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REVIEW

Emerging Role of ACOD1/Itaconate in Cancer: Bridging Metabolic Reprogramming and Signaling in the Tumor Microenvironment

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ABSTRACT: Itaconate, produced by aconitate decarboxylase 1 (ACOD1, also known as IRG1), acts as a key immunometabolite that inhibits succinate dehydrogenase (SDH) and can engage reduction-oxidation (redox)-sensitive signaling programs. This review summarizes the emerging, context-dependent roles of the ACOD1-itaconate axis in cancer, while critically distinguishing between the effects of endogenous itaconate and its cell-permeable derivatives. In tumor cells, endogenous *ACOD1* expression or uptake via solute carrier family 13 member 3 (SLC13A3) alters oxidative phosphorylation and glycolysis. In the tumor microenvironment, myeloid-derived itaconate contributes to immune tolerance by reducing dendritic-cell cross-priming and limiting $CD8^+$ T-cell metabolic activity. Moreover, interactions between ACOD1-derived endogenous itaconate and stress-responsive signaling pathways, including Extracellular Signal-Regulated Kinase (ERK)1/2 and AMP-activated Protein Kinase (AMPK), couple mitochondrial metabolic perturbation to adaptive cellular responses, whereas electrophilic itaconate derivatives can additionally engage ERK- and Nuclear Factor Erythroid 2-related factor 2 (NRF2)-linked cytoprotective programs. Collectively, these findings highlight the ACOD1/itaconate axis as a context-dependent node of metabolic control, offering new perspectives for a stratified therapeutic approach based on tumor lineage and transporter expression.

KEYWORDS: Aconitate decarboxylase 1; AMP-activated protein kinase; itaconate; cancer; extracellular signal-regulated kinase; mitochondrial metabolism; nuclear factor erythroid 2-related factor 2; reduction-oxidation signaling

1 Introduction

1.1 Overview of Aconitate Decarboxylase 1 (ACOD1)/Itaconate Pathway

Aconitate decarboxylase 1 (ACOD1), historically identified as immune-responsive gene 1 (IRG1), is the rate-limiting enzyme responsible for the production of itaconate. Located within the mitochondrial matrix, ACOD1 catalyzes the non-oxidative decarboxylation of the tricarboxylic acid (TCA) cycle intermediate cis-aconitate to produce itaconate [1].

Notably, the enzymatic feasibility of this reaction had been established well before its immunological relevance was appreciated. Early biochemical studies characterized cis-aconitate decarboxylase activity in microbial systems, including its purification and enzymatic properties in Aspergillus terreus, thereby

demonstrating the capacity for itaconate biosynthesis at the enzymatic level [2]. However, the physiological significance of this reaction in mammalian cells remained unclear for many years.

This gap was later resolved by peer-reviewed studies showing that *ACOD1* is inducibly expressed in myeloid cells, particularly macrophages and dendritic cells, in response to pro-inflammatory stimuli such as lipopolysaccharide (LPS), interferons (IFNs), and other Toll-like receptor (TLR) agonists. Under these conditions, ACOD1 catalyzes itaconate production as part of an immunometabolic response, thereby linking mitochondrial metabolism to immune regulation [1].

Following its synthesis, itaconate accumulates intracellularly and functions as a competitive inhibitor of succinate dehydrogenase (SDH), also known as Complex II of the electron transport chain. By competing with succinate for the SDH active site, itaconate blocks the oxidation of succinate to fumarate, leading to a significant accumulation of intracellular succinate and a phenomenon often described as a break in the TCA cycle [3]. This metabolic rewiring halts mitochondrial respiration and is closely associated with altered mitochondrial reactive oxygen species (ROS) production. However, distinct effects are observed depending on the form used, with cell-permeable derivatives such as dimethyl itaconate (DI) and 4-octyl itaconate (4-OI) being linked to suppression of reactive oxygen and nitrogen species (ROS/RNS) and broader oxidative and nitrosative stress, although the precise redox outcome—whether enhanced or attenuated oxidative/nitrosative signaling—depends on the timing and intensity of the inflammatory response [4,5].

Beyond its role as a metabolic inhibitor, electrophilic signaling is most prominently observed with itaconate derivatives rather than native itaconate. Crucially, while endogenous itaconate is a weak electrophile, its derivatives (e.g., 4-OI) exhibit significantly higher reactivity toward cysteine residues [6]. For instance, studies utilizing 4-OI have demonstrated that it alkylates key glycolytic enzymes, including aldolase A (ALDOA) [7] and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [8]. This modification inhibits their catalytic activity, thereby dampening glycolytic flux that typically fuels the acute phase of macrophage activation.

Furthermore, 4-OI has been shown to covalently modify Kelch-like ECH-associated protein 1 (KEAP1) at critical cysteine residues (e.g., Cys151), thereby activating the NRF2-dependent antioxidant response [9]. Under basal conditions, KEAP1 binds to Nuclear factor erythroid 2-related factor 2 (NRF2) and promotes its degradation via the ubiquitin-proteasome pathway. Alkylation of KEAP1 by electrophilic itaconate derivatives disrupts this interaction, leading to NRF2 stabilization and nuclear translocation. In the nucleus, NRF2 induces the transcription of cytoprotective and anti-inflammatory genes, including heme oxygenase-1 (*HMOX1*), thereby contributing to redox homeostasis and attenuation of inflammatory signaling [9]. Similarly, DI treatment has been linked to distinct metabolic effects, although these effects may not fully recapitulate endogenous itaconate signaling [6].

In parallel, 4-OI modulates innate immune signaling complexes to exert anti-inflammatory effects. It inhibits the activation of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome, a multiprotein complex responsible for interleukin 1 beta (IL-1β) maturation. Mechanistically, 4-OI disrupts the interaction between NLRP3 and NIMA-related kinase 7 (NEK7), which is required for inflammasome oligomerization and activation [10]. Additionally, itaconate derivatives have been shown to alkylate Janus kinase 1 (JAK1), thereby inhibiting downstream signal transducer and activator of transcription (STAT) signaling [11]. Together, these mechanisms contribute to a redox-protective and anti-inflammatory cellular state that limits excessive tissue damage during immune responses.

