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REVIEW

Cytokine signalling in vaginal epithelial cells: mechanistic insights into epithelial immunity and inflammatory milieu in vulvovaginal candidiasis

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ABSTRACT: Vulvovaginal candidiasis (VVC) is one of the most prevalent mucosal infections worldwide, experienced by women throughout their reproductive years. *Candida albicans* is involved in 85–95% of all VVC cases and given the stronger correlation between the severity of epithelial cytokine responses, rather than fungal burden, with VVC symptoms, this disease is fundamentally immunopathological. VVC is believed to be initiated by a cascade of events that leads to vaginal epithelial cell (VEC) damage. These cells act as immune sentinels and can detect fungal morphotypes as well as virulence factors through diverse pattern recognition receptors, such as TLRs, C-type lectin receptors, and nucleotide-binding oligomerization domain-like receptors. Recognition of *C. albicans* can trigger complex intracellular signalling cascades in VECs that involve NF-κB, MAPK, and activator protein-1, which culminate in robust production of proinflammatory cytokines, chemokines, and alarmins. The hypha-specific peptide toxin, candidalysin can also initiate VEC membrane damage, which leads to nucleotide-binding oligomerization domain, leucine-rich repeat family and pyrin domain-containing protein 3 inflammasome assembly in the VECs. The resulting inflammatory events lead to robust recruitment of neutrophils, which, although they fail to effectively clear the fungus, add to even more tissue damage, contributing to the severity of VVC symptoms. This review synthesises the molecular- and cellular-based evidence to clarify the role of VEC-related immune activation in the development of VVC and to provide a new understanding that VVC signs and symptoms are predominantly immune-related.

KEYWORDS: Vulvovaginal candidiasis, vaginal epithelial cells, cytokine signalling, candidalysin, inflammasome, immunopathology

1 Introduction

1.1 Epidemiology and Clinical Burden of VVC

Vulvovaginal candidiasis (VVC) is one of the most common gynaecological infections worldwide. Epidemiological studies demonstrated that around 75% of women have at least one episode of VVC during their reproductive years [1]. Recurrent vulvovaginal candidiasis (RVVC) where three or more acute symptomatic episodes of VVC occur within 12 months, is associated with approximately 5–8% of women [2]. *C. albicans* is the dominant aetiological agent, accounting for approximately 85–95% of VVC [3]. As a commensal, *Candida* spp. is found in 20–30% of asymptomatic women at any one time [4]. Transition to symptomatic infection is promoted by environmental and host-associated factors such as broad-spectrum antibiotics, oestrogen-driven hormonal fluctuations, immunosuppression, or poor glycaemic control as in diabetes [5,6]. Understanding the cytokine signalling pathways in Vaginal Epithelial Cells (VECs) that lead to symptomatic disease is essential for clarifying VVC pathogenesis. These prevalence estimates are still supported by recent epidemiological research, which also emphasises the worldwide impact of VVC [7].

1.2 Vaginal Epithelium as an Immune Barrier

The vaginal epithelium is composed of stratified squamous epithelia and constitutes a dynamic, active mucosal defence system. These epithelia play a crucial role in mucosal surveillance, including sensing fungal morphology through pattern recognition receptors (PRRs), secreting cytokines and alarmins, and orchestrating local inflammatory responses and neutrophil recruitment [8–10]. VECs express multiple PRRs, such as Toll-like Receptors (TLRs), C-type lectin receptors (CLRs), and NOD-like receptors (NLRs) that recognise conserved microbial pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMPs) [11,12]. Upon recognition, VECs induce rapid innate immune responses characterised by production of proinflammatory cytokines, chemokines, antimicrobial peptides, and alarmins, leading to robust recruitment of immune cells to the sites of infection [9,11,13]. The capacity of VECs to

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differentiate between different *C. albicans* morphotypes is essential during infections, as the shift from yeast to hyphal form represents a critical virulence transition. This transition activates epithelial signalling pathways, wherein candidalysin, a hypha-specific peptide toxin that causes direct VEC membrane damage, provides the activating signal for NLR family pyrin domain containing 3 (NLRP3) inflammasome assembly.

