given one hour before habitual sleep time) reduced clamp-derived peripheral insulin sensitivity in men with type 2 diabetes, despite no clear decrement in canonical insulin signaling readouts in skeletal muscle biopsies. The authors noted measurable daytime melatonin on the metabolic test day and a modest delay in sleep/circadian timing, raising the possibility that residual daytime exposure and/or phase-shifting effects contributed to the adverse clamp signal. They also emphasized that fasting indices commonly reported in supplementation trials (for example HOMA-based outcomes) predominantly reflect hepatic insulin sensitivity, whereas the insulin clamp quantifies glucose disposal under standardized hyperinsulinemia and therefore mainly reflects peripheral (predominantly skeletal-muscle) insulin sensitivity. Thus, providing a plausible explanation for why melatonin may appear neutral or beneficial in some cohorts, yet reduce peripheral insulin sensitivity in established diabetes. Importantly, also acute supra-physiological melatonin exposure (four oral doses of 10 mg, total 40 mg) in a double-blinded randomized crossover trial in healthy young men, significantly reduced hyperinsulinaemic–euglycaemic clamp–derived insulin sensitivity in the overall cohort [132].

5.2 Mitochondrial Biogenesis, Oxidative Phosphorylation, and Calcium Handling

Mitochondria are both a major extranuclear site of melatonin synthesis and a preferential intracellular compartment for melatonin accumulation, which is particularly relevant in skeletal muscle with its high mitochondrial density and oxidative demand. In rats fed a high-fat diet, chronic melatonin treatment (4 mg/kg/day in drinking water, 12 weeks) prevented the development of skeletal muscle mitochondrial dysfunction. In a group of melatonin-treatment, animals show higher respiratory control ratios, preserved complex I and IV activities, increased ATP production, reduced mitochondrial H_2O_2 generation, and improved insulin-stimulated glucose uptake in soleus, together with upregulation of PGC-1α, nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (TFAM) in muscle [73]. In Zücker diabetic fatty (ZDF) rats, oral melatonin (10 mg/kg/day, 12 weeks) similarly restored mitochondrial oxidative capacity in vastus lateralis muscle, increasing respiratory control ratio, oxidative phosphorylation efficiency, and fatty acid oxidation, while enhancing activities of complexes I, III and IV [73,75]. These adaptations were accompanied by an increased proportion of type I/IIa oxidative fibers and activation of NRF2–regulator of calcineurin (RCAN)–calcineurin–MEF2 signaling, indicating coordinated effects on mitochondrial metabolism and fiber-type specification in an obese-diabetic milieu [73].

At the structural level, melatonin normalizes mitochondrial dynamics and autophagy in diabetic skeletal muscle. In vastus lateralis muscle of ZDF rats, melatonin partially corrects an imbalance between fission and fusion by increasing fission 1 protein (Fis1) and dynamin-related protein 1 (DRP1) expression and reducing optic atrophy 1 (OPA1) and mitofusin 2 (Mfn2), and restores autophagic flux as shown by increased microtubule-associated protein 1A/1B-light chain 3B (LC3B-II/I ratio) and sequestosome 1 (p62) levels, together with higher SIRT1 expression, ATP production and superoxide dismutase (SOD) activity and reduced nitrite accumulation [75]. These changes are associated with improved oxidative phenotype and reduced intramyocellular lipid content, providing a mechanistic link between melatonin, mitochondrial quality control and the reversal of obesity- and diabetes-associated skeletal muscle “metabolic inflexibility” [73,75].

In addition to improving mitochondrial oxidative capacity, melatonin may influence skeletal muscle lipid handling upstream at the level of substrate influx. Physiological-range melatonin has been shown to acutely inhibit long-chain fatty acid uptake in rodent hind-limb skeletal muscle *in vivo*, with concomitant suppression of tissue cAMP, indicating that melatonin can modulate lipid substrate influx independently of glucose uptake [133]. This lipid-handling dimension provides a complementary mechanism linking nocturnal melatonin tone to reduced intramyocellular lipid accumulation and improved insulin responsiveness.

In vitro studies in myogenic cells provide direct evidence that melatonin preserves mitochondrial integrity under oxidative and calcium stress. In C2C12 myotubes, melatonin prevents H_2O_2-induced loss of mitochondrial membrane potential, inhibits opening of the mitochondrial permeability transition pore, reduces cytochrome c release into the cytosol and attenuates caspase-3 activation, thereby limiting apoptosis [134]. In differentiated skeletal muscle cells exposed to pro-oxidant conditions, melatonin increases SOD and catalase activities, preserves mitochondrial ultrastructure, maintains ATP content and reduces Bcl-2-associated X protein/B-cell lymphoma 2 (Bax/Bcl-2 ratio) and DNA fragmentation [74]. These effects are concentration-dependent in the micromolar range and are abrogated by the antagonist of melatonin receptors, luzindole, supporting a receptor-mediated component in addition to direct radical scavenging [74,134].

Ischemia–reperfusion (I/R) and septic models extend these findings to acute severe stress *in vivo*. In a rat cremaster muscle preparation subjected to 4 h warm ischemia followed by 2 h reperfusion, melatonin (10 mg/kg, i.p., pre- and early post-reperfusion) significantly increases arteriolar diameter, capillary perfusion and endothelium-dependent vasodilation, thereby improving microvascular oxygen delivery to muscle [135]. In a related gracilis muscle I/R model, melatonin administered around reperfusion preserves mitochondrial membrane potential, reduces cytochrome c release from mitochondria to cytosol and attenuates I/R-induced mitochondrial dysfunction, consistent with stabilization of the respiratory chain under acute oxidative stress [136]. In cecal ligation and puncture-induced sepsis, melatonin counteracts inducible mitochondrial nitric oxide synthase (i-mtNOS)–dependent inhibition of electron transport chain complexes in hind limb skeletal muscle, restores ATP production and decreases mitochondrial oxidative/nitrosative damage, effects that are absent in iNOS-knockout mice, indicating a specific interaction with inducible NO pathways in mitochondria [137].

Although detailed signaling studies in skeletal muscle are still limited, work in other high-energy tissues provides mechanistic plausibility for similar mitochondrial signaling modules in myofibers. In type 1 diabetic rat myocardium subjected to ischemia–reperfusion, melatonin activates AMPK–PGC-1α–SIRT3 signaling, increases mitochondrial superoxide dismutase (SOD2), NRF1 and TFAM expression, enhances mitochondrial SOD activity, ATP production and oxidative phosphorylation complex activities, while reducing mitochondrial lipid peroxidation and H_2O_2 formation [138]. Pharmacological inhibition of AMPK or genetic silencing of SIRT3 abolish these effects [138]. The same AMPK–PGC-1α–SIRT axis, together with SIRT1-dependent deacetylation, is central to mitochondrial biogenesis and antioxidant defense in skeletal muscle and is upregulated by melatonin in muscle from diet-induced obese and ZDF rats [73].

5.3 Antioxidant and Anti-Inflammatory Effects in Muscle and Perimuscular Adipose Depots

Melatonin combines direct free radical scavenging with transcriptional control of antioxidant and inflammatory pathways, which is highly relevant for skeletal muscle and its surrounding adipose depots. At the cellular level, melatonin suppresses pro-inflammatory signaling in macrophages by inhibiting NF-κB and STAT1 activation and reducing nitric oxide and IL-6 production in lipopolysaccharide

(LPS)-stimulated RAW264.7 cells [139]. In parallel, melatonin upregulates antioxidant defences and reduces lipid peroxidation in multiple tissues, as summarized in detailed mechanistic work on its radical scavenging and NRF2-linked antioxidant actions [140]. These pathways are expressed in infiltrating immune cells and stromal elements within skeletal muscle and adipose tissue, providing a plausible mechanistic basis for tissue-level anti-inflammatory and antioxidant effects in obesogenic and catabolic states.

In rodent models of obesity and type 2 diabetes, melatonin attenuates systemic low-grade inflammation and oxidative stress while improving insulin sensitivity. In young Zucker diabetic fatty rats, oral melatonin at 10 mg/kg/day for 6 weeks lowers circulating IL-6 by about 10%, TNF-α by ~10%, and C-reactive protein by ~20%, and reduces both basal and induced plasma lipid peroxidation, consistent with a global reduction of oxidative and inflammatory burden [141]. In rats with diet-induced metabolic syndrome, chronic melatonin normalizes clinical and biochemical markers of mild inflammation, decreases oxidative stress indices, and improves insulin resistance [142]. These systemic changes are accompanied by improved glucose tolerance and lipid profiles, which indirectly relieve metabolic and inflammatory stress on skeletal muscle.

High-fat diet models show that melatonin not only improves systemic metabolic parameters but also reshapes adipose tissue inflammation, including depots contiguous with skeletal muscle. In mice fed a high-fat diet, nightly melatonin (10 mg/kg) prevents obesity, reduces visceral fat mass, lowers TNF-α and IL-6 expression in adipose tissue, and shifts the gut microbiota toward a composition associated with reduced endotoxemia and adipose inflammation. A follow-up study in high-fat-fed mice demonstrates that melatonin reprograms the microbiota and improves lipid dysmetabolism while decreasing adipose tissue macrophage infiltration and pro-inflammatory cytokine expression [143]. Although these studies do not isolate perimuscular fat specifically, they support the concept that melatonin dampens inflammatory signaling in adipose depots that contribute to myosteatosis, ectopic fat accumulation, and cytokine spillover toward skeletal muscle.

Direct evidence for antioxidant protection in skeletal muscle comes from toxin and trauma models. In rats exposed to carbon tetrachloride, melatonin (10 mg/kg) reduces malondialdehyde levels, restores glutathione content, and normalizes the activities of SOD, catalase, and glutathione peroxidase in gastrocnemius muscle, paralleled by improved histological preservation of myofibers [144]. In standardized muscular trauma models, melatonin (10 mg/kg) markedly attenuates nitrotyrosine staining, myeloperoxidase activity, and NF-κB nuclear translocation in injured muscle, while improving regenerative histology and fiber diameter distribution [145]. These data indicate that melatonin reduces oxidative and nitrosative stress and suppresses neutrophil-driven inflammation directly within skeletal muscle tissue.