In summary, the ACOD1–itaconate axis constitutes a central metabolic–immunoregulatory pathway. By integrating mitochondrial reprogramming, redox signaling, and electrophilic stress responses, itaconate functions as a metabolic brake, restraining inflammation and helping maintain cellular homeostasis.

1.2 The Dual Role of ACOD1 and Itaconate in Cancer Biology

Although the ACOD1–itaconate pathway was initially thought to be restricted to the immune system, recent discoveries extend this idea beyond immunology. In cancer, itaconate plays a dual role, acting either as a tumor suppressor [12–14] or a promoter [15–17] depending on the cell type, tissue origin, and immune-metabolic microenvironment.

In estrogen receptor (ER)-positive (ER^+) breast cancer, endogenous itaconate has been shown to functionally target extracellular signal-regulated kinase 2 (ERK2) in a Cys254-dependent manner, an event associated with altered ERK2 phosphorylation dynamics and reduced tumor cell proliferation, particularly in drug-resistant settings [18]. Complementary studies further demonstrate that ACOD1/itaconate-driven metabolic reprogramming suppresses ER^+ breast cancer growth by inhibiting succinate dehydrogenase (SDH), elevating reactive oxygen species (ROS), and activating AMP-activated protein kinase (AMPK), collectively restoring metabolic homeostasis [14].

Beyond breast cancer, pharmacological treatment with the cell-permeable itaconate derivative 4-octyl itaconate (4-OI) inhibits glycolytic flux by alkylating glyceraldehyde-3-phosphate dehydrogenase (GAPDH), thereby promoting cuproptotic cell death in colorectal cancer models [13]. Similarly, tumor cell–intrinsic ACOD1 expression in melanoma enhances antigen presentation and immune activation through the receptor-interacting serine/threonine-protein kinase 3 (RIPK3)–interferon regulatory factor 1 (IRF1)–transcription factor EB (TFEB) axis, leading to increased tumor immunogenicity and improved responsiveness to immune checkpoint blockade [12].

Conversely, in the immune compartment, myeloid-derived itaconate frequently exerts pro-tumor and immunosuppressive effects. Myeloid-specific deletion of *Acod1* enhances antitumor immunity and boosts responses to anti-PD-1/PD-L1 therapy across various tumor types, including melanoma, colon [15,16], as well as peritoneal/ovarian tumor models [17]. Mechanistically, macrophage-derived itaconate suppresses dendritic cell cross-priming and antigen presentation under interferon-γ-driven *Acod1* upregulation [19], while directly inhibiting cytotoxic $CD8^+$ T-cell metabolism and effector function [16]. Meanwhile, neutrophil-derived itaconate promotes metastasis by activating NRF2-dependent ferroptosis resistance, enabling tumor-infiltrating neutrophils to survive and facilitate the spread of ER^- breast cancer [20]. At the interface of immunity and tumor metabolism, itaconate import via the Solute carrier family 13 member 3 (SLC13A3) transporter contributes to immune evasion by alkylation (Cys272)-mediated stabilization of PD-L1 [21] and by enhancing ferroptosis resistance, collectively leading to resistance to immunotherapy [22]. Additionally, Acod1-high prostate cancer cells secrete immunosuppressive peptides that blunt $CD8^+$ T-cell activation, providing yet another route of tumor immune evasion [23].

Together, these findings indicate that itaconate's overall impact on tumor progression is context-dependent. Specifically, tumor cell-intrinsic ACOD1 activity functions as a double-edged sword, promoting immune evasion [23] in some contexts while conversely enhancing tumor immunogenicity [12] or suppressing cell growth [14,18] in others. In contrast, myeloid-derived itaconate fosters an immunosuppressive microenvironment [15–17] and promotes metastasis via neutrophil-dependent ferroptosis resistance [20]. Ultimately, the net outcome relies on specific metabolic vulnerabilities, such as SLC13A3-mediated transport and the regulation of ferroptosis or cuproptosis [13,21,22].

To facilitate a concise comparison across tumor contexts, Table 1 summarizes the dominant, context-dependent roles of the ACOD1–itaconate axis in cancer, highlighting how cellular origin (tumor-intrinsic versus myeloid-derived), metabolic engagement (endogenous synthesis versus transporter-mediated uptake), and downstream stress-response pathways collectively shape divergent tumor-promoting or tumor-suppressive outcomes.

Table 1: Context-dependent roles of the ACOD1/itaconate axis in cancer.

Cancer Context	Net Role	Dominant Mechanism	Cellular Source/Context	Key Reference(s)
Breast cancer (ER^+)	Anti-tumor	Cys254-dependent functional targeting of ERK2 alters phosphorylation dynamics and suppresses proliferation	Tumor cell–intrinsic ACOD1/endogenous itaconate	[18]
Breast cancer (ER^+)	Anti-tumor	SDH inhibition → metabolic stress → AMPK activation	Tumor cell–intrinsic ACOD1–itaconate	[14]
Colorectal Cancer	Anti-tumor	GAPDH alkylation induces cuproptosis	Pharmacological 4-octyl itaconate (4-OI) treatment	[13]
Melanoma	Anti-tumor	RIPK3–IRF1–TFEB–dependent enhancement of antigen presentation	Tumor cell–intrinsic ACOD1	[12]
Melanoma/Colon	Pro-tumor	Suppression of dendritic cell cross-priming and $CD8^+$ T-cell effector function	Macrophage-derived itaconate (paracrine)	[15,16,19]
Breast Cancer (ER^-, Metastatic)	Pro-tumor	NRF2-dependent ferroptosis resistance enabling metastasis	Neutrophil-derived itaconate	[20]
$SLC13A3^+$ Tumors	Pro-tumor	PD-L1 stabilization (Cys272) and enhanced ferroptosis resistance	Extracellular itaconate uptake via SLC13A3	[21,22]
Prostate Cancer	Pro-tumor	Secretion of inhibitory peptides suppresses $CD8^+$ T-cell activation	Tumor cell–intrinsic ACOD1	[23]
Melanoma	Anti-tumor	Electrophilic itaconate–induced mitochondrial dysfunction, oxidative stress, senescence, and DNA damage	4-octyl itaconate (4-OI) treatment	[24]

Note: Net role reflects the predominant effect reported in each experimental context and does not preclude context-dependent or opposing functions in other tumor settings.