The assembly of this inflammasome has also been implicated in VEC-mediated immune responses following priming via PRR-driven NF-κB signalling [14–16]. VECs also influence adaptive immune responses through cytokine production that affects T cell differentiation, including Th17 lineages with complex roles in conferring immunity against fungal infection [17–19].

1.3 Paradigm Shift: VVC as Immunopathology

The conceptual understanding of VVC has shifted away from the traditional infectious disease paradigm which mainly focused on fungal burden towards an immunopathological paradigm centred on the hyper-inflammatory innate immune response and, specifically, the recruitment of non-protective, functionally impaired neutrophils as the key driver of disease symptoms [9,13,20]. This shift is supported by observations indicating that the severity of clinical symptoms correlates more strongly with the intensity of epithelial and mucosal inflammatory response rather than with fungal load per se [5,21,22]. Symptomatic VVC is invariably accompanied by elevated proinflammatory mediators including IL-1β, IL-8, S100 calcium-binding proteins A8/A9 (S100A8/A9), TNF-α, and IL-1α and marked infiltration of neutrophils into the vaginal epithelia. Crucially, these neutrophils are frequently functionally impaired in the vagina, perpetuating inflammation and tissue damage [21,23]. Despite massive neutrophil recruitment to the vaginal mucosa during VVC, these cells fail to achieve fungal clearance while contributing to tissue damage and clinical symptoms [21,23].

1.4 Scope and Objectives

This review presents detailed mechanistic insights into the role of cytokine signalling in vaginal epithelia during *C. albicans* infection, highlighting the immunopathological basis of VVC. The following areas are addressed: VEC recognition of *C. albicans*, intracellular signalling cascades triggered upon PRR engagement, cytokines and chemokines produced by VECs, and downstream consequences of epithelial inflammatory programmes on mucosal immunopathology.

2 Fungal Virulence Determinants and Epithelial Recognition

2.1 Morphological Plasticity and Epithelial Discrimination

C. albicans is characterised by morphological plasticity and can exist in multiple forms: yeast (blastospores), pseudohyphae, or true hyphae, each with distinct biological properties and immunological consequences [24,25]. The transition from yeast to hyphae is induced by environmental factors such as temperature (37°C), neutral to alkaline pH, serum, CO_2, N-acetylglucosamine, and/or nutrient-related signals [25,26]. Yeast forms are linked to commensal colonisation, whereas hyphal forms are characterised by increased adhesion to epithelial surfaces, active penetration into host tissues, and potent induction of epithelial inflammatory responses [24,27].

In vitro studies demonstrate that VECs elicit far greater inflammatory responses to hyphal than to yeast forms of *C. albicans*, manifested by increased expression of IL-1α, IL-8, and GM-CSF, with IL-6 production being less pronounced, and corresponding activation of NF-κB and the MAPK pathway, including c-Fos (downstream of EGFR-ERK1/2) specifically induced by hyphal morphotypes [15,28]. This morphotype discrimination is mediated by differential PRR engagement, such that hyphal-specific structures (exposed β-glucans, altered mannan epitopes, and candidalysin) trigger a higher level of PRR signalling than yeast-associated PAMPs [12,15,28,29].

2.2 Key Virulence Factors

2.2.1 Adhesins

The Agglutinin-Like Sequence gene family encodes cell surface glycoproteins responsible for *C. albicans* adhesion to host cells and binding to extracellular matrix [30]. Agglutinin-like sequence 3 (ALS3) emerged as a multifunctional adhesin and invasin mediating binding to epithelial cells and stimulating endocytosis by engaging E-cadherin, N-cadherin, and epidermal growth factor receptor (EGFR) [31–33]. The interaction of ALS3 with host cell cadherins induces epithelial cell endocytosis and is associated with activation of EGFR and downstream MAPK signalling pathways [31,33,34].