Crush-injury experiments provide additional insight into the muscle-intrinsic anti-inflammatory actions of melatonin. In rats with standardized hind-limb muscle crush, daily melatonin accelerates the recovery of twitch and tetanic force, increases the number of paired box protein 7 (Pax7)-positive satellite cells, and decreases terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive apoptotic nuclei in regenerating muscle [146]. The functional recovery correlates with lower expression of TNF-α and IL-1β and reduced oxidative damage markers, suggesting that melatonin creates a more permissive redox and cytokine environment for muscle regeneration. Together with ischemia–reperfusion studies showing reduced muscle superoxide generation and improved mitochondrial function under melatonin treatment [136,147], these findings support a consistent myoprotective pattern across diverse injury paradigms.

Human exercise studies offer a translational window into melatonin's antioxidant and anti-inflammatory effects in human skeletal muscle. In adult male runners completing a 50-km mountain ultramarathon, pre-exercise melatonin supplementation significantly blunts the post-exercise rise in circulating TNF-α and

IL-6, and decreases urinary 8-hydroxy-2′-deoxyguanosine and isoprostane excretion, indicating reduced systemic oxidative DNA and lipid damage [148]. In a complementary rat model of exhaustive treadmill running, melatonin reduces muscular lipid peroxidation and inflammatory cytokine expression and simultaneously increases IGF-1 and vascular endothelial growth factor (VEGF) levels in muscle, consistent with enhanced growth factor signaling during recovery [149]. While these studies rely on systemic and muscle-biopsy biomarkers rather than direct imaging of perimuscular fat, they demonstrate that melatonin modulates redox and inflammatory responses in the exercising muscle microenvironment.

Collectively, cell, animal, and human data converge on a model in which melatonin attenuates oxidative stress and inflammatory signaling both within skeletal muscle fibers and in adjacent adipose depots. By lowering TNF-α and IL-6, reducing neutrophil and macrophage infiltration, and strengthening endogenous antioxidant systems, melatonin is poised to counter the chronic low-grade inflammation and redox imbalance that couples obesity, myosteatosis, and sarcopenic muscle dysfunction to an elevated cancer risk.

5.4 Effects on Myogenesis, Satellite Cells, and Muscle Regeneration after Injury or Radiotherapy

Skeletal muscle regeneration depends on satellite cells, a population of quiescent myogenic stem cells located between the sarcolemma and basal lamina of myofibers. These cells express the paired box transcription factor Pax7 and, upon activation, upregulate a muscle-specific transcription factor, myogenic differentiation 1 (MyoD) and myogenic factor 5 (Myf5), enter the cell cycle, and later induce myogenin and myogenic regulatory factor 4 (MRF4) to drive terminal differentiation and fusion into regenerating myofibers. Genetic ablation of $Pax7^+$ cells in mice completely abolishes injury-induced regenerative myogenesis in tibialis anterior and extensor digitorum longus muscles, demonstrating that $Pax7^+$ satellite cells are the indispensable stem cell source for adult skeletal muscle regeneration [150]. These lineage-tracing and loss-of-function data provide the conceptual framework for interpreting melatonin's effects on myogenesis, because modulation of satellite cell number, survival, or transcriptional programs will have direct consequences for long-term muscle mass and function [151].

5.4.1 In Vitro Effects on Myoblast Differentiation and Atrophy Signaling

In myogenic cell lines, melatonin influences key transcriptional and catabolic pathways that govern myogenesis. In C2C12 myoblasts, physiological to pharmacological concentrations of melatonin (10^{-9}–10^{-5} mol/L) accelerate myogenic differentiation, with increased myotube diameter and elevated expression of MyoD, myogenin, and myosin heavy chain, while also reducing markers of oxidative stress and apoptosis [152,153]. Su and colleagues recently showed that melatonin enhances myotube formation even when Pax7 expression is knocked down. In Pax7-deficient C2C12 cells, melatonin restored mitochondrial membrane potential, increased PGC-1α and SOD2 expression, and partially rescued fusion index and myotube diameter, suggesting that mitochondrial and redox pathways can compensate for defective Pax7 signaling *in vitro* [154]. This work also implicated Wnt/β-catenin signaling in melatonin-induced myogenesis, with increased β-catenin nuclear localization and upregulation of Wnt target genes.

Melatonin also counteracts cytokine-induced atrophy programs. In L6 myotubes, TNF-α exposure induces a robust atrophic response characterized by reduced myotube diameter, increased expression of the E3 ligases MuRF1 and atrogin-1 (Fbxo32), activation of NF-κB and p38 MAPK, and increased ROS generation [155,156]. Treatment with melatonin attenuates TNF-α–induced myotube thinning, suppresses MuRF1/atrogin-1 induction, and reduces NF-κB activation and oxidative stress, indicating that melatonin directly interferes with catabolic signaling cascades in myocytes [156]. One study on C2C12 myoblast cells

showed that melatonin-induced autophagy clears MyoD at late stages of differentiation, and that melatonin fine-tunes the balance between proliferation, differentiation, and proteolysis in a way that favors formation and maintenance of functional myotubes [157].

5.4.2 Satellite Cell Activation, Pax7, and Regeneration In Vivo

Crush and blunt trauma models in rodents provide *in vivo* confirmation that melatonin enhances the satellite cell–driven regenerative response. In a standardized rat gastrocnemius crush model, daily melatonin administration increased the number of $Pax7^+$ satellite cells in injured muscle during the early regenerative phase, reduced TUNEL-positive apoptotic nuclei, and improved recovery of twitch and tetanic force compared with vehicle-treated animals [145,146]. Histological evaluation of injured rat skeletal muscle shows that melatonin treatment attenuates trauma-induced myofiber disruption and inflammatory infiltrate, as well as leads to better preservation of overall muscle architecture. This tissue-level protection is accompanied by reduced lipid peroxidation (TBARS) and normalization of antioxidant enzyme activities (SOD), glutathione peroxidase (GPx) within the damaged muscle, linking satellite cell dynamics to melatonin's redox effects *in vivo* [145].

Independent trauma models have reported convergent findings. In rats subjected to standardized muscular trauma, melatonin administered at 10 mg/kg reduced leukocyte infiltration, decreased expression of pro-apoptotic markers (Bax, cleaved caspase-3), and increased satellite cell proliferation indices in the injured muscle. These molecular effects translated into higher contractile force and improved histological regeneration at 7–14 days post-injury compared with untreated controls [146]. Collectively, these animal studies support a model in which melatonin coordinates three components of the regenerative response: satellite cell expansion and differentiation, suppression of apoptosis in nascent myofibers, and mitigation of inflammatory damage.

5.4.3 Dystrophic and Chronic Myopathy Models

Chronic myopathic conditions offer a more stringent test of regenerative support because satellite cells are repeatedly activated and vulnerable to exhaustion. In the dystrophic mdx5Cv mouse, which lacks functional dystrophin, chronic melatonin treatment improves forelimb grip strength and specific muscle force, reduces central nucleation and fiber size variability, and lowers markers of oxidative damage and nitrosative stress in skeletal muscle [158]. Indeed, NF-κB contributes to the perpetuation of the dystrophic damage and its blockade produces beneficial effects on functional, biochemical, and morphological parameters in mdx mice [159]. Observed functional gains due to melatonin application were associated with increased expression of utrophin, enhanced mitochondrial antioxidant defenses, and reduced NF-κB activation, suggesting that melatonin improves the microenvironment in which satellite cells and regenerating fibers operate [158].

Human data in dystrophic muscle, although still limited, are consistent with these preclinical findings. In a longitudinal study of ten boys with Duchenne muscular dystrophy treated with high-dose melatonin (60 mg at 21:00 plus 10 mg at 09:00), plasma levels of TNF-α, IL-1β, IL-2, IL-6, interferon-γ, lipid peroxidation products, and nitrite/nitrate were markedly reduced over 3–9 months of treatment, indicating a substantial attenuation of systemic and muscle-related oxidative–inflammatory stress [160]. Although direct measures of satellite cell activity were not obtained, the normalization of inflammatory and nitrosative markers is expected to lessen the hostile milieu that accelerates satellite cell dysfunction and fibrofatty replacement in dystrophic muscle.

5.4.4 Radiotherapy-Associated Muscle Injury and Radioprotection

Ionizing radiation used in cancer therapy can damage skeletal muscle within the radiation field, contributing to weakness, fibrosis, and exacerbation of cancer-associated sarcopenia. Direct evidence that melatonin protects irradiated muscle comes from a rat hind-limb model in which a single local dose of 10 gray (Gy) γ-irradiation to the gastrocnemius muscle produced marked myofiber degeneration, interstitial edema, elevated malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG), and reduced SOD and catalase activities. Pre-treatment with melatonin (30 or 100 mg/kg, i.p., 30 min before irradiation) significantly decreased MDA and 8-OHdG levels, increased SOD and catalase activities, and improved histological architecture, with fewer necrotic fibers and less interstitial edema compared with irradiated controls [161]. Electrophysiological measures of muscle function were also partially preserved, indicating that structural protection translated into functional neuromuscular benefit. In addition, melatonin suppresses radiotherapy-induced pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, thereby limiting the catabolic processes that lead to muscle wasting associated with ionizing radiation–based cancer therapy [162]. By attenuating inflammation- and oxidative stress-driven muscle catabolism, melatonin protects against sarcopenia and preserves skeletal muscle mass and strength through its antioxidant and mitochondrial protective effects [163].

These muscle-focused data align with a broader body of animal work showing that melatonin mitigates radiation-induced oxidative and inflammatory injury in non-muscle tissues. In rats exposed to 8 Gy whole-body or abdominal irradiation, melatonin reduces lipid peroxidation, restores glutathione, and improves antioxidant enzyme activities in liver, lung, kidney, brain, and intestine, while improving 30-day survival [164,165]. In mice, oral melatonin (1–20 mg/mL) administered before whole-body γ-irradiation elevates the D_0 of intestinal crypt survival curves and dose-dependently preserves jejunal crypts, demonstrating true radioprotection at the tissue level [166]. Additional models of acute radiation enteritis show that melatonin given before or shortly after abdominal or pelvic irradiation attenuates villus atrophy, crypt loss, mucosal ulceration, and inflammatory infiltrates, and reduces oxidative stress markers in jejunum and ileum [167,168].