1.3 Methodological Considerations: Endogenous Itaconate vs. Electrophilic Derivatives

A critical distinction must be made between endogenous itaconate produced by ACOD1 and the cell-permeable ester derivatives (e.g., 4-octyl itaconate [4-OI] and dimethyl itaconate [DI]) that are widely used in experimental systems. Although these derivatives are often employed as surrogates to mimic intracellular itaconate accumulation, accumulating evidence indicates that they differ substantially from endogenous itaconate in chemical reactivity, cellular entry, and downstream biological effects (Table 2).

In particular, 4-OI is markedly more electrophilic than native itaconate and potently activates NRF2 through KEAP1 alkylation, an effect that is comparatively weak or absent with endogenous itaconate under physiological conditions. A systematic comparative analysis by Swain et al. demonstrated that endogenous itaconate, 4-OI, and DI exert divergent effects on inflammasome activation and type I interferon responses, underscoring that these compounds are not functionally interchangeable [6]. Moreover, DI may not be efficiently hydrolyzed to itaconate in all cell types and can induce mitochondrial toxicity independent of ACOD1 activity.

Table 2: Comparison of endogenous itaconate and electrophilic derivatives.

Compound	Chemical Property	Primary Use	Caveats & Limitations
Endogenous Itaconate	Weak electrophile; Charged (polar)	Physiological signaling studies	Hard to deliver exogenously; Limited alkylation capability compared to derivatives [6].
4-Octyl Itaconate (4-OI)	Strong electrophile; Cell-permeable	NRF2 activation; Alkylation target identification	More reactive than native itaconate; Potential for off-target alkylation.
Dimethyl Itaconate (DI)	Cell-permeable ester	Metabolic inhibition	May not hydrolyze fully to itaconate; Can exert direct mitochondrial toxicity independent of itaconate.

Note: Phenotypes observed with electrophilic itaconate derivatives (4-OI, DI) should not be assumed to reflect endogenous itaconate signaling unless supported by genetic ACOD1 manipulation or direct metabolite quantification.

Importantly, many mechanistic conclusions in the current literature rely predominantly on pharmacologic exposure to electrophilic derivatives rather than genetic manipulation of ACOD1. Because 4-OI readily alkylates multiple cysteine-containing proteins, some reported phenotypes, particularly robust NRF2 activation, redox reprogramming, and mitochondrial stress, may reflect generalized electrophile stress rather than bona fide endogenous itaconate signaling [6,9].

Dose and exposure duration further complicate interpretation. Endogenous itaconate accumulates intracellularly following ACOD1 induction, whereas extracellular itaconate concentrations in human tumors remain poorly defined. In contrast, 4-OI is frequently applied at supraphysiologic concentrations that may not be achieved *in vivo*. Consequently, extrapolation of derivative-based findings to physiological contexts should be made cautiously and, where possible, supported by genetic validation or direct metabolite quantification.

Taken together, these considerations highlight the need to clearly distinguish ACOD1-dependent endogenous itaconate signaling from the effects of electrophilic derivatives when interpreting mechanistic studies and assessing therapeutic implications. These key distinctions between endogenous itaconate and electrophilic derivatives are summarized schematically in Fig. 1.

2 Itaconate Reprograms Mitochondrial Metabolism and Bioenergetics

2.1 Tumor-Cell Intrinsic Effects

In tumor cell-intrinsic settings, particularly in ER^+ breast cancer, ACOD1-derived itaconate imposes substantial mitochondrial metabolic stress. A recent analysis of the TCGA-BRCA Pan-Cancer Atlas via cBioPortal revealed that tumors harboring *ACOD1* deletion exhibited significantly worse overall survival, with approximately 70% of such cases classified as ER^+, underscoring the clinical relevance of ACOD1 in hormone-dependent diseases [14]. It is worth noting that this sensitivity may be subtype-specific. ER^+ tumors (e.g., MCF7, T47D, BT474, ZR75B) appear more sensitive to itaconate-induced bioenergetic disruption than ER^- counterparts (e.g., BT549, Hs578T, MDA-MB-231, SUM159), likely reflecting their greater dependence on oxidative metabolism. On the other hand, enforced *ACOD1* expression or exogenous itaconate in ER^+ breast cancer cell models resulted in a marked decline in glycolytic and TCA cycle intermediates, suppressed lipid biosynthesis, and reduced intracellular ATP levels. Mechanistically, itaconate competitively inhibits SDH, thereby disrupting electron transport and redox equilibrium, which leads to

increased mitochondrial ROS production and decreased adenylate kinase activity. Together, these events create a mitochondrial energy crisis that impairs proliferation and triggers apoptosis [14].