2.3 Secreted Aspartyl Protease (SAP)

A family of 10 secreted aspartyl proteinases (SAP1–SAP10) secreted by *C. albicans* participates in tissue invasion, nutrient acquisition, immune evasion, and modulation of the host immune response [35]. SAP4–6, which share approximately 75–89% sequence homology, are expressed preferentially during hyphal growth and required for parenchymal organ invasion and SAP4–6 and related SAP family members modulate epithelial cytokine responses by inducing IL-1α and IL-8 while modulating TNF-α expression [10,35–37].

2.4 Candidalysin

Candidalysin is a cytolytic peptide toxin produced by the hyphal forms of *C. albicans* and has been recognised as the key proximal trigger of epithelial damage and inflammatory signalling in VVC [9,15]. This 31-amino-acid amphipathic α-helical peptide is encoded by the ECE1 gene and is released by sequential

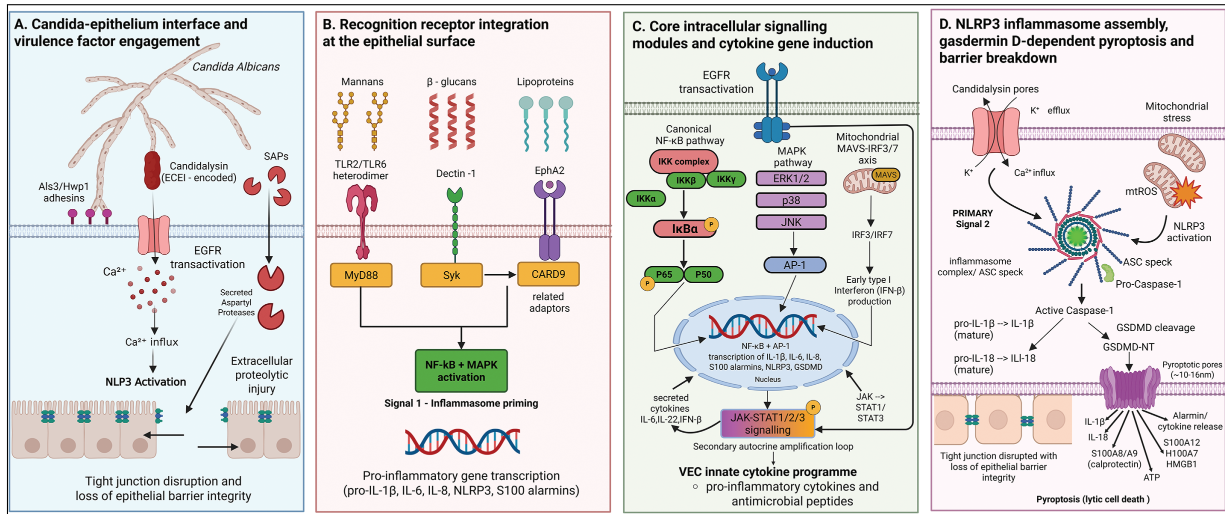

Figure 1: Sequential epithelial sensing and inflammasome activation in *Candida*-induced vaginal mucosal injury. (**A**) Hyphal *C. albicans* engages VECs via adhesins (e.g., Als1/3, Hwp1), SAPs, and the hypha-specific peptide toxin candidalysin. Candidalysin directly permeabilises the epithelial membrane, inducing EGFR transactivation via metalloprotease-mediated ligand shedding and initiating downstream damage responses, while SAPs mediate extracellular proteolytic injury. Together these virulence factors disrupt intercellular tight junctions and compromise epithelial barrier integrity. (**B**) Fungal cell-wall components i.e., mannans, β-glucans, and lipoproteins are recognised at the epithelial surface by pattern-recognition receptors including TLR2/TLR6 (signalling via MyD88) and C-type lectin receptors including Dectin-1 and EphA2 (signalling via Syk-CARD9 and related adaptors). These converge on NF-κB and MAPK activation, providing Signal 1 (priming) for downstream inflammasome-related gene transcription. (**C**) Intracellular signalling integrates canonical NF-κB (IKK-IκBα-p65/p50 nuclear translocation) and MAPK (ERK1/2, p38, JNK) cascades amplified by EGFR transactivation with a mitochondrial MAVS-IRF3/7 axis driving IFN-β production, and secondary autocrine JAK-STAT1/2/3 signalling. Together these pathways drive the VEC innate cytokine programme, inducing pro-inflammatory cytokines (IL-1β, IL-6, IL-8) and antimicrobial peptides. (**D**) Candidalysin-induced membrane pore formation, producing K^+ efflux and Ca^{2+} influx, together with mitochondria-associated NLRP3 activation (via mtROS and mitochondrial stress), provides Signal 2 and triggers NLRP3 inflammasome assembly, ASC speck oligomerisation, and caspase-1 activation. Caspase-1 cleaves GSDMD, whose N-terminal domain oligomerises to form pyroptotic pores (~10–16 nm) in the plasma membrane, driving lytic cell death (pyroptosis) and release of processed IL-1β, IL-18, S100 alarmins (A8/A9 calprotectin; A12, A7), HMGB1, and ATP, with concomitant disruption of tight junctions and loss of epithelial barrier integrity. (Created with BioRender). Note: EGFR: Epidermal Growth Factor Receptor; SAPs: Secreted Aspartyl