More recently, fractionated radiotherapy regimens that resemble clinical practice have been examined. In a rat model of fractionated abdominal radiotherapy, systemic melatonin reduced histological small-intestinal injury, decreased TNF-α and IL-1β expression, and enhanced tight junction integrity [169]. Similar protection against radiation-induced intestinal damage has been reported with melatonin given at 5–15 mg/kg i.p., where villus height and crypt depth are largely preserved and apoptosis indices are reduced compared with irradiated controls [166,167,169]. Although these studies focus on gut, the mechanisms involved (ROS scavenging, NF-κB inhibition, upregulation of endogenous antioxidant defenses) are shared with skeletal muscle and likely contribute to the muscle-protective effects seen in the hind-limb model.

In humans, several randomized trials have evaluated melatonin as an adjuvant during chemoradiation, primarily targeting oral mucositis and symptom burden rather than muscle endpoints. In head and neck cancer, adjuvant oral melatonin (20 mg/day) significantly reduced the incidence of severe (grade 3–4) oral mucositis, decreased unplanned treatment interruptions, and lowered opioid requirements compared with placebo during concurrent chemoradiation [170]. Topical and systemic melatonin have since been tested in multiple trials. For example, melatonin-containing oral gels or rinses reduced mucositis severity and pain scores in patients receiving head and neck radiotherapy, with favorable safety profiles [171]. In breast cancer, phase III trials show that melatonin (20 mg nightly during radiotherapy) can attenuate radiotherapy-related fatigue and improve selected quality-of-life domains, although effects on objective performance measures are modest and not consistently replicated [172,173].

Despite this emerging clinical experience, systematic human studies directly quantifying skeletal muscle mass, strength, or satellite cell markers in irradiated cancer patients treated with melatonin are still lacking. Existing trials largely focus on mucosal, intestinal, or systemic symptoms rather than muscle structure or function. At present, extrapolation of radioprotective effects observed in animal skeletal muscle to human oncology remains hypothesis-generating and highlights a clear translational gap. Carefully designed trials incorporating imaging-based muscle assessment (e.g., CT-derived muscle cross-sectional area), dynamometry, and myokine profiling in patients receiving loco-regional radiotherapy plus melatonin will be required to determine whether the robust preclinical radioprotection in muscle translates into clinically meaningful preservation of muscle mass and function.

5.4.5 Integration and Implications for Sarcopenia and the Obesity–Cancer Axis

Taken together, the *in vitro* and *in vivo* evidence indicate that melatonin modulates myogenesis at multiple levels: it enhances myoblast differentiation, restrains catabolic cytokine signaling, supports satellite cell expansion and survival after injury, and improves regeneration in chronic myopathic conditions. By normalizing the inflammatory and oxidative milieu in which satellite cells reside, melatonin may delay satellite cell exhaustion and preserve regenerative capacity in settings of chronic metabolic stress, such as obesity and cancer. The demonstration that melatonin can partially rescue myogenic differentiation even in Pax7-deficient cells and dystrophic muscle further suggests that its benefits are not restricted to "ideal" regenerative contexts but extend to compromised muscle microenvironments.

From the perspective of the obesity–cancer axis, these regenerative and anti-atrophic actions are mechanistically relevant because they help maintain skeletal muscle mass and quality, thereby sustaining myokine production and limiting myosteatosis and inflammatory signaling that promote tumor progression. Future trials in obese and oncologic populations will need to determine whether appropriately timed melatonin supplementation can preserve satellite cell function, mitigate treatment-related muscle loss, and improve tolerance to anticancer therapy.

5.5 Regulation of Intramuscular Fat, Fiber Type Composition, and Sarcopenic Obesity Phenotypes

In high-fat diet rodent models, melatonin not only improves insulin signaling and mitochondrial function but also reduces ectopic lipid accumulation in skeletal muscle. Chronic melatonin administration decreases intramyocellular triglyceride content and normalizes muscle diacylglycerol (DAG) and ceramide levels, changes that align with improved insulin signaling and reduced activation of stress kinases implicated in insulin resistance [174]. Increased expression of PGC-1α, CPT-1, and other β-oxidation enzymes in muscle suggests that melatonin enhances fatty acid oxidation capacity and limits lipotoxic lipid species. These findings support a model in which melatonin improves metabolic flexibility by reducing intramyocellular lipid burden and favoring oxidative substrate handling.

Melatonin also appears to modulate fiber type-related adaptations. In a rat model of knee instability with secondary muscle stress, a combination of melatonin treatment and treadmill exercise promotes oxidative adaptations in gastrocnemius muscle and normalizes early CHOP-mediated autophagy signaling, consistent with protection of fatigue-resistant fiber populations [175]. Other models of chronic pain and myalgia indicate that melatonin improves mitochondrial function and reduces oxidative damage specifically in type I and IIa fibers, preserving fiber size distribution and preventing the shift toward glycolytic, atrophy-prone phenotypes [176,177]. However, most evidence remains indirect (phenotypic and mitochondrial readouts), and future studies should explicitly quantify fiber-type transitions and contractile performance alongside receptor-selective interventions.

With respect to sarcopenia, melatonin has been evaluated in both animal models and humans. In aged mice, chronic melatonin supplementation preserves gastrocnemius muscle structure, maintains muscle fiber number, improves locomotor activity and frailty index, and counteracts aging-associated mitochondrial damage, consistent with attenuation of sarcopenia-related changes and stimulation of mitochondrial biogenesis pathways [178]. In complementary rodent models of skeletal muscle oxidative injury, melatonin reduces malondialdehyde (MDA) levels and protein oxidative damage, restores activities of antioxidant enzymes such as SOD, catalase and glutathione peroxidase, and ameliorates histological muscle fiber disorganization, indicating reduced protein carbonylation and lipid peroxidation in skeletal muscle [144,179]. Collectively, these preclinical data are consistent with a primarily mitochondrial–redox mechanism, which may be most relevant in ageing phenotypes characterized by oxidative damage and impaired bioenergetics.

Observational data further show that lower urinary melatonin excretion is associated with a higher prevalence of sarcopenia in postmenopausal women, supporting a clinical link between melatonin status and muscle health [180]. Similarly, in a cross-sectional analysis of the HEIJO-KYO cohort, elderly individuals with lower nocturnal urinary 6-sulfatoxymelatonin excretion had reduced handgrip strength and poorer physical performance, independent of age, sex, and BMI [181]. Although these associations do not establish causality, they are compatible with the hypothesis that diminished nocturnal melatonin signaling co-segregates with impaired muscle function in ageing populations.

On contrary, interventional evidence in humans is limited and highlights potential reasons for null results. A pilot randomized trial in sarcopenic elderly patients tested a 4-week intervention with melatonin (1 mg/day), essential amino acids, or their combination. The combination of melatonin plus essential amino acids increased total fat-free mass compared with placebo and melatonin alone, whereas melatonin alone showed minimal effects on body composition and did not clearly improve muscle strength or inflammatory markers [182]. This null or weak signal for melatonin monotherapy should be interpreted in light of (i) the low dose (1 mg), (ii) the short intervention duration (4 weeks), which may be insufficient for measurable changes in muscle mass or strength, and (iii) the lack of enrichment for participants with low endogenous melatonin output or circadian disruption, in whom a chronobiotic intervention would be more likely to show benefit. Moreover, the observed improvement in the combination arm is consistent with an anabolic contribution from essential amino acids, such that any incremental role of melatonin may be permissive (sleep/circadian support and mitochondrial protection) rather than directly hypertrophic. Future trials should therefore consider longer duration, phenotype stratification (including baseline nocturnal 6-sulfatoxymelatonin), and functional endpoints (strength/power and physical performance) to determine whether melatonin provides a clinically meaningful benefit alone or mainly as an adjunct to anabolic or exercise interventions. Although these data are associative, they support the concept that optimal melatonin signaling is linked to better muscle function in ageing populations, which is relevant for sarcopenic obesity and cancer outcomes.

5.6 Chronopharmacology of Melatonin and Muscle Metabolism

The metabolic actions of melatonin are tightly linked to circadian timing, a factor that is crucial for any attempt to leverage its myometabolic effects therapeutically. The acute crossover trial by Rubio-Sastre et al. showed that a single 5 mg melatonin dose given shortly before an OGTT impairs glucose tolerance both in the morning and evening, by reducing insulin secretion in the morning and insulin sensitivity in the evening [127]. Follow-up randomized studies demonstrate that late-evening meals consumed during high

endogenous melatonin levels (close to habitual bedtime) worsen glucose tolerance, particularly in carriers of the MTNR1B rs10830963 risk allele [183].

Genetic data reinforce the importance of receptor signaling timing and intensity. Common variants in MTNR1B, especially rs10830963, are robustly associated with higher fasting glucose, impaired early insulin secretion, and increased type 2 diabetes risk across multiple populations [77]. Functional studies indicate that the risk allele is associated with increased MTNR1B expression in pancreatic β-cells and enhanced melatonin-mediated inhibition of insulin release [184]. While these studies are focused on islets rather than muscle, they underscore that overactivation or mistimed activation of melatonin receptors in the fed state can be metabolically detrimental.

For skeletal muscle-targeted strategies, these chronobiological constraints imply that melatonin (or MT_2-biased agonists) should be administered at times that maximize beneficial effects on muscle and adipose tissue while minimizing interference with β-cell function and postprandial glucose handling. Conceptually, nocturnal administration aligned with endogenous melatonin peaks and sufficiently separated (≥2–3 h) from the last carbohydrate-rich meal appears more consistent with the favorable profiles observed in rodent models of obesity and sarcopenia. Conversely, morning or pre-meal dosing in individuals with existing insulin resistance or MTNR1B risk genotypes could worsen glycemic control, potentially attenuating any indirect benefits on the obesity–cancer axis.