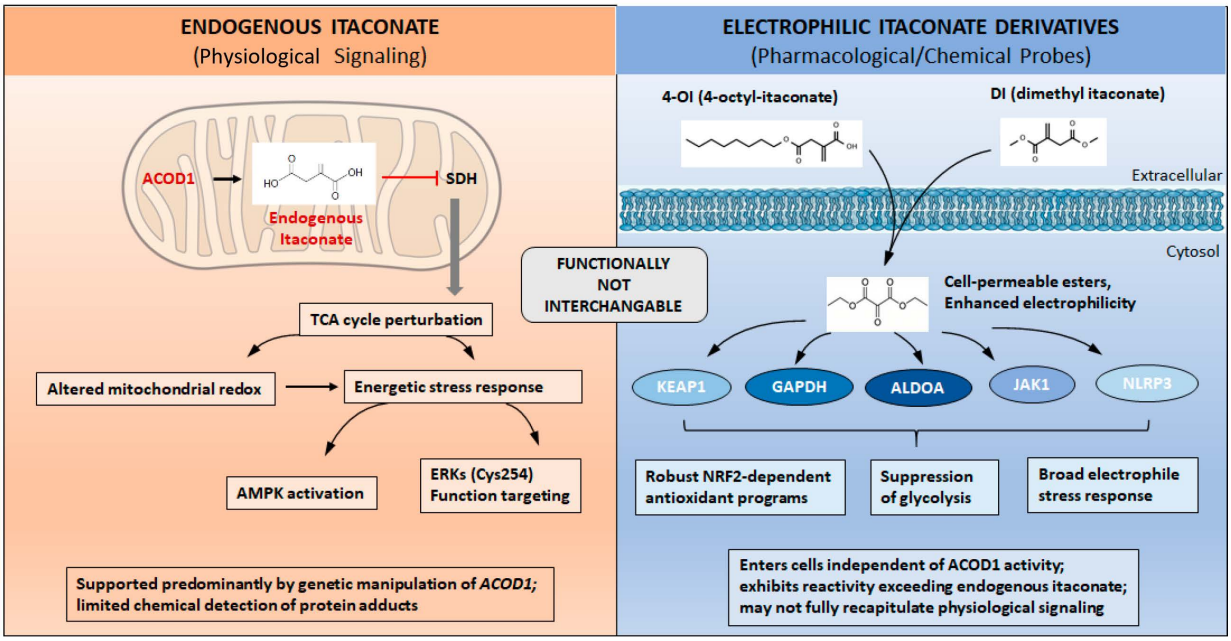

Figure 1: Conceptual separation between endogenous itaconate and electrophilic itaconate derivatives. Endogenous itaconate is produced intracellularly by ACOD1 within mitochondria and primarily functions as a metabolic regulator by inhibiting succinate dehydrogenase, thereby perturbing mitochondrial redox balance and energy homeostasis. In contrast, cell-permeable itaconate derivatives such as 4-octyl itaconate (4-OI) and dimethyl itaconate (DI) exhibit heightened electrophilicity, readily alkylate cysteine residues on multiple target proteins, and robustly activate NRF2-dependent antioxidant and stress-response pathways. Although derivative-based studies have been instrumental in identifying potential molecular targets, their phenotypes should not be assumed to fully recapitulate endogenous itaconate biology. This distinction provides a conceptual framework for interpreting mechanistic studies throughout the manuscript. This figure was created by the authors using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA).

Consistent with this, Yang et al. [13] reported that 4-OI inhibits GAPDH, suppressing aerobic glycolysis and promoting cuproptosis, a form of mitochondrial copper-dependent cell death driven by destabilization of TCA-linked proteins. This supports the concept that electrophilic itaconate derivatives, such as 4-OI, can induce bioenergetic collapse by concurrently inhibiting glycolysis and SDH-linked mitochondrial metabolism.

Moreover, Wang et al. [12] found that in melanoma cells, cancer-cell-intrinsic biosynthesis of itaconate enhances immunogenicity through redox modulation and altered mitochondrial metabolism, providing further evidence that tumor cell-intrinsic itaconate perturbs oxidative phosphorylation (OXPHOS). Likewise, studies in melanoma treated with 4-OI have shown mitochondrial dysfunction, GSH depletion, ROS accumulation, and induction of senescence and DNA damage, highlighting a direct mitochondrial toxicity of electrophilic itaconate analogs [24].

Lin et al. [22] reported that tumor cells can import extracellular itaconate via the SLC13A3 transporter. The reduced glycolytic flux and elevated mitochondrial oxygen consumption rate (OCR) following SLC13A3-mediated itaconate uptake indicate a parallel role in bioenergetic modulation.

Together, these findings suggest that tumor cell-intrinsic itaconate may induce bioenergetic stress by modulating mitochondrial metabolism, leading to mitochondrial dysfunction, impaired proliferation, and cell death.

2.2 Tumor Microenvironment/Myeloid-Derived Effects

Unlike tumor cell–intrinsic effects, myeloid-derived itaconate frequently promotes immune suppression by rewiring mitochondrial metabolism in multiple immune compartments. In peritoneal tumor models, Weiss et al. demonstrated that tumor-educated macrophages upregulate ACOD1 and itaconate production, resulting in enhanced OXPHOS and mitochondrial ROS that support tumor growth [17]. Genetic silencing of *Acod1* reduced macrophage OXPHOS and slowed tumor progression.

Beyond macrophages, macrophage-derived itaconate also suppresses dendritic cell (DC) function. IFNγ-induced *Acod1* expression increases itaconate synthesis, which impairs DC cross-priming capacity and glycolytic activity, thereby contributing to acquired resistance to anti–PD-1 therapy [19].

In parallel, myeloid-derived suppressor cells (MDSCs) release itaconate that is taken up by $CD8^+$ T cells, where it inhibits SDH, disrupts mitochondrial metabolism, and suppresses cytotoxic effector function [16]. In neutrophils, ACOD1-driven itaconate activates NRF2-dependent antioxidant programs, conferring resistance to ferroptosis and promoting metastatic progression in ER^- breast cancer [20].

3 Itaconate Links Mitochondrial Metabolism to Cellular Signaling Networks

3.1 ERK2 as a Metabolic Signaling Hub within Endogenous Itaconate- and Derivative-Induced Stress Responses in Cancer

ERK1/2 serves as a central signaling hub linking extracellular cues to mitochondrial dynamics and metabolic regulation. Upon sustained activation, ERK2 translocates to mitochondria, where it regulates mitochondrial membrane potential, the balance between mitochondrial fission and fusion, and permeability transition pore activity, thereby influencing oxidative phosphorylation (OXPHOS) efficiency, reactive oxygen species (ROS) production, and apoptosis sensitivity [25–27].

Beyond its mitochondrial functions, ERK1/2 orchestrates broader anabolic metabolic programs. ERK-mediated phosphorylation of pyruvate kinase M2 (PKM2) enhances c-Myc–driven glycolysis, while activation of sterol regulatory element-binding proteins (SREBP-1a/1c) promotes fatty acid biosynthesis [28,29].

ERK signaling also intersects with nutrient-sensing pathways to coordinate growth with energy availability. Phosphorylation of tuberous sclerosis complex 2 (TSC2) by ERK activates mechanistic Target of Rapamycin Complex 1 (mTORC1) under nutrient-rich conditions, whereas energy stress–induced AMPK activation suppresses Rapidly Accelerated Fibrosarcoma (RAF)–ERK signaling to restrain anabolic growth [30,31].

Within this integrative framework, itaconate emerges as a mitochondria-derived metabolite that modulates ERK-regulated pathways by perturbing mitochondrial metabolism and redox balance, in part by inhibiting succinate dehydrogenase. This metabolic reprogramming shifts ERK signaling from a growth-promoting mode toward a stress-adaptive mode, influencing OXPHOS efficiency, ROS homeostasis, and downstream transcriptional circuits such as *NRF2* and *ATF3*. Collectively, these observations position itaconate as a metabolic signal that couples mitochondrial redox status to reprogramming of the ERK pathway.