Proteases; VECs: Vaginal Epithelial Cells; PAMPs: Pathogen-Associated Molecular Patterns; DC-SIGN: Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-integrin; MR: Mannose Receptor; EphA2: Ephrin Type-A Receptor 2; MyD88: Myeloid Differentiation Primary Response Protein 88; Syk: Spleen Tyrosine Kinase; CARD9: Caspase Recruitment Domain-Containing Protein 9; IKK: IκB Kinase Complex; IκBα: Inhibitor of Kappa-B Alpha; ERK1/2: Extracellular Signal-Regulated Kinases 1 and 2; JNK: c-Jun N-Terminal Kinase; MAVS: Mitochondrial Antiviral Signalling Protein; IRF3/7: Interferon Regulatory Factors 3 and 7; JAK: Janus Kinase; STAT: Signal Transducer and Activator of Transcription; ASC: Apoptosis-Associated Speck-Like Protein Containing a CARD; GSDMD: Gasdermin D; HMGB1: High Mobility Group Box 1.

proteolytic processing of the 271-amino-acid prepro-protein Ece1p: first by Kex2p at Arg61 and Arg93 to generate immature candidalysin, and then by Kex1p, which removes the C-terminal arginine to yield the mature 31-amino-acid toxin [15]. Candidalysin intercalates into epithelial cell membranes, forming pores that disrupt ionic homeostasis and cause calcium influx (*figure 1A*). This triggers cell lysis at high concentrations, or sublytic membrane damage at lower concentrations, activating the EGFR-MAPK danger response, whereby calcium influx drives Matrix Metalloproteinase activation, EGFR ligand shedding, EGFR phosphorylation, and ERK1/2-mediated c-Fos induction, while p38 independently promotes IL-6 release [15,38,39]. The paramount role of candidalysin in VVC immunopathology is confirmed by the severely reduced virulence of ece1Δ/Δ and candidalysin-specific mutant strains (ece1Δ/Δ + ECE1Δ184–279) in VVC models [9,15,40], and the sequential processes of epithelial interaction, pathogen recognition, intracellular signalling, and inflammasome activation are summarised in *figure 1*.

3 PRRs in VECs

3.1 *Toll-Like Receptors (TLR2/4/6)*

TLRs, as a major family of PRRs, enable VECs to recognise conserved structures on microbes (PAMPs) and initiate innate immune responses quickly [12,41]. TLR2, TLR4, and TLR6 have been most implicated in recognition of *C. albicans* [41–43]. TLR2 acts mainly as a heterodimer with either TLR1 or TLR6 and recognises a wide range of microbial lipoproteins, lipopeptides, and glycolipids. TLR2/TLR6 heterodimers recognise *C. albicans* phospholipomannan [41,43]. O-linked mannans are recognised by TLR4, while N-linked mannans are recognised by the mannose receptor [41]. Signalling pathways downstream of TLR activation travel mainly through the adaptor protein myeloid differentiation primary response protein 88 (MyD88), and recruit IL-1 receptor-associated kinase family kinases and TRAF6 to form complexes that activate the NF-κB and MAPK pathways to produce proinflammatory cytokines [12,44,45] (*figure 1B*). TLR4 is also able to signal through Toll/IL-1 receptor domain-containing adaptor-inducing interferon beta adaptor protein, leading to interferon regulatory factor 3 activation and

type I interferon production, the latter plays a role in antifungal host defence [41,44,46].