6 Melatonin–MT_1/MT_2 Signaling and Oncogenic Pathways

6.1 MT_1/MT_2 Signaling in Skeletal Muscle and Myokine-Mediated Modulation of Tumor Biology

Experimental work in skeletal muscle indicates that melatonin acts as a metabolic signal that converges on insulin signaling and mitochondrial networks in a way that is highly relevant to the obesity–cancer axis. In palmitate-treated primary rat myotubes and in pinealectomized rats, melatonin restores insulin-stimulated AKT phosphorylation, preserves oxidative phosphorylation, and rescues CREB–PGC-1α–driven mitochondrial biogenesis [174]. These effects are mediated, at least in part, by MT_1/MT_2 signaling and CaMKII–CREB activation, placing melatonin upstream of mitochondrial quality control and fiber oxidative phenotype in skeletal muscle [174]. More recently, in Zücker diabetic fatty rats, chronic oral melatonin (10 mg/kg, 12 weeks) activated a CaMKII/AMPK/PGC-1α axis in vastus lateralis, increased mitochondrial biogenesis and thermogenic gene expression, and improved whole-body metabolic status [71]. Given that PGC-1α–driven oxidative, mitochondria-rich fibers are preferentially associated with a myokine program (e.g., Fibronectin type III domain-containing protein 5 (FNDC5/irisin)) and show greater resistance to obesity-related insulin resistance [185], this melatonin-induced shift in muscle metabolism is likely to modify the endocrine output of muscle toward an anti-inflammatory, anti-tumor milieu, although direct myokine profiling after melatonin treatment *in vivo* remains scarce.

The myokine secreted protein acidic and rich in cysteine (SPARC) provides a key proof-of-principle that muscle-derived factors can directly restrain tumor growth. In an azoxymethane colon carcinogenesis model, endurance exercise increased SPARC expression in skeletal muscle and colonic mucosa, and SPARC knockout mice exhibited an increased number of colonic tumors [113]. Recombinant SPARC induced caspase-dependent apoptosis in colon cancer cells and reduced tumor burden when administered systemically [113]. Although no study has yet demonstrated that melatonin upregulates SPARC in skeletal muscle, melatonin's promotion of oxidative metabolism, mitochondrial fitness, and resistance to lipotoxicity in muscle [71] may enhance the same exercise-responsive myokine programs that include SPARC, thereby indirectly contributing to tumor suppression.

Irisin, the cleaved product of FNDC5, is another exercise-inducible myokine with relevance to obesity-associated cancer. In mice, muscle PGC-1α overexpression increases FNDC5/irisin expression, drives browning of white adipose tissue, elevates UCP1, and enhances whole-body energy expenditure and glucose tolerance, establishing irisin as a key mediator of exercise-induced metabolic remodeling [185]. Several *in vitro* studies report that exogenous irisin can inhibit malignant cell behavior. For example, in osteosarcoma cells, irisin (100 ng/mL) suppresses proliferation, migration, and invasion and reverses IL-6-induced epithelial–mesenchymal transition by inhibiting STAT3/Snail signaling [186]. Then, in breast cancer cells, irisin reduces clonogenicity and motility while exerting minimal effects on non-malignant breast epithelial cells [187]. On the other side, research in obesity-related cancer cell lines such as endometrial (KLE and RL95-2), colon (HT29 and MCA38), thyroid (SW579 and BHP7) and esophageal (OE13 and OE33) showed no antiproliferative effect of irisin at physiologic or high-physiologic concentrations [188].

In diet-induced obese Sprague–Dawley rats, chronic melatonin administration (10–50 mg/kg for 8 weeks) significantly increases circulating irisin levels, reduces body-weight gain and adipocyte hypertrophy, and upregulates PGC-1α and UCP1 expression in inguinal white adipose tissue [189]. These findings indicate that melatonin can amplify an irisin-associated axis linking skeletal muscle PGC-1α/FNDC5 activity, adipose-tissue browning, and systemic metabolic improvement. When integrated with the skeletal-muscle mitochondrial and insulin-sensitizing data [71], a coherent model emerges in which MT_1/MT_2 signaling in muscle enhances oxidative capacity and insulin sensitivity, modifies myokine secretion (e.g., SPARC, irisin), and secondarily shifts adipose tissue from a pro-inflammatory, lipotoxic depot toward a more oxidative, metabolically flexible phenotype. Through this multi-organ network, melatonin has the potential to attenuate obesity-driven tumor promotion, even though *direct in vivo* demonstrations that melatonin-induced myokine changes reduce tumor incidence or progression in obese hosts remain limited. This hypothesis will require dedicated tumor models combining high-fat feeding, melatonin treatment, and longitudinal myokine profiling.

6.2 Melatonin, Adipokines, and Muscle–Fat Cross-Talk in Obesity-Related Cancer

Obesity is characterized by a shift in adipokine balance toward elevated leptin and reduced adiponectin, together with increased IL-6 and TNF-α secretion from hypertrophic adipocytes and infiltrating macrophages. This pattern promotes insulin resistance and creates a pro-tumorigenic milieu. In human endometrial cancer cells, leptin activates JAK2–STAT3, PI3K–AKT, and MAPK/ERK pathways and induces cyclooxygenase-2 (COX-2) expression, thereby enhancing proliferation, survival, and pro-inflammatory signaling [190]. In contrast, adiponectin exerts anti-proliferative and pro-apoptotic actions in colorectal and other cancer cell models by activating AMPK, inhibiting mTOR and ERK, and downregulating cyclin D1 [191,192]. These complementary actions suggest that a high leptin/low adiponectin state directly favors oncogenic signaling in epithelial and stromal compartments, while adiponectin counters these pathways.

Melatonin robustly modulates this adipokine network in obese rodents. In Wistar rats fed either a normal or high-fat diet, chronic melatonin in drinking water (25 μg/mL for 9–11 weeks) attenuated body-weight gain, reduced fasting glucose, triglycerides and insulin, and partially normalized diet-induced hyperleptinemia and adiponectin disturbances. Melatonin also restored the 24-h rhythmicity of adiponectin, insulin, and cholesterol that had been blunted by high-fat feeding [120]. In high-fat diet–fed mice, melatonin supplementation reduced adipocyte hypertrophy and crown-like structures, lowered TNF-α and IL-6 expression in white adipose tissue, and improved systemic insulin sensitivity and lipid profile [193]. Together, these studies indicate that melatonin dampens the emergence of an inflamed, insulin-resistant adipose tissue microenvironment that would otherwise support oncogenic signaling in obesity.

At the level of intramuscular adipose tissue, melatonin reduces fat infiltration and improves mitochondrial function. In porcine intramuscular preadipocytes, melatonin inhibited cell proliferation, promoted lipolysis via PKA and ERK1/2 activation, increased PGC-1α expression and mitochondrial respiratory capacity, and decreased triglyceride accumulation. *In vivo*, melatonin-treated mice showed reduced intramuscular fat deposition and improved muscle mitochondrial biogenesis and oxidative phosphorylation [194]. Given the strong association between intramuscular fat, skeletal muscle insulin resistance, and systemic metabolic dysfunction, the research data support a direct remodeling of the muscle–fat interface by melatonin, which is mechanistically relevant for sarcopenic obesity and obesity-related cancer risk.

Genetic and pharmacological data indicate that intact MT_1/MT_2 signaling is required for appropriate leptin sensitivity. Rats lacking endogenous melatonin (pinealectomy or melatonin deficiency) develop overweight and selective leptin resistance in arcuate nucleus neurons, with diminished leptin-induced STAT3 phosphorylation and impaired anorexigenic signaling; physiological melatonin replacement reverses these defects and normalizes energy balance [195]. In high-fat/high-sucrose-fed rats, chronic treatment with the melatoninergic agonist NEU-P11 reduces weight gain, lowers fasting insulin and triglycerides, improves insulin sensitivity, and decreases visceral adiposity [196]. Thus, melatonin signaling maintains leptin responsiveness, whereas melatonin deficiency amplifies leptin-driven, obesity-associated pro-tumor signals.

From an oncologic perspective, the adipokine-modulating actions of melatonin are highly relevant. Hyperleptinemia and high leptin: adiponectin ratios have been associated with increased endometrial cancer risk in case–control and cohort analyses. In Chinese women, higher leptin and lower adiponectin levels independently increased endometrial cancer risk after adjustment for BMI, insulin, and metabolic covariates, and the leptin: adiponectin ratio showed particularly strong associations [197]. In postmenopausal women, an elevated leptin: adiponectin ratio was associated with increased endometrial cancer risk [198], and circulating adiponectin levels have been inversely related to endometrial cancer incidence in large prospective cohorts [199,200]. By reducing visceral and intramuscular adiposity, attenuating hyperinsulinemia and inflammatory cytokines, and partially normalizing leptin and adiponectin levels and rhythms [120,193,194], melatonin is well positioned to shift systemic adipokine signaling away from a pro-oncogenic profile. These converging data link circadian melatonin signaling, adipose–muscle crosstalk, and cancer susceptibility at both metabolic and endocrine levels.

6.3 Convergence on Insulin/IGF-1 and PI3K–AKT–mTOR Oncogenic Signaling

Hyperinsulinemia and elevated IGF-1 are central mediators linking obesity to increased cancer risk. In the Physicians' Health Study, men in the highest quintile of plasma C-peptide had a multivariable-adjusted relative risk of colorectal cancer of 2.7 compared with the lowest quintile, indicating that chronic high insulin exposure strongly predicts colorectal carcinogenesis [201]. In the Nurses' Health Study, higher fasting C-peptide and lower insulin-like growth factor binding protein 1 (IGFBP-1) were associated with increased colon cancer risk in women, consistent with sustained activation of insulin/IGF signaling [202]. At the cellular level, IGF-1 promotes proliferation and survival of colon cancer cells through IGF-1 receptor–dependent activation of PI3K–AKT and downstream anti-apoptotic effectors such as Bcl-xL and survivin [203]. IGF-1 also induces hypoxia-inducible factor 1 α (HIF-1α) and VEGF expression via PI3K/AKT in colon carcinoma cells, thereby enhancing angiogenesis and further supporting tumor progression [204]. Together, these data place the insulin/IGF-1–PI3K–AKT axis at the core of obesity-associated oncogenic signaling. Importantly, melatonin can intersect with this axis through two conceptually distinct, non-mutually exclusive mechanisms that should be considered separately: (i) attenuation of the systemic endocrine driver

(hyperinsulinemia/IGF tone) via improved skeletal muscle insulin sensitivity, and (ii) direct suppression of PI3K–AKT–mechanistic target of rapamycin (mTOR signaling within tumor cells.