3.1.1 Functional Targeting of ERK2 Cys254 by Endogenous Itaconate and 4-OI

In ER^+ breast cancer models, a recent study demonstrated that the ACOD1-itaconate axis functionally targets ERK2 at Cys254 to induce a signaling switch. Specifically, endogenous ACOD1 overexpression stabilized ERK2 in an active yet antiproliferative conformation, an effect that was abolished in cells expressing the alkylation-resistant ERK2-C254S mutant [18]. While the direct alkylation event was biochemically modeled using the cell-permeable derivative 4-OI, the finding that the endogenous ACOD1-driven phenotype relies strictly on the integrity of Cys254 supports the conclusion that this residue is a bona fide physiological target. This metabolite-driven phospho-switch changes a typical growth-promoting kinase into a stress-responsive regulator, establishing a mechanistic link between itaconate metabolism and ERK signaling reprogramming.

3.1.2 Paracrine Activation via the Itaconate–Oxoglutarate Receptor 1 (OXGR1) Pathway

Zeng et al. [32] identified OXGR1 (GPR99) as a G-protein-coupled receptor responsive to extracellular itaconate. Ligand engagement induces Gq/11-dependent Ca^{2+} mobilization and ERK1/2 phosphorylation through β-arrestin recruitment. *In vivo*, ACOD1-derived itaconate accumulates in infected airways and activates OXGR1 to enhance mucociliary clearance; however, deletion of *Acod1* or *Oxgr1* compromises host defense. These findings demonstrate that extracellular itaconate can engage ERK1/2-dependent cytoprotective signaling, complementing but not necessarily recapitulating endogenous itaconate-mediated regulatory mechanisms. Whether this OXGR1-mediated ERK activation operates at physiologically relevant itaconate concentrations within the tumor microenvironment remains to be determined.

3.1.3 Cytoprotective ERK Activation by 4-Octyl-Itaconate

Hu et al. further reported that the electrophilic itaconate derivative 4-octyl itaconate (4-OI) activates Protein Kinase B (AKT) and ERK1/2 in hepatocytes under oxidative stress, promoting the expression of NRF2 and NAD^+-dependent protein deacetylase sirtuin-3 (SIRT3). Pharmacologic inhibition of ERK or AKT abrogates this protection, indicating that ERK1/2 serves as a central mediator linking itaconate signaling to mitochondrial antioxidant and cytoprotective responses [33]. These effects are therefore best interpreted as derivative-induced cytoprotective signaling rather than direct evidence of endogenous itaconate activity.

3.1.4 Redox-Dependent ERK Cysteine Oxidation

Complementary biochemical analyses reveal that ERK2 oxidation at Cys159 within its D-recruitment site induced by physiological H_2O_2 forms a transient sulfenic acid that alters substrate preference without inactivating kinase function [34]. This redox switch exemplifies how mitochondrial ROS, potentially elevated by SDH inhibition, fine-tunes ERK signaling.

Together, these mechanistic findings demonstrate a bidirectional itaconate-ERK axis, in which intracellular itaconate can functionally target ERK2 in a Cys254-dependent manner, while extracellular itaconate activates OXGR1 to trigger ERK signaling in neighboring cells. Both routes intersect with ROS-driven redox control, creating a feedback loop that links mitochondrial metabolism to signal transduction, cellular stress response, and growth regulation.

Collectively, these findings underscore that itaconate-mediated signaling is highly context-dependent and can engage distinct stress-responsive kinases. Beyond ERK-centered signaling reprogramming, accumulating evidence indicates that AMPK represents another critical node through which itaconate links mitochondrial dysfunction to growth control. The signaling outcome of SDH-associated ROS is therefore

determined by amplitude, duration, and cellular buffering capacity, rather than by a fixed quantitative threshold.

3.2 Itaconate-AMPK Crosstalk as a Metabolic Checkpoint in Cancer

Emerging evidence highlights a context-dependent interaction between itaconate signaling and AMPK that guides metabolic stress adaptation and tumor cell fate. In ER^+ breast cancer, a recent study demonstrated that ACOD1-derived itaconate induces widespread metabolic reprogramming, disrupting glycolysis, the TCA cycle, and lipid metabolism, leading to mitochondrial dysfunction and energetic stress. This metabolic imbalance activates AMPK signaling, which acts as a metabolic checkpoint to limit tumor growth and promote apoptotic cell death [14]. In this context, AMPK functions as a cellular energy sensor, connecting itaconate-induced bioenergetic stress to an anti-proliferative response and linking mitochondrial redox imbalance with growth control.

Consistent with itaconate's previously described involvement in AMPK signaling, recent studies have added an additional regulatory layer, showing that itaconate influences the α-ketoglutarate (α-KG)-Y-box binding protein 1 (YBX1)-AMPK axis. Mi et al. demonstrate that α-KG deficiency inhibits Ten-Eleven Translocation (TET)-dependent transcription of *YBX1*, an RNA-binding protein that supports AMPK mRNA translation and thereby sustains AMPK protein abundance. Notably, metabolites that antagonize α-KG–dependent dioxygenase activity, such as succinate and itaconate, mimic this effect, leading to reduced AMPK synthesis and heightened glucose deprivation sensitivity in human liver and lung cancer cells [35]. This finding emphasizes a transcriptional-translational checkpoint that may function in parallel with the bioenergetic stress pathway described in the ER^+ breast cancer model.

Together, these studies establish a dual-mode regulatory paradigm in which itaconate can act either downstream, as a mitochondrial stressor that triggers AMPK activation in response to energy depletion, or upstream, as a metabolic modulator that limits AMPK availability by inhibiting the α-KG-YBX1-TETsignaling axis. This bidirectional control positions the itaconate-AMPK axis as a pivotal and druggable metabolic checkpoint that integrates mitochondrial redox signaling, carbon flux, and translational control to determine cancer cell viability and therapeutic responsiveness. These two modes of regulation are not mutually exclusive and may operate in parallel depending on tumor lineage, metabolic state, and itaconate availability.