3.2 C-Type Lectin Receptors (Dectin-1, Dectin-2/3, MR)

CLRs represent a diverse family of PRRs that recognise carbohydrate structures on pathogens [47,48]. CLEC7A specifically recognises β-1,3-glucans [49,50]. Dectin-1 contains a single tyrosine residue within its cytoplasmic tail that constitutes a hemITAM motif, which recruits spleen tyrosine kinase (Syk) upon receptor clustering, thereby initiating downstream signalling cascades [51–53]. Syk-dependent signalling induced by Dectin-1 is mediated by CARD9-dependent signalling involving caspase recruitment domain-containing protein 9–B-cell lymphoma/leukaemia 10–mucosa-associated lymphoid tissue lymphoma translocation protein 1 (CARD9–BCL10–MALT1) complex, which activates NF-κB via a pathway distinct from MyD88-dependent TLR pathways [52,54]. *CARD9* gene deficiency in human is primarily associated with systemic fungal infections including central nervous system candidiasis [55–57]. In addition to Dectin-1, CLRs including Dectin-2, Dectin-3, and mannose receptor (CD206) contribute to innate immune recognition of *C. albicans* primarily through myeloid cell populations such as macrophages and dendritic cells, via recognition of specific carbohydrate epitopes (*figure 1B*) [47,58,59]. Integration of CLR signalling and TLR pathways enables amplified inflammatory responses to *Candida* spp. [12,48,60,61].

3.3 NLRs and NLRP3 Inflammasome

NLRs are intracellular PRRs that recognise PAMPs and DAMPs and are central to inflammasome activation and production of inflammatory cytokines [14,62]. NLRP3 inflammasome is a tripartite protein complex comprising a sensor, an adaptor protein (apoptosis-associated speck-like protein containing a CARD, encoded by the gene PYCARD), and an effector (pro-caspase-1), that assembles in response to cellular stresses such as potassium efflux, mitochondrial dysfunction, lysosomal damage, and reactive oxygen species generation [62–64]. Activation leads to NF-κB-induced transcription of NLRP3 and pro-IL-1β, and also formation of the inflammasome and caspase-1 activation [62,65]. During *C. albicans* infection, NF-κB–mediated transcription of NLRP3 and pro-IL-1β is conferred by PRR engagement, while inflammasome assembly and caspase-1 activation are driven by infection-induced cellular stress, with hyphal growth and candidalysin being important signalling triggers [16,65,66]. The consequences of NLRP3 inflammasome activation also include pyroptosis—an inflammatory form of programmed cell death mediated by caspase-1-dependent cleavage of gasdermin D (GSDMD), which liberates the N-terminal GSDMD domain to oligomerise and form membrane pores, resulting in plasma membrane rupture and release of intracellular contents [67,68].

4 Core Intracellular Signalling Modules

4.1 NF-κB Signalling in VECs

NF-κB is a central family of transcription factors that regulate expression of proinflammatory cytokines, chemokines, adhesion molecules, and antimicrobial peptides during mucosal responses against *C. albicans* [28,69,70]. The NF-κB family consists of five structurally related proteins—RelA (p65), RelB, c-Rel, p50 (NF-κB1), and p52 (NF-κB2), which exist in homo- and heterodimers that regulate different gene programmes [70,71]. NF-κB dimers are retained in the cytoplasm through interaction with IκB proteins. Phosphorylation and subsequent degradation of IκB by the inhibitor of kappa B kinase (IKK) complex allows NF-κB nuclear translocation and transcriptional activation of target genes [71,72]. Upon PRR engagement by *C. albicans* (via PRRs such as TLRs and CLRs), upstream adaptor molecules such as MyD88, tumour necrosis factor receptor-associated factor 6, and transforming growth factor beta-activated kinase 1 activate the IKK complex, composed of IKKγ (κB essential modulator) and the catalytic subunits IKKα and IKKβ [70–72]. Activated IKK results in phosphorylation and degradation of IκB proteins, allowing NF-κB dimers to translocate to the nucleus and bind κB enhancer elements in promoters of inflammatory genes [72,73]. The canonical NF-κB pathway, involving IκBα degradation and activation of the p65/p50 heterodimer, is induced rapidly within minutes of exposure to *C. albicans*, contributing to initial expression of genes such as IL-1β, IL-6, IL-8, and chemokines that promote recruitment of neutrophils [28,70,73,74].