6.3.1 Mechanism 1: Reduction of the Systemic Driver (Hyperinsulinemia) via Skeletal Muscle Metabolic Remodeling

Melatonin's actions in skeletal muscle directly oppose several upstream drivers of hyperinsulinemia. In palmitate-treated rat skeletal muscle cells and in pinealectomized rats, melatonin restored insulin-stimulated AKT phosphorylation, corrected defects in oxidative phosphorylation, normalized tricarboxylic acid cycle intermediates, and upregulated CREB–PGC-1α signaling in skeletal muscle [73] These changes were accompanied by improved whole-body insulin sensitivity and reduced intramyocellular lipid accumulation *in vivo* [71]. In C2C12 myotubes exposed to tunicamycin, melatonin prevented ER stress–induced insulin resistance by suppressing PERK/eIF2α and CHOP activation, reducing JNK-mediated IRS-1 Ser phosphorylation, and preserving insulin-stimulated AKT activation and glucose uptake [123].

By increasing skeletal muscle glucose disposal and correcting mitochondrial dysfunction, melatonin can, at least in principle, reduce the need for compensatory hyperinsulinemia, thereby attenuating chronic activation of insulin/IGF-1 receptors in peripheral tissues. Clinical data, while heterogeneous, support this direction of effect. In patients with metabolic syndrome, 5 mg melatonin nightly for two months significantly improved lipid profile and oxidative stress markers and modestly lowered fasting glucose, with trends toward improved insulin-related parameters [205]. In obese women on a hypocaloric diet, 6 mg/day melatonin for 40 days significantly reduced plasma TNF-α and IL-6 and improved oxidative stress indices, with accompanying improvements in cardiometabolic risk markers [206]. A broader meta-analysis of randomized controlled trials concluded that melatonin supplementation modestly reduces fasting insulin and HOMA-IR, particularly in individuals with elevated baseline cardiometabolic risk [207]. From a cancer biology standpoint, this systemic mechanism is most directly aligned with cancer prevention (or risk modification), because it targets the chronic, long-duration endocrine and metabolic milieu that sustains insulin/IGF-1 receptor activation in insulin-sensitive epithelia over years.

6.3.2 Mechanism 2: Direct Tumor-Cell Suppression of PI3K–AKT–mTOR and Related Pro-Survival Pathways

In parallel, melatonin exerts direct oncostatic effects on tumor cells by modulating PI3K–AKT–mTOR and related pathways. In gallbladder cancer cell lines and xenografts, melatonin inhibited proliferation, migration, and invasion and induced apoptosis by suppressing phosphorylation of PI3K, AKT, and mTOR, with associated increases in pro-apoptotic Bax and cleaved caspase-3 [208]. In an azoxymethane/dextran sodium sulfate (AOM/DSS)-induced colon carcinogenesis model, melatonin administered in drinking water (0.4–10 ppm) dose-dependently reduced adenocarcinoma incidence and multiplicity. In more detail, colonic tumors from melatonin-treated rats showed decreased COX-2 expression, reduced proliferating cell nuclear antigen (PCNA) staining, and increased apoptotic indices [209]. Additional work in KRAS-mutant non–small cell lung cancer models showed that melatonin downregulated PD-L1 expression, altered tumor-infiltrating lymphocyte composition, and enhanced antitumor immunity, mechanistically involving inhibition of PI3K–AKT and NF-κB signaling [210]. This tumor-cell–intrinsic mechanism is most relevant to therapy (or adjuvant therapy), because it targets signaling nodes within established tumors, including survival pathways and immune-evasion checkpoints. Many of these oncostatic effects are observed at micromolar melatonin concentrations *in vitro*, which exceed typical nocturnal plasma levels. Therefore, for prevention, the systemic mechanism (improving muscle insulin sensitivity and reducing hyperinsulinemia/IGF drive) is likely to be the more plausible dominant pathway at physiological replacement-like exposures and over long time scales. Conversely, for therapy, direct inhibition of PI3K–AKT–mTOR (often at pharmacologic

exposures or in tumor microenvironments where higher local concentrations may occur) may contribute meaningfully, particularly when positioned as an adjunct that enhances apoptosis, reduces inflammatory signaling, or improves antitumor immunity. Accordingly, a balanced model is that melatonin may lower obesity-related cancer risk primarily by dampening the chronic endocrine driver (insulin/IGF tone) while retaining the potential to modulate tumor-cell signaling and immune contexture at higher exposures or in combination regimens.

6.4 Translational Implications and Testable Clinical Hypotheses

Melatonin's dual role as a circadian hormone and a modulator of skeletal muscle metabolism suggests several translational applications in obesity-related cancer prevention and supportive care. However, rigorous clinical testing is still sparse and often methodologically heterogeneous.

Randomized controlled trials in humans, although small, indicate that chronic melatonin supplementation can improve components of the metabolic syndrome and related cardiometabolic risk factors. Key human trials are summarized in Table 2. In patients with metabolic syndrome, 5 mg of melatonin administered 2 h before bedtime for 2 months significantly reduced systolic and diastolic blood pressure, total cholesterol, low-density lipoprotein (LDL)-cholesterol, and markers of oxidative stress, without major adverse events [205]. In another randomized, double-blind, crossover trial in adults with metabolic syndrome, nightly melatonin (8 mg for 10 weeks in each arm) improved systolic blood pressure and increased high-density lipoprotein HDL-cholesterol, with a reduction in the proportion of participants meeting full metabolic syndrome criteria [211]. In obese women, 6 mg/day of melatonin for 40 days reduced circulating TNF-α, IL-6, high-sensitivity C-reactive protein (hsCRP) and malondialdehyde, and increased total antioxidant capacity, supporting anti-inflammatory and antioxidant actions in a high-risk metabolic phenotype [206]. In postmenopausal women treated for one year, 1–3 mg of melatonin nightly reduced fat mass and increased lean mass, without relevant safety concerns, indicating that long-term nocturnal melatonin is feasible and can favorably modify body composition in an at-risk group [212,213]. Although none of these trials directly quantified skeletal muscle insulin sensitivity or intramuscular fat, they collectively show that chronic melatonin can beneficially modulate blood pressure, lipids, inflammation, and body composition parameters relevant to the obesity–cancer axis.

In contrast, acute human studies highlight critical chronopharmacological constraints. In a randomized, double-blind, crossover study in healthy women, a single 5 mg dose of melatonin given 15 min before a 75 g oral glucose load significantly impaired glucose tolerance in both morning and evening tests, with reduced β-cell responsivity in the morning and decreased insulin sensitivity in the evening [127]. In a randomized crossover trial of overweight or obese women, late dinner (1 h before habitual bedtime, coinciding with high endogenous melatonin) led to higher postprandial glucose excursions and lower insulin responses than early dinner (4 h before bedtime), with these adverse effects confined to MTNR1B rs10830963 risk-allele carriers [183]. A larger randomized crossover study in 845 adults confirmed that a late dinner during high endogenous melatonin resulted in higher glucose AUC and lower insulin AUC, again with a stronger impairment of β-cell function in MTNR1B G-allele carriers [214]. From these clinical findings can be learned that any long-term melatonin regimen in individuals at risk for obesity-related cancer should avoid temporal overlap between melatonin exposure and major carbohydrate loads, and that MTNR1B genotype may be an important modifier of glycemic responses.

In oncology, several small randomized and non-randomized trials have used melatonin (commonly 20 mg at night) as an adjuvant to chemotherapy or radiotherapy. A systematic review and meta-analysis of 10 randomized trials (n = 643) reported that adjunctive melatonin reduced 1-year mortality (relative risk $\approx$0.66)

and decreased chemotherapy-related toxicities, including myelosuppression, neurotoxicity, and asthenia, across various solid tumors [215]. A subsequent meta-analysis focusing on chemo-/radiochemotherapy combinations confirmed reduced risk of treatment-related adverse events and suggested a survival benefit, although all contributing studies originated from a single research group and were generally unblinded [216]. None of these trials stratified by obesity or insulin resistance, nor did they assess skeletal muscle mass, radiodensity, or myokines/adipokines, so their relevance to the obesity–cancer axis is indirect and only hypothesis-generating.

Based on the mechanistic and early clinical evidence summarized above, we propose several testable hypotheses to guide future clinical trial design. First, in adults with obesity, insulin resistance, and high visceral fat, administering low-dose (3–5 mg) melatonin at bedtime with explicit carbohydrate separation, with a minimum 2–3 h interval after the last meal, will improve skeletal muscle insulin sensitivity (clamp-based or OGTT-derived indices), reduce intramuscular fat (MRI/CT), and attenuate pro-oncogenic biomarkers (fasting insulin, IGF-1, leptin: adiponectin ratio, hs-CRP) over 6–12 months. This design explicitly incorporates the adverse acute effects observed when melatonin and carbohydrate loads coincide [183,206,214]. Second, in patients with obesity and colorectal or breast cancer awaiting surgery or adjuvant therapy, a combined intervention of supervised exercise and nocturnal melatonin (3–5 mg) will more effectively preserve or increase skeletal muscle mass, improve myokine profiles (SPARC, irisin, IL-6, IL-10), and reduce treatment toxicity compared to exercise alone, with secondary exploration of disease-free survival. Preclinical data showing melatonin-mediated enhancement of muscle insulin signaling and mitochondrial function [73] and exercise-induced myokine-mediated suppression of colon carcinogenesis [113] provide a mechanistic rationale, but dedicated trials are required. Third, in genotype-informed precision approaches, individuals carrying MTNR1B risk alleles (e.g., rs10830963), both exogenous melatonin and late-timed meals during high endogenous melatonin will worsen glucose tolerance, primarily via β-cell dysfunction [183,206,214]. Genotype-stratified trials can test whether strict separation between melatonin dosing and evening meals mitigates this risk while preserving potential muscle and metabolic benefits.