3.3 Itaconate-Mediated ERK2–AMPK Crosstalk in Cancer

Taken together, the ERK-centered signaling reprogramming described in Section 3.1 and the AMPK-based metabolic checkpoint outlined in Section 3.2 converge on a shared response to itaconate-induced mitochondrial stress.

The above evidence supports the notion that itaconate acts as a metabolic and redox rheostat, influencing ERK2 signaling and AMPK activation to coordinate mitochondrial stress responses in cancer cells. Mechanistically, this dual regulation positions itaconate at the interface of redox and energetic signaling, in which mitochondrial ROS derived from itaconate-mediated SDH blockade can activate ERK2, while concomitant energy stress engages AMPK as a compensatory metabolic checkpoint. Crosstalk between these pathways is further reinforced by AMPK's ability to phosphorylate upstream ERK1/2 regulators, limiting sustained ERK1/2 hyperactivation and restoring metabolic equilibrium. As illustrated in Fig. 1, such a reciprocal ERK2–AMPK feedback loop may contribute to redox–metabolic homeostasis under itaconate-induced stress, thereby potentially influencing tumor cell fate decisions (Fig. 2).

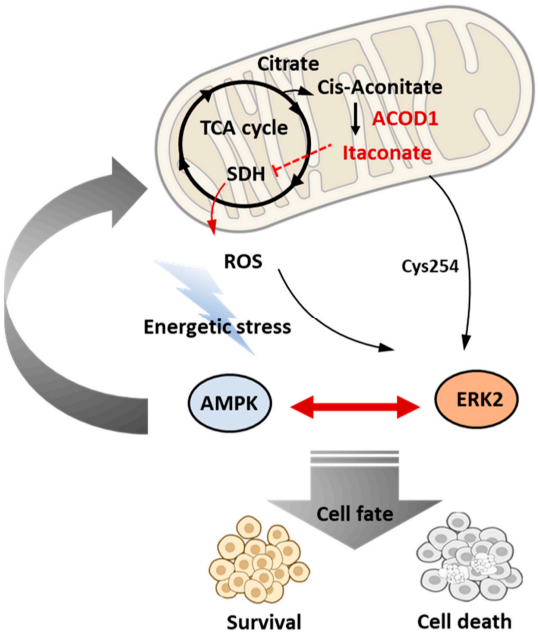

Figure 2: Mechanistic model depicting how ACOD1-derived itaconate–induced mitochondrial stress can be integrated through ERK2 and AMPK signaling to shape cancer cell fate. ACOD1 converts cis-aconitate into itaconate within mitochondria, diverting carbon flux from the TCA cycle and inhibiting SDH. This metabolic perturbation disrupts oxidative phosphorylation and elevates mitochondrial energetic and redox stress. These stress signals activate AMPK as a metabolic checkpoint, while concurrently reprogramming ERK2 signaling toward a stress-responsive state. Reciprocal crosstalk between AMPK and ERK2 integrates bioenergetic stress with growth-regulatory signaling, forming a feedback loop that constrains anabolic programs and shapes downstream cell fate decisions. Depending on cellular context and metabolic state, this coordinated ERK2–AMPK response may bias cancer cells toward growth suppression, stress adaptation, or survival outcomes. This schematic is intended to summarize the ERK2–AMPK integration discussed in Section 3, whereas the conceptual and methodological distinction between endogenous itaconate and electrophilic derivatives is presented in Fig. 1. This figure was created by the authors using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA).

4 ACOD1/Itaconate in the Tumor Microenvironment and Stromal Crosstalk

The tumor microenvironment (TME) is a complex ecosystem composed of tumor and immune cells, as well as stromal fibroblasts, adipocytes, and endothelial cells. Recent research shows that the ACOD1–itaconate axis acts as a shared metabolic and redox signal across immune and tumor compartments, where it modulates mitochondrial metabolism, redox balance, and antitumor immunity [9,14,15]. In parallel, emerging evidence from fibrotic and stromal remodeling models suggests that itaconate-dependent redox regulation can influence extracellular matrix remodeling, cellular stress adaptation, and stromal cell function, thereby shaping the metabolic landscape of the TME [36–38].

4.1 Myeloid-Derived Itaconate as a Paracrine Metabolic Signal

In the TME, myeloid-derived itaconate functions as a key metabolic regulator of immune suppression. Weiss et al. [17] first demonstrated that macrophage-derived itaconate in peritoneal tumor-associated macrophages promotes OXPHOS and ROS production, thereby supporting tumor growth. In contrast, loss of *Acod1* in macrophages disrupts this metabolic program, resulting in reduced tumor burden in multiple murine models. Consistently, Chen et al. [15] showed that genetic ablation of *Acod1* in myeloid cells leads

to increased $CD8^+$ T-cell infiltration and tumor regression in melanoma (B16-F10) and colon carcinoma (MC38) models. Mechanistically, ACOD1-derived itaconate suppresses TET-mediated epigenetic remodeling and limits the expression of chemokines necessary for the recruitment of cytotoxic T cells. Together, these findings identify myeloid ACOD1 as a metabolic redox rheostat that maintains an immunosuppressive macrophage phenotype and constrains anti-tumor immunity.

Building on this paradigm, Zhao et al. [16] demonstrated that MDSCs secrete itaconate as a soluble immunometabolic compound. The exported metabolite is taken up by $CD8^+$ T cells, where it suppresses serine and aspartate biosynthesis, thereby diminishing cytokine production, proliferation, and cytotoxicity. Deletion of *Acod1* in myeloid cells restored T-cell effector function and enhanced responsiveness to anti-PD-1 therapy. Thus, myeloid ACOD1 acts as a metabolic checkpoint of T-cell exhaustion and immune evasion.

At the tumor interface, Lin et al. [22] identified the sodium-coupled dicarboxylate transporter SLC13A3 as a major importer of extracellular itaconate. Tumor cells expressing SLC13A3 internalize macrophage-derived itaconate, which stabilizes NRF2, enhances antioxidant capacity, and confers ferroptosis resistance. Pharmacologic or genetic inhibition of *SLC13A3* restored lipid peroxidation and sensitized tumors to checkpoint blockade, establishing a paracrine metabolic circuit linking myeloid ACOD1 activity to tumor redox adaptation.

Together, these findings converge on a key role for myeloid-derived ACOD1/itaconate in suppressing the antitumor immune response, highlighting the potential to therapeutically target this metabolic signal to enhance antitumor immunity.