4.2 MAPK Pathways and EGFR Transactivation

MAPK signalling cascades function in parallel to NF-κB in epithelial cells and are activated in response to *C. albicans*, contributing to transcriptional regulation of inflammatory genes, and epithelial responses to stress and damage [15,28]. The three major families of MAPK i.e., ERK1/2, p38, and c-Jun N-terminal kinase are activated through a tiered phosphorylation cascade (MAP3K → MAP2K → MAPK) with different upstream activators, substrate specificities, and functional consequences [75–77].

In epithelial cells infected with *C. albicans*, MAPK activation is driven by direct PRR engagement, hypha-associated damage, and EGFR transactivation [12,15,28,38]. Candidalysin-induced membrane injury triggers both ligand-dependent and ligand-independent EGFR activation: the former via calcium influx followed by matrix metalloproteinase-mediated EGFR ligand (epiregulin, epigen) shedding; the latter via Src-mediated EGFR phosphorylation. The p38 pathway is activated by MAPK 3/6 and Src independently of EGFR, driving IL-6 release, while the EGFR-ERK pathway mediates c-Fos activation and neutrophil-activating chemokine production [38]. Transactivated EGFR thus acts as an upstream central signalling hub integrating fungal and damage signals to promote ERK1/2, p38, and phosphoinositide 3-kinase–protein kinase B activation (*figure 1C*),

collectively leading to transcription of inflammatory genes that maintain epithelial barrier function (*figure 1C*) [15,38,78,79]. Epithelial cells coordinate a biphasic response to *C. albicans*: an early phase marked by c-Jun activation and morphology-independent NF-κB/MAPK signalling, and a late phase characterised by MAPK phosphatase 1 induction and c-Fos activation, dependent on hyphal formation and fungal burden, and strongly associated with proinflammatory and damage-associated responses [28,80].

4.3 Type I Interferon Signal Module

Type I interferons contribute to early antifungal responses in VECs against *C. albicans* [8,11,81]. Type I interferon signalling in epithelial cells is coordinated by mitochondria-associated pathways with mitochondrial antiviral signalling protein on the outer mitochondrial membrane functioning as a key adaptor downstream of cytosolic RNA sensors such as retinoic acid-inducible gene I and melanoma differentiation-associated protein 5. Nevertheless, the precise upstream sensors and mechanisms driving this pathway during *C. albicans* infection in VECs remain to be fully identified [12,81,82]. Upon mitochondrial antiviral signalling protein activation, tumour necrosis factor receptor-associated factor 3 and TANK-binding kinase 1 are recruited to form signalling complexes that phosphorylate interferon regulatory factor 3/7 where the latter emerges as the predominant transcription factor induced in epithelial cells during *C. albicans* infection. Interferon regulatory factor 7 subsequently dimerises, translocates into the nucleus, and binds interferon-stimulated response elements in promoters of type I interferon genes and interferon-stimulated genes [44]. Functionally, epithelial type I interferon responses include both antifungal and immunomodulatory effects. However, the role of type I interferon in VVC pathogenesis is less well characterised than other pathways, and further studies are warranted [8,81,83,84].