To implement these hypotheses, future trials should include body composition (DXA, CT muscle area and radiodensity), muscle function (handgrip, chair-stand, gait speed), metabolic profiling (insulin, glucose, OGTT/clamp indices, lipids), myokines (SPARC, irisin, IL-6/IL-10), adipokines (leptin, adiponectin), and cancer-relevant outcomes (treatment toxicity, pathological response, recurrence). Importantly, melatonin should be treated not only as an oncostatic agent but as a chronobiotic and myometabolic modulator, with dosing and timing optimized accordingly.

Table 2: Human clinical trials of melatonin in metabolic syndrome/obesity-related phenotypes and cancer supportive care, emphasizing metabolic endpoints and skeletal muscle–related assessments.

Study	Population and Study Design	Melatonin Regimen (Oral)	Duration of Melatonin Treatment	Primary Metabolic Outcomes (Selected)	Muscle-Related Parameters Assessed?
Metabolic syndrome/obesity/NAFLD/type 2 diabetes					
Koziróg et al., 2011 [205]	Metabolic syndrome; controlled clinical trial vs. untreated healthy volunteers (MS n = 30; controls n = 33). Controlled clinical trial (randomization not stated).	5 mg/day, 2 h before bedtime.	2 months	SBP and DBP decreased (132.8→120.5 mmHg; 81.7→75.0 mmHg). LDL-C decreased (149.7→139.9 mg/dL). Oxidative stress improved (↓TBARS; ↑CAT).	No (no muscle imaging/function/biopsy).
Goyal et al., 2014 [211]	Metabolic syndrome; n = 39. Double-blind, placebo-controlled, crossover Phase II pilot.	8 mg nightly vs. placebo; 6-week washout between periods (placebo-controlled crossover)	2 × 10 weeks per period	Systolic BP improved vs. placebo (−2.7 vs. +4.7 mmHg; $p = 0.013$). Modest, mostly non-significant changes in weight/BMI/waist/TG. Fasting glucose not improved.	No (anthropometrics only).
Alamdari et al., 2015 [206]	Obese women; n = 44. Randomized, double-blind, placebo-controlled.	6 mg/day (timing not stated)	40 days	Improved inflammatory/oxidative stress profile (reductions in pro-inflammatory cytokines and oxidative stress markers; increased antioxidant capacity).	No.
Szewczyk-Golec et al., 2017 [217]	Obesity (BMI ≥ 30); n = 30 (n = 15/arm). Randomized, double-blind, placebo-controlled; both arms received calorie restriction and a physical activity program.	10 mg/day, 1 h before bedtime; with calorie restriction	30 days	Weight reduction significant only in melatonin group; ↑adiponectin & omentin-1; ↓MDA; ↑GPx (lower oxidative stress)	No.
Mohammadi et al., 2021 [213]	Overweight or class-I obesity; n = 38 recruited (n = 19/group completed). Randomized, double-blind, placebo-controlled; both groups on a hypocaloric diet.	3 mg/day, 2 h before bedtime.	12 weeks	Body fat mass percentage decreased in the melatonin arm; late-phase reductions in weight/BMI/WC were observed only in the melatonin arm.	No (bioimpedance only).
Amstrup et al., 2016 [212]	Postmenopausal women; n = 81. Randomized, double-blind, placebo-controlled.	1 mg or 3 mg nightly (pooled melatonin arms vs. placebo).	1 year	Fat mass decreased by 6.9% vs. placebo; lean mass increased after BMI adjustment (+2.6%). No significant change in insulin/glucose homeostasis markers.	Yes (DXA lean mass; no functional/biopsy outcomes).
Farrokhian et al., 2019 [218]	Type 2 diabetes; triple-blind randomized placebo-controlled trial (melatonin n = 34; placebo n = 36)	6 mg at bedtime.	8 weeks	No differences were observed in FBG, HbA1C, and hs-CRP changes between the trial groups.	No.
Lauritzen et al., 2022 [131]	Male type 2 diabetes; randomized placebo-controlled crossover trial (n = 17 completers).	10 mg, 1 h before bedtime.	3 months per period	Insulin sensitivity decreased by ~12% during melatonin vs. placebo (clamp methodology).	Body composition assessed (DXA noted in report); no direct muscle function/biopsy

Table 2: *Cont.*

Study	Population and Study Design	Melatonin Regimen (Oral)	Duration of Melatonin Treatment	Primary Metabolic Outcomes (Selected)	Muscle-Related Parameters Assessed?
Bahrami et al., 2020 [219]	Non-alcoholic fatty liver disease; randomized double-blind placebo-controlled trial (n = 24 in melatonin group; n = 21 in placebo).	6 mg/day; 1 h before bedtime	12 weeks	Significant improvements vs. placebo in weight, waist/abdominal circumference, SBP/DBP, leptin, hs-CRP, ALT/AST, and fatty liver grade	No.
Marqueze et al., 2021 [220]	Female permanent night-shift nurses with excess weight; randomized, double-blind, placebo-controlled crossover trial (n = 27)	3 mg on nights participants slept at night (between shifts/days off).	2 × 12 weeks per period + washout	Reduced circadian misalignment; body weight reduction observed in early chronotypes.	No.
Cancer (metabolic-relevant outcomes and/or frequently cited RCTs)					
Seely et al., 2021 [221]	NSCLC after surgical resection; pilot randomized placebo-controlled trial.	20 mg nightly.	1 year	Cancer-oriented endpoints. Primary: 2-y DFS (no overall effect); secondary: 5-y DFS (overall null), possible benefit in stage III/IV subgroup (survival/QoL) with cachexia-relevant measures (eg, weight change) reported; not muscle-specific.	No.
Del Fabbro et al., 2013 [222]	Advanced lung/GI cancer with anorexia-cachexia; randomized double-blind placebo-controlled trial.	20 mg nightly.	28 days	Cachexia-oriented endpoints (appetite/weight and symptoms); generally, no meaningful benefit vs. placebo reported.	No (weight only; no lean mass or muscle performance)
Mukhopadhyay et al., 2024 [172]	Early-stage breast cancer receiving radiotherapy (RT); randomized, double-blind, placebo-controlled trial.	20 mg starting the night before RT until 2 weeks post-RT	During the RT course	Improved patient-reported fatigue and sleep-related outcomes; metabolic endpoints not assessed.	No.

Note: Controlled human trials of oral melatonin reporting outcomes relevant to metabolic syndrome, obesity/overweight, type 2 diabetes, NAFLD, or cancer-related weight/symptom endpoints. Muscle-related parameters were defined as any direct assessment of skeletal muscle mass (e.g., DXA lean mass), strength, function, imaging, or biopsy-derived endpoints. BMI, body mass index; BP, blood pressure; CAT, catalase; DXA, dual-energy X-ray absorptiometry; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NSCLC, non-small cell lung cancer; QoL, quality of life; RCT, randomized controlled trial; RT, radiotherapy; SBP/DBP, systolic/diastolic blood pressure; TBARS, thiobarbituric acid reactive substances; TG, triglycerides; WC, waist circumference. Symbol key: ↑ and ↓ denote increased or decreased processes/levels, respectively.

7 Knowledge Gaps and Future Research Directions

7.1 MT_1 Versus MT_2 Receptor–Specific Actions in Human Skeletal Muscle

Preclinical work in rodent models and human primary myoblasts has begun to delineate MT_2 as a key mediator of melatonin's thermogenic and oxidative actions in skeletal muscle. In Zucker diabetic fatty rats, chronic melatonin treatment increases oxidative fiber proportion, enhances mitochondrial dynamics and autophagy, and improves insulin sensitivity, but receptor-selective pharmacology was not systematically addressed [75]. In human primary myoblasts, MTNR1B knockdown abolishes melatonin-induced upregulation of SERCA1/2, sarcolipin, and CaMKII/AMPK/PGC-1α signaling and prevents activation of a non-shivering thermogenic program, providing strong evidence that MT_2 is necessary for these responses [51].

However, several critical questions remain unresolved. First, the relative expression of MT_1 versus MT_2 across human muscle fiber types (type I versus type IIa/x), satellite cells, fibro–adipogenic progenitors, and vascular/endothelial cells is poorly characterized *in vivo*. Available transcriptomic datasets typically do not resolve MTNR1A/MTNR1B expression at sufficient spatial or cellular resolution to infer receptor-specific functions in intact muscle, particularly in obesity, type 2 diabetes, or cancer cachexia. Second, whether MT_1/MT_2 expression, coupling efficiency, and downstream pathway "bias" are preserved versus rewired in catabolic states (e.g., cancer cachexia) compared with obesogenic myosteatosis is essentially unknown and represents a key barrier to clinical translation. Also, almost no data exist on biased agonism or differential coupling of MT_1 versus MT_2 to canonical metabolic pathways (IRS-1/PI3K/Akt, AMPK, SIRT1/PGC-1α) specifically in human skeletal muscle. Importantly, common MTNR1B variants that modulate glycemic traits and type 2 diabetes risk have not been linked to muscle-specific phenotypes or to differential response of muscle metabolism to exogenous melatonin in humans [211].

Receptor-selective ligands and genetic models provide an opportunity to dissect MT_1 versus MT_2 contributions to myocellular insulin signaling, mitochondrial biogenesis, and thermogenesis. To date, no clinical study has combined pharmacological MT_1/MT_2 targeting with muscle biopsies, phosphoproteomics, or single-cell RNA-seq to define receptor-specific signaling fingerprints in human skeletal muscle under metabolic stress in clinical conditions of obesity, sarcopenic obesity, or cancer therapy.

7.2 Melatonin Dosing, Formulations, and Chronopharmacology for Myometabolic Versus Chronobiotic Effects

Most human trials of melatonin in metabolic disorders were designed to test cardiovascular or global metabolic endpoints rather than skeletal muscle–centric outcomes. In patients with metabolic syndrome, 5 mg melatonin nightly for two months improved blood pressure, LDL cholesterol, and oxidative stress markers, but did not include muscle-specific readouts such as insulin-stimulated glucose uptake in muscle, myosteatosis, or myokine profiles [205]. A crossover phase II trial in subjects with metabolic syndrome used 8 mg melatonin for 10 weeks and reported modest improvements in several metabolic syndrome components and blood pressure, but again lacked muscle imaging, biopsies, or functional measures of muscle metabolism [211].