4.2 Stromal Fibroblasts and Extracellular Matrix Remodeling

While direct evidence of ACOD1 activity in cancer-associated fibroblasts is lacking, data from fibrotic models imply that itaconate may influence stromal remodeling via NRF2-mediated antioxidant signaling. By attenuating TGF-β/Smad and NF-κB activation, 4-octyl-itaconate (4-OI) reduces collagen synthesis and oxidative stress [36–38], providing a conceptual framework for exploring how itaconate-dependent redox control might shape the tumor stroma.

Taken together, these findings suggest, by analogy with fibrotic disease models, that electrophilic itaconate derivatives may reprogram fibroblast redox signaling; whether endogenous ACOD1-derived itaconate plays a similar role in cancer-associated fibroblasts remains unknown.

4.3 Adipocyte-Tumor Metabolic Coupling

Mammary adipose tissue supplies lipids and energy that support breast tumor metabolism. In coculture and analysis of human samples, mammary adipocytes transfer fatty acids to nearby cancer cells, promoting adipose triglyceride lipase (ATGL)-dependent lipolysis in adipocytes and fatty acid oxidation (FAO) in tumor cells; pharmacological blockade of ATGL/FAO prevents the invasion phenotype [39]. Building on this foundation, reviews of cancer-associated adipocytes (CAAs) explain how metabolites, adipokines, and matrix cues from adipocytes influence breast tumor bioenergetics and behavior [40]. While these studies establish a metabolic framework for adipocyte–tumor coupling, direct evidence linking ACOD1 or itaconate signaling to cancer-associated adipocytes is currently lacking.

Although ACOD1 expression in cancer-associated adipocytes has not been directly reported, the metabolic parallels between adipose-tumor coupling and myeloid-derived itaconate signaling suggest a potential intersection. Myeloid-derived itaconate may diffuse into the adipose-tumor interface and, upon SLC13A3-mediated uptake, activate NRF2-dependent antioxidant programs and sustain fatty acid

oxidation [22]. We therefore hypothesize that macrophage-derived itaconate may help maintain the oxidative, OXPHOS-dominant phenotype of ER^+ breast cancer cells within the mammary adipose niche.

4.4 Endothelial and Vascular Interfaces

Although direct investigations of itaconate's roles in tumor vasculature remain limited, evidence from endothelial and ischemic models suggests that itaconate exerts redox-driven effects on vascular homeostasis. In pulmonary microvascular endothelial cells, activation of the ACOD1/itaconate-NRF2 axis protects against free fatty acid-induced mitochondrial oxidative stress and inflammation, indicating an endothelium-intrinsic cytoprotective mechanism [41].

5 Therapeutic Perspectives: Targeting the ACOD1/Itaconate Axis in Cancer

Although direct *in vivo* targeting of the ACOD1/itaconate axis remains limited, accumulating metabolic and immunologic evidence suggests potential therapeutic relevance. Genetic manipulation studies demonstrate that myeloid-specific deletion of *Acod1* or disruption of SLC13A3-mediated itaconate uptake can restore antitumor immunity and enhance responsiveness to immune checkpoint blockade [15,16,22]. These findings provide the strongest current *in vivo* support for therapeutic modulation of this pathway.

In contrast, pharmacologic modulation of ACOD1 or systemic administration of electrophilic itaconate derivatives faces substantial challenges. These include limited selectivity, uncertain pharmacokinetics, off-target cysteine alkylation, and potential toxicity associated with broad NRF2 activation. Consequently, most pharmacologic strategies targeting the ACOD1/itaconate axis remain conceptual and require rigorous preclinical validation.

The first strategy focuses on tumor cell-intrinsic modulation of the itaconate pathway. Controlled induction of *ACOD1* (supported primarily by genetic models) or pharmacological application of electrophilic itaconate derivatives (supported mainly by *in vitro* studies), such as 4-OI, can emulate metabolic and oxidative stress, triggering adaptive antioxidant programs. Mechanistically, these compounds alkylate cysteine residues within KEAP1, most notably Cys151, thereby stabilizing NRF2 and upregulating genes such as *HMOX1* and *NQO1* [9]. Concurrently, *ACOD1* induction has been shown to activate AMPK signaling, thereby restoring metabolic homeostasis in specific cancer contexts [14,42]. However, the ultimate impact of this redox modulation is likely to be strongly influenced by tumor type, baseline oxidative status, and oncogenic signaling context, which collectively determine whether itaconate signaling results in cytoprotection or growth suppression. Notably, to our knowledge, no selective ACOD1 inhibitors have yet advanced to clinical evaluation in oncology, and systemic inhibition of ACOD1 or succinate dehydrogenase may carry potential risks of immune dysregulation.

The second strategy targets the stromal and immune microenvironment, where ACOD1 exerts context-dependent immunometabolic effects. In murine melanoma, myeloid-derived itaconate suppresses $CD8^+$ T-cell serine and aspartate metabolism, limiting effector cytokine production. Deletion of *Acod1* has been shown to restore T-cell cytotoxicity and can enhance responsiveness to immune-checkpoint blockade [15,16]. Beyond immune cells, recent studies have revealed that cancer cells themselves can import itaconate via the plasma membrane transporter SLC13A3, which can activate NRF2-associated antioxidant programs and increase resistance to ferroptosis, an adaptive mechanism observed in melanoma and lung carcinoma, and supported by subsequent studies [43]. These findings collectively suggest that both the production and uptake of itaconate may influence therapeutic outcomes in the tumor microenvironment.

Integrative combination therapies may yield synergistic benefits. For instance, endocrine agents paired with itaconate mimetics could potentially attenuate ER-driven transcription and mitochondrial respiration

in ER^+ tumors. Preclinical evaluation will be required to determine whether combining 4-OI with complex I or II inhibitors indeed amplifies mitochondrial stress while engaging AMPK-NRF2-mediated adaptive quiescence [42]. Likewise, metabolic modulators such as metformin or 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)-AMPK activators, which are known to reduce ERα expression and inhibit SREBP-1c-dependent lipogenesis in ER^+ cells [44,45], may complement itaconate signaling to reinforce metabolic restraint. From an immunologic perspective, it is plausible that combining immune-checkpoint inhibitors with myeloid-selective ACOD1 inhibitors or SLC13A3 blockers could mitigate stromal immunosuppression and enhance anti-tumor T-cell activity [16,22].