4.4 JAK-STAT Signalling

JAK-STAT signalling is a core membrane-to-nucleus pathway triggered downstream of cytokine receptors involved in autocrine and paracrine enhancement of inflammatory and barrier responses during mucosal *Candida* infections [85,86]. The pathway is initiated following cytokine (e.g., IL-6, type I interferons, IL-10, or IL-22) binding to their respective receptors, leading to receptor dimerisation and trans-phosphorylation of associated Janus kinase family kinases (JAK1, JAK2, JAK3, TYK2), which phosphorylate tyrosine residues on receptor cytoplasmic tails to generate docking sites for STAT proteins [86]. Recruited signal transducer and activator of transcription proteins are then phosphorylated, dimerise, translocate to the nucleus, and bind defined promoter elements to regulate transcription of immune effector genes, feedback regulators, and barrier proteins. In epithelial responses to *C. albicans*, notable JAK-STAT modules include IL-6/IL-22/IL-10-activated signal transducer and activator of transcription 3 module, type I and type II interferon-activated signal transducer and activator of transcription 1 module, and signal transducer and activator of transcription 5, involved in downstream cytokine and growth factor signalling [18,86,87]. Signal transducer and activator of transcription 3 activation has a complex role in mucosal immunity, promoting epithelial regeneration, modulating inflammatory cytokines, and mediating responses to IL-22, which is important for antimicrobial peptide (AMP) production and mucosal barrier reinforcement [17,88]. IL-22 is mainly produced by innate lymphoid cell group 3 and T helper 17 cells and signals through IL-22 receptor on epithelial cells, activating JAK1 and TYK2 and phosphorylating signal transducer and activator of transcription 3, driving expression of β-defensin proteins, S100 proteins, and regenerative programmes [18,88]. While T helper 17 responses are crucial for mucosal antifungal immunity, their overactivation can drive immunopathological effects, influenced by fungal load, epithelial damage signals, and the cytokine milieu [5,89]. Signal transducer and activator of transcription 1 activation through interferon signalling promotes epithelial antifungal defence while IL-6 released during *C. albicans* infection can act in autocrine or paracrine fashion to amplify inflammatory signalling through JAK/STAT3, creating positive feedback loops that perpetuate inflammation [81,90,91].

5 Epithelial Cytokines and Chemokines Secretion

5.1 IL-1 Family Cytokines: IL-1α and IL-1β

Owing to their proinflammatory properties, IL-1α and IL-1β are a critical node in the immunopathology of VVC, driving epithelial cytokine responses, neutrophil recruitment, and tissue damage (*figure 2*) [92,93].

IL-1α is constitutively expressed in the VECs and is stored as a biologically active precursor in the cytoplasm and nucleus. Upon cellular damage or stress as mediated by candidalysin, i.e., membrane perturbation or pyroptosis, IL-1α is released as an alarmin which acts as a danger signal to trigger rapid inflammatory responses [9,94,95]. IL-1β, by contrast, is synthesised as an inactive pro-IL-1β in response to NF-κB-dependent transcriptional upregulation and requires proteolytic processing by caspase-1 in the NLRP3 inflammasome complex for activation (*figure 2A*) [92,93,96]. This two-step activation ensures that the release of IL-1β is controlled and occurs following cellular stress induced by candidalysin [16,92,97].

Both IL-1α and IL-1β signal via IL-1 receptor type 1 and recruit the adaptor protein MyD88, which leads to NF-κB and MAPK pathway activation and amplifies the response to inflammatory cytokines in an autocrine and paracrine manner [92,93,98]. Elevated levels of IL-1β are strongly correlated with symptomatic disease, where inflammasome-deficient mice (Nlrp3−/− or caspase-1−/−) were found to have attenuated neutrophil infiltration and less severe VVC [14,99,100]. IL-1 receptor antagonist is an endogenous competitive inhibitor of IL-1 receptor type 1 and a natural constraint on the downstream proinflammatory effects of IL-1 and its dysregulation predisposes to RVVC [92,101].