These studies reveal several knowledge gaps. First, the dose–response relationship for melatonin's effects on skeletal muscle metabolism is almost entirely unexplored in humans. Animal studies typically employ supraphysiological doses (e.g., 20 mg/kg in high-fat–fed mice), which enhance energy expenditure, activate brown adipose tissue (BAT), and increase skeletal muscle fatty acid oxidation and AMPK phosphorylation [117], but the human equivalent doses and safety at such exposures remain uncertain. Second, formulations differ. Most clinical studies used fast-release melatonin, whereas sustained-release

or timed micro-dosing could produce very different receptor occupancy profiles in muscle during the nocturnal fasting period, postprandially, or around exercise. Third, chronopharmacology is underexplored. Endogenous melatonin secretion shows a nocturnal peak; misalignment between dosing time, intrinsic circadian phase, and feeding/exercise cycles may blunt beneficial metabolic effects or, in some settings, worsen glucose tolerance. Existing trials rarely stratify participants by chronotype, shift work, or circadian phase markers and typically administer melatonin 1–2 h before habitual bedtime [205,211]. Finally, there is almost no integration of *MTNR1B* genotype or baseline nocturnal melatonin levels into dose selection or stratified analyses, despite evidence that melatonin signaling variants modulate glycemic traits.

7.3 Incomplete Characterization of Melatonin-Driven Myokine and Adipokine Remodeling

The conceptual framework that melatonin can reprogram skeletal muscle toward an oxidative, insulin-sensitive phenotype implies parallel remodeling of the myokine and adipokine milieu, which could influence systemic inflammation and cancer risk. Yet direct measurements of myokines in response to melatonin remain sparse. In diet-induced obesity models, melatonin reduces adipose tissue inflammation, improves hepatic steatosis, and increases skeletal muscle fatty acid oxidation via AMPK activation [117], but myokines such as irisin (FNDC5), myostatin, IL-6, IL-15, SPARC, and decorin were not systematically quantified.

Similarly, preclinical studies in Zucker diabetic fatty rats demonstrate that melatonin improves muscle mitochondrial dynamics, autophagy, and fiber-type composition [75], but they do not provide a comprehensive secretome analysis that would clarify how melatonin-conditioned muscle communicates with adipose tissue, liver, and immune cells. At the clinical level, randomized controlled trials (RCTs) in metabolic syndrome or obesity have measured classical metabolic biomarkers (lipids, glucose, blood pressure, CRP) but not myokines or adipokines that could mediate crosstalk along the obesity–cancer axis [205,211].

The absence of integrated "muscle–fat–tumor" secretome profiling severely limits mechanistic inference. It remains unknown whether melatonin consistently promotes an anti-inflammatory, anti-oncogenic myokine profile, particularly in sarcopenic obesity or during chemotherapy or radiotherapy. Likewise, the impact of melatonin on adipokines with recognized roles in cancer biology (leptin, adiponectin, resistin, visfatin) in the setting of altered muscle mass has not been characterized in a hypothesis-driven manner.

7.4 Interaction with Exercise, Nutrition, and Standard Oncologic Therapies

Exercise and dietary interventions are cornerstone strategies to counteract sarcopenic obesity and cancer-related muscle wasting, yet their potential synergy or antagonism with melatonin has been only superficially explored. Animal studies indicate that melatonin enhances skeletal muscle oxidative capacity, improves mitochondrial quality control, and increases non-shivering thermogenesis in the context of high-fat feeding [75,117]. Conceptually, these adaptations could potentiate the benefits of endurance or resistance training on muscle mass and function and might attenuate treatment-related fatigue and metabolic derangements in oncology patients. However, rigorously controlled experiments combining defined exercise regimens with melatonin, with mechanistic muscle readouts, are largely lacking.

Nutritional context is another blind spot. High-fat and hypercaloric diets have been used in animal studies to induce obesity and insulin resistance before melatonin treatment, but the interaction of melatonin with specific macronutrient compositions (high-protein, ketogenic, low-carbohydrate diets) on muscle metabolism and myostatin/myokine balance has not been delineated. In completed human RCTs, diet was usually not tightly controlled beyond standard lifestyle advice, confounding the interpretation of melatonin's specific metabolic actions.

Finally, in oncology, melatonin has been evaluated as an adjunct to chemotherapy or radiotherapy to improve quality of life, reduce toxicity, or modestly improve survival in some settings, but muscle mass, myosteatosis, and sarcopenic obesity have not been incorporated as primary or secondary endpoints. There is essentially no trial-level evidence addressing whether melatonin, combined with exercise and nutritional support, can preserve muscle mass and function during systemic therapy in obese or sarcopenic patients. Moreover, essentially no studies have interrogated whether standard anticancer regimens alter MT_1/MT_2 receptor abundance, coupling, or downstream signaling competence within skeletal muscle.

7.5 Trial Design Priorities for Targeting the Obesity–Cancer Axis via Skeletal Muscle

Despite compelling preclinical evidence that melatonin improves muscle oxidative metabolism, reduces adiposity, and modulates inflammatory pathways, there are no randomized trials designed specifically to test whether melatonin can modulate the obesity–cancer axis through skeletal muscle. Existing RCTs in metabolic syndrome, obesity, or insomnia typically enroll small samples ($n \approx 30–80$), last 6–12 weeks, and prioritize cardiometabolic or sleep outcomes. They neither enrich for obese patients with sarcopenia or myosteatosis, nor incorporate cancer incidence, progression, or treatment response as outcomes.

Future clinical trials should explicitly target populations at the intersection of obesity, muscle impairment, and cancer risk or burden: (i) obese individuals with/computed tomography (CT) or magnetic resonance imaging (MRI)-defined myosteatosis; (ii) patients with sarcopenic obesity before or during chemotherapy, endocrine therapy, or immunotherapy; and (iii) survivors of obesity-related cancers with persistent metabolic syndrome and muscle loss. Key design features would include: (a) adequately powered, parallel-group designs with ≥6–12 months of follow-up; (b) melatonin dosing that is informed by preclinical myometabolic data and chronopharmacology; (c) deep muscle phenotyping (biopsy-based signaling, mitochondrial function, and fiber-type analysis; imaging of muscle mass and quality; strength and performance tests); and (d) comprehensive profiling of systemic metabolic, inflammatory, and oncologic biomarkers.

At the oncologic end, endpoints could include chemotherapy tolerance, treatment delays, dose reductions, hospitalization, and survival, with stratification by baseline muscle mass and myosteatosis. Given the pleiotropic actions of melatonin, factorial designs combining melatonin with exercise and dietary interventions may be necessary to detect clinically meaningful effects on sarcopenic obesity and cancer outcomes.

7.6 The Role of Skeletal Muscle Melatonin Signaling in Cancer Cachexia Versus Obesity-Related Cancer States

Cancer cachexia is a distinct systemic metabolic syndrome characterized by ongoing loss of skeletal muscle (with or without fat loss), driven by inflammation, anorexia, neuroendocrine disruption, and net catabolic signaling that cannot be fully reversed by conventional nutritional support. Mechanistically, the dominant muscle biology in cachexia (proteolysis, impaired anabolism, mitochondrial dysfunction, and inflammatory cytokine signaling) differs qualitatively from obesogenic insulin resistance and myosteatosis. Thus, the melatonin–MT_1/MT_2 axis may operate under different constraints and may yield different functional endpoints, e.g., anti-catabolic/anti-inflammatory versus insulin-sensitizing/thermogenic. Although melatonin has been explored clinically as part of supportive care in advanced cancer with reported benefits on symptom burden and, in some reports, cachexia-related outcomes, these studies generally lack muscle-centric mechanistic endpoints (muscle biopsies, MTNR1A/B expression, receptor coupling, or phosphoproteomic readouts) [215].

Accordingly, a priority gap is to define whether endogenous melatonin rhythms, tissue availability, and MT_1/MT_2 signaling competence in skeletal muscle are preserved, downregulated, or adaptively rewired across the spectrum from obesity-associated cancer risk to established cancer cachexia. Bridging this gap will require stratified human studies (pre-cachexia vs. cachexia; obese vs. non-obese), longitudinal sampling, and harmonized muscle phenotyping (mass, quality, mitochondrial function, and catabolic/anabolic signaling) to determine whether melatonin is more plausibly positioned for prevention (obesity–cancer axis) versus adjunct therapy (cachexia mitigation).

7.7 Impact of Common Cancer Treatments on Skeletal Muscle MT_1/MT_2 Expression and Signaling

Systemic anticancer treatments frequently induce or amplify muscle dysfunction through direct myotoxicity and/or endocrine–inflammatory remodeling. Chemotherapies are linked to skeletal muscle wasting and mitochondrial impairment, corticosteroids promote proteolysis and weakness, and androgen deprivation therapy in prostate cancer is associated with adverse body composition changes, including loss of lean mass [223,224]. In parallel, cancer treatment can perturb circadian organization and melatonin output in patients, raising the possibility that receptor occupancy patterns (timing and amplitude) and downstream signaling dynamics in muscle are altered during therapy [223].

Despite these converging lines of physiology, there is a near-complete absence of data testing whether chemotherapy, chronic glucocorticoid exposure, or endocrine therapies change MTNR1A/MTNR1B expression, receptor desensitization/internalization behavior, or coupling bias (Gi/o–cAMP vs. PI3K/Akt vs. ERK/β-arrestin) in skeletal muscle. This gap is clinically actionable, as therapy-induced changes in receptor abundance or signaling efficiency could plausibly explain heterogeneous responses to melatonin supplementation (benefit, neutrality, or harm), and could inform timing (chronotherapy), formulation (immediate vs. prolonged release), and patient selection (baseline melatonin rhythm integrity; cachexia status; MTNR1B genotype). A pragmatic research strategy would pair (i) prospective muscle biopsies or minimally invasive transcriptomic sampling before/during treatment, (ii) objective circadian phenotyping (e.g., dim-light melatonin onset, urinary 6-sulfatoxymelatonin), and (iii) deep muscle readouts (mitochondrial respiration, proteostasis markers, and insulin signaling), to directly test how anticancer regimens modify melatonin receptor signaling competence in human muscle.