For clinical translation, biomarker-guided patient selection and pharmacodynamic validation will be essential. Candidate biomarkers may include tumor *ACOD1* and *SLC13A3* expression, succinate-to-itaconate ratios, *NRF2/KEAP1* mutational status, and enrichment of oxidative-phosphorylation gene signatures. In the stromal compartment, *ACOD1* expression within tumor-associated macrophages, coupled with $CD8^+$ T-cell infiltration profiles, may help identify patients most likely to benefit from ACOD1- or transporter-targeted therapies.

Nonetheless, several caveats must be considered. Sustained NRF2 activation, while protective against oxidative stress, can promote chemoresistance and survival of dormant tumor cells if prolonged. Systemic inhibition of succinate dehydrogenase may carry the risk of off-target mitochondrial toxicity, underscoring the need for tumor-specific delivery systems or pro-drug formulations of itaconate analogs. Additionally, the strong electrophilic reactivity of 4-OI necessitates the development of next-generation derivatives with improved selectivity to minimize non-specific cysteine alkylation and off-target effects [9].

Together, these insights position the ACOD1/itaconate axis as a multifaceted target in cancer therapy, bridging metabolic, redox, and immune regulation. Future translational efforts should aim to delineate the tumor-versus-host-directed consequences of modulating this pathway, thereby enabling the rational integration of precision metabolic-immunotherapy frameworks.

6 Conclusion

The ACOD1/itaconate pathway has emerged from a macrophage-centered immunometabolic program into a broader regulatory axis relevant to cancer metabolism, signaling, and the tumor microenvironment. Accumulating evidence indicates that itaconate acts as a mitochondrial-derived metabolite that couples metabolic stress to redox-sensitive signaling pathways, thereby influencing cellular adaptation rather than serving as a uniform oncogenic or tumor-suppressive factor.

In tumor cells, ACOD1-derived itaconate can perturb mitochondrial metabolism, oxidative phosphorylation, and ferroptosis susceptibility in a highly context-dependent manner. In specific models, such as ER^+ breast cancer, endogenous itaconate directly modifies signaling proteins, including ERK2, shifting kinase activity toward stress-responsive states and engaging energy-sensing pathways such as AMPK. In contrast, in immune and stromal compartments, myeloid-derived itaconate has been shown to predominantly exert immunosuppressive effects by constraining dendritic cell priming and T-cell metabolic fitness, thereby shaping antitumor immunity.

Importantly, the biological consequences of itaconate signaling depend on multiple layers of regulation, including cellular origin, metabolic state, transporter expression (e.g., SLC13A3), and the distinction between endogenous itaconate and electrophilic derivatives such as 4-octyl itaconate. While derivative-based studies have been instrumental in uncovering potential molecular targets, their heightened electrophilicity and off-target effects necessitate careful interpretation when extrapolating to physiological itaconate biology.

Rather than defining a single linear pathway, current evidence supports an integrative, context-dependent model in which itaconate interfaces with ERK2- and AMPK-regulated signaling networks to modulate redox balance, metabolic stress responses, and cell-fate decisions. This framework highlights itaconate as a metabolic rheostat whose effects vary across tumor lineages and microenvironmental niches.

Looking forward, key unresolved questions remain, including the physiological concentrations and spatial distribution of itaconate within human tumors, the prevalence and functional relevance of SLC13A3-mediated uptake across cancer types, and the conditions under which itaconate signaling may promote tumor suppression versus immune evasion. Addressing these gaps will be essential for translating insights from ACOD1/itaconate biology into therapeutic strategies. Future efforts should emphasize biomarker-guided patient stratification and a clear separation between evidence-supported mechanisms and hypothesis-driven models, enabling rational integration of metabolic and immunologic approaches in cancer therapy.

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Abbreviations

ACOD1	aconitate decarboxylase 1
AICAR	5-aminoimidazole-4-carboxamide ribonucleotide
AKT/PKB	protein kinase B
ALDOA	aldolase A
AMPK	AMP-activated protein kinase
ATF3	activating transcription factor 3
ATGL	adipose triglyceride lipase
CAA(s)	cancer-associated adipocyte(s)
DC	dendritic cell(s)
DI	dimethyl itaconate
ER	estrogen receptor
ERα	estrogen receptor alpha
ERK1/2	extracellular signal-regulated kinases 1/2
ERK2	extracellular signal-regulated kinase 2
FAO	fatty acid oxidation
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GPR99	G protein–coupled receptor 99
GSH	glutathione

HMOX1	heme oxygenase 1
IFN-γ	interferon gamma
IFNs	interferons
IL-1β	interleukin 1 beta
IL-6	interleukin 6
IL-12	interleukin 12
IRF1	interferon regulatory factor 1
IRG1	immune-responsive gene 1
ITA	itaconate
JAK1	Janus kinase 1
KEAP1	Kelch-like ECH-associated protein 1
α-KG	α-ketoglutarate
LPS	lipopolysaccharide
MDSC(s)	myeloid-derived suppressor cell(s)
mTORC1	mechanistic target of rapamycin complex 1
NEK7	NIMA-related kinase 7
NLRP3	NLR family pyrin domain-containing 3
NRF2	nuclear factor erythroid 2-related factor 2
OCR	oxygen consumption rate
OXGR1	oxoglutarate receptor 1
4-OI	4-octyl itaconate
OXPHOS	oxidative phosphorylation
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PKM2	pyruvate kinase M2
RAF	rapidly accelerated fibrosarcoma
RIPK3	receptor-interacting serine/threonine-protein kinase 3
RNS	reactive nitrogen species
ROS	reactive oxygen species
SDH	succinate dehydrogenase
SIRT3	sirtuin 3
SLC13A3	solute carrier family 13 member 3
SREBP-1a/1c	sterol regulatory element-binding protein 1a/1c
STAT1	signal transducer and activator of transcription 1
TCA	tricarboxylic acid
TET	ten-eleven translocation
TFEB	transcription factor EB
TLR	Toll-like receptor
TME	tumor microenvironment
TSC2	tuberous sclerosis complex 2
YBX1	Y-box binding protein 1

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