8 Conclusions and Translational Outlook

Obesity, insulin resistance and associated components of the metabolic syndrome are convincingly linked with increased incidence and mortality of several cancers, including colorectal, postmenopausal breast and endometrial cancer. Mechanistically, excess adiposity promotes chronic low-grade inflammation, hyperinsulinaemia, and sustained activation of the insulin/IGF-1 axis, which converge on PI3K–AKT–mTOR and related oncogenic pathways in epithelial and stromal cells. Within this pathophysiological context, skeletal muscle emerges as both a major target and an active regulator: it is a central determinant of whole-body glucose disposal, lipid oxidation and myokine secretion, and its loss or qualitative deterioration (sarcopenia, myosteatosis) predicts poorer cancer outcomes independent of body mass index.

The evidence synthesized in this review supports a coherent model in which melatonin–MT_1/MT_2 signaling in skeletal muscle may modulate key nodes of the obesity–cancer axis. The available evidence supports a plausible, mechanistically grounded hypothesis that nocturnal melatonin, acting via MT_1/MT_2 receptors in skeletal muscle and adipose tissue, can enhance muscle insulin sensitivity and mitochondrial function, reduce intramuscular and visceral fat, rebalance myokines and adipokines, and thereby attenuate the metabolic and inflammatory drivers of obesity-related cancer, while also exerting direct oncostatic

effects on tumor cells. Testing this hypothesis will require next-generation clinical studies that (i) enrich for individuals with obesity, sarcopenia, or myosteatosis and elevated cancer risk or burden; (ii) apply melatonin with an appropriate dose, formulation and circadian timing; (iii) incorporate deep muscle and adipose phenotyping; and (iv) include oncologic endpoints. Only through such integrative, mechanistically informed trials can the true potential of melatonin–MT_1/MT_2 signaling in skeletal muscle as a lever on the obesity–cancer axis be determined.

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Abbreviations

5-HT_2C	5-hydroxytryptamine (serotonin) receptor subtype 2C
8-OHdG	8-hydroxy-2′-deoxyguanosine (oxidative DNA damage biomarker)
A_2B (receptor)	Adenosine A_2B receptor
AANAT	Arylalkylamine N-acetyltransferase (key enzyme in melatonin biosynthesis)
AFMK	N^1-acetyl-N^2-formyl-5-methoxykynuramine
Akt	Protein kinase B (PKB)
AMK	N^1-acetyl-5-methoxykynuramine
AMPK	AMP-activated protein kinase
AOM	Azoxymethane (colon carcinogenesis initiator in experimental models)
AOM/DSS	Azoxymethane/dextran sodium sulfate (combined inflammation-associated colon carcinogenesis model)
ASMT	Acetylserotonin O-methyltransferase (melatonin biosynthesis enzyme)
ATP	Adenosine triphosphate
AUC	Area under the curve (commonly glucose/insulin response over time)
BAT	Brown adipose tissue
Bax	Bcl-2-associated X protein (pro-apoptotic regulator)
Bcl-2	B-cell lymphoma 2 (anti-apoptotic regulator)
BMI	Body mass index
Ca^{2+}	Calcium ion
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CHO	Chinese hamster ovary (cell line)
CHOP	C/EBP homologous protein (ER stress-associated transcription factor; also known as DDIT3)
CLP	Cecal ligation and puncture (experimental sepsis model)
COX-2	Cyclooxygenase-2
CPT-1	Carnitine palmitoyltransferase 1 (mitochondrial fatty-acid import enzyme)

CREB	cAMP response element-binding protein
CRP	C-reactive protein
CT	Computed tomography
CYP1A2	Cytochrome P450 1A2 (major hepatic enzyme involved in melatonin metabolism)
DAG	Diacylglycerol
DRP1	Dynamin-related protein 1 (mitochondrial fission mediator)
DSS	Dextran sodium sulfate
DXA	Dual-energy X-ray absorptiometry
eIF2α	Eukaryotic initiation factor 2 alpha (ER stress signaling node)
eNOS	Endothelial nitric oxide synthase
EGFR	Epidermal growth factor receptor
EMT	Epithelial–mesenchymal transition
ERK1/2	Extracellular signal-regulated kinases 1 and 2
EASO	European Association for the Study of Obesity
ESPEN	European Society for Clinical Nutrition and Metabolism
EWGSOP2	European Working Group on Sarcopenia in Older People (2nd consensus definition)
Fis1	Fission 1 protein (mitochondrial dynamics/fission)
FoxO	Forkhead box O transcription factors
FNDC5	Fibronectin type III domain-containing protein 5 (precursor of irisin)
GLUT4	Glucose transporter type 4
GPCR	G protein–coupled receptor
GPx	Glutathione peroxidase
GTEx	Genotype-Tissue Expression project (human transcriptomic resource)
Gq/11	G protein alpha subfamily q/11
Gi/o	G protein alpha subfamily i/o
H_2O_2	Hydrogen peroxide
HbA1c	Glycated hemoglobin A1c
HDL	High-density lipoprotein
HEK293	Human embryonic kidney 293 (cell line)
HIF-1α	Hypoxia-inducible factor 1 alpha
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
hsCRP	High-sensitivity C-reactive protein
IGF	Insulin-like growth factor
IGF-1	Insulin-like growth factor 1
IGF-2	Insulin-like growth factor 2
IGFBP-1	Insulin-like growth factor binding protein 1
IL	Interleukin
IL-1β	Interleukin-1 beta
IL-1ra	Interleukin-1 receptor antagonist
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-15	Interleukin-15
i.p.	Intraperitoneal administration
IRE1	Inositol-requiring enzyme 1 (ER stress sensor)
IR	Insulin resistance
IRS-1	Insulin receptor substrate 1
IRS-2	Insulin receptor substrate 2
I/R	Ischemia–reperfusion
IVGTT	Intravenous glucose tolerance test
iNOS	Inducible nitric oxide synthase
i-mtNOS	Inducible mitochondrial nitric oxide synthase (as described in the cited sepsis/mitochondrial literature)
JAK2	Janus kinase 2
JNK	c-Jun N-terminal kinase

KRAS	Kirsten rat sarcoma viral oncogene homolog (oncogenic GTPase)
LC3B	Microtubule-associated protein 1A/1B-light chain 3B (autophagy marker)
LDL	Low-density lipoprotein
LPS	Lipopolysaccharide (endotoxin)
MAFbx (atrogin-1)	Muscle atrophy F-box protein (E3 ubiquitin ligase; Fbxo32)
MAPK	Mitogen-activated protein kinase
MDA	Malondialdehyde (lipid peroxidation marker)
MEF2	Myocyte enhancer factor 2 (transcription factor family)
Mfn2	Mitofusin 2
Myf5	Myogenic factor 5
MyoD	Myogenic differentiation 1
MRF4	Myogenic regulatory factor 4
mTOR	Mechanistic target of rapamycin
MT_1	Melatonin receptor 1 (encoded by MTNR1A)
MT_2	Melatonin receptor 2 (encoded by MTNR1B)
MTNR1A	Melatonin receptor 1A gene; (encodes MT_1)
MTNR1B	Melatonin receptor 1B gene (encodes MT_2)
MuRF1	Muscle RING-finger protein 1 (E3 ubiquitin ligase; TRIM63)
mdx5Cv	Duchenne muscular dystrophy mouse model variant (dystrophin-deficient)
NAS	N-acetylserotonin
NF-κB	Nuclear factor kappa B
NQO2	NAD(P)H quinone dehydrogenase 2 (also known as quinone reductase 2; proposed MT_3 target)
NRF1	Nuclear respiratory factor 1
NRF2	Nuclear factor erythroid 2–related factor 2
NO	Nitric oxide
OGTT	Oral glucose tolerance test
OPA1	Optic atrophy 1 (mitochondrial inner membrane fusion protein)
p38 MAPK	p38 mitogen-activated protein kinase
p62	Sequestosome 1 (SQSTM1; autophagy adaptor)
Pax7	Paired box protein 7
PCNA	Proliferating cell nuclear antigen
Pdx-1	Pancreatic and duodenal homeobox 1 (β-cell transcription factor)
PERK	Protein kinase RNA-like ER kinase (ER stress sensor)
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K	Phosphoinositide 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol 3,4,5-trisphosphate
PKA	Protein kinase A
PKB	Protein kinase B (synonymous with Akt)
PKCζ	Protein kinase C zeta
PLC	Phospholipase C
p70S6K	70-kDa ribosomal protein S6 kinase
QR2	Quinone reductase 2 (synonymous with NQO2; historically linked to MT_3)
QUICKI	Quantitative Insulin Sensitivity Check Index
RAW264.7	Murine macrophage cell line (RAW 264.7)
RCAN	Regulator of calcineurin (RCAN family; calcineurin signaling modulator)
RCT	Randomized controlled trial
ROS	Reactive oxygen species
ROR/RZR	Retinoic acid receptor-related orphan receptor/receptor family historically proposed as nuclear melatonin targets
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RTKs	Receptor tyrosine kinases
SAMP8	Senescence-accelerated mouse prone 8 (aging/metabolic phenotype model)
SCN	Suprachiasmatic nucleus

SCN2.2	Rat suprachiasmatic nucleus-derived cell line
SERCA	Sarco(endo)plasmic reticulum Ca^{2+}-ATPase
SIRT1	Sirtuin 1 (NAD^+-dependent deacetylase)
SIRT3	Sirtuin 3 (mitochondrial NAD^+-dependent deacetylase)
SOD	Superoxide dismutase
SOD2	Mitochondrial superoxide dismutase (MnSOD)
SPARC	Secreted protein acidic and rich in cysteine
STAT1	Signal transducer and activator of transcription 1
STAT3	Signal transducer and activator of transcription 3
TBARS	Thiobarbituric acid reactive substances (lipid peroxidation assay class)
TFAM	Mitochondrial transcription factor A
TGF-β	Transforming growth factor beta
TNF-α	Tumor necrosis factor alpha
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling (apoptosis assay)
UCP1	Uncoupling protein 1
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
ZDF	Zucker diabetic fatty (rat model)
Wnt	Wingless-related integration site

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