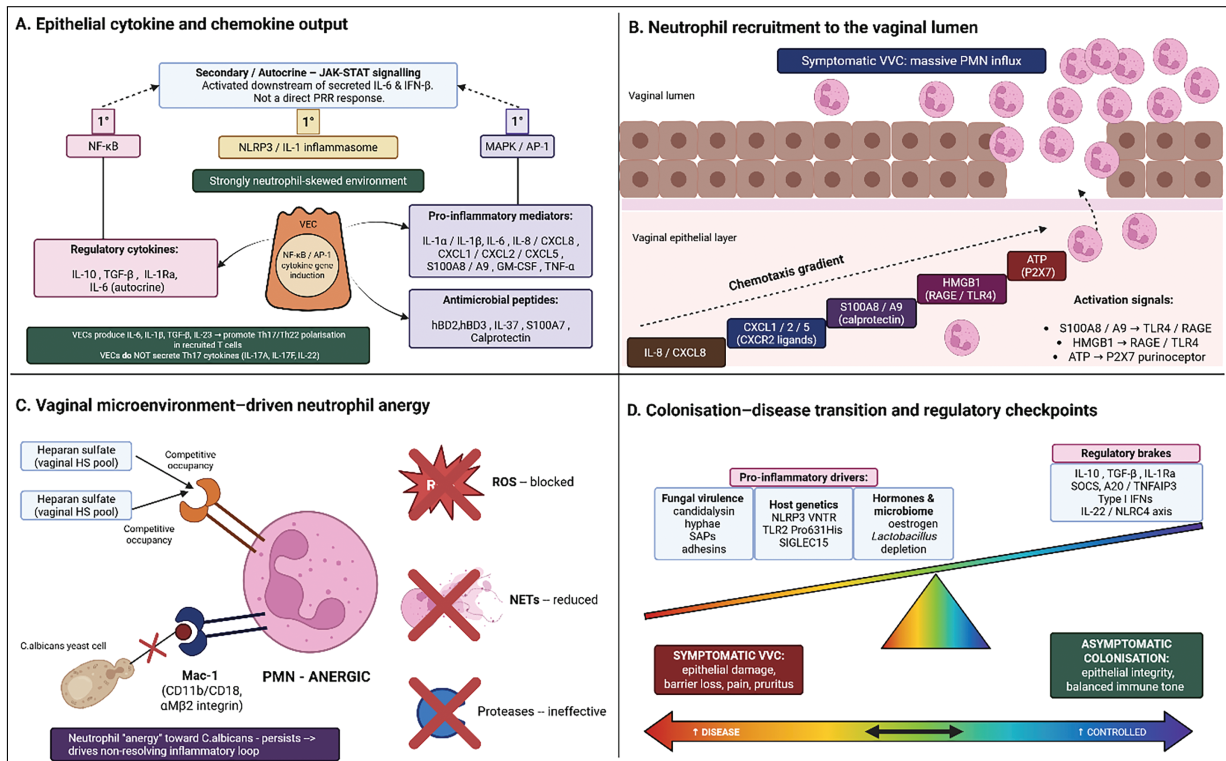

Figure 2: Epithelial cytokines, neutrophil recruitment, anergy, and immunopathology in VVC. (**A**) VECs integrate NF-κB and MAPK/AP-1 as primary signalling modules, together with NLRP3/IL-1 inflammasome activation, to produce pro-inflammatory cytokines (IL-1α/β, IL-6, IL-8/CXCL8, CXCL1/2/5), alarmins (S100A8/A9), and antimicrobial peptides. A mitochondrial MAVS-IRF3/7 axis drives secondary type I IFN production. JAK-STAT functions as a secondary autocrine amplification loop downstream of secreted IL-6 and IFNs—not a primary PRR-driven module. The resulting cytokine milieu promotes Th17/Th22 polarisation of recruited T cells; VECs themselves do not secrete Th17/Th22 cytokines. Regulatory outputs include IL-10 and TGF-β. (**B**) Chemokines and alarmins drive CXCR1/CXCR2-mediated neutrophil recruitment into the vaginal lumen and lamina propria, resulting in massive neutrophil influx during symptomatic VVC. (**C**) Vaginal microenvironmental factors, including heparan sulfate and pANCA, induce neutrophil anergy by competitively occupying Mac-1 (CD11b/CD18), blocking Mac-1-Pra1p interaction and downstream antifungal signalling (reactive oxygen species, NETs, proteases). (**D**) The transition from asymptomatic colonisation to immunopathology is controlled by fungal virulence, host genetics, hormonal status, and microbiome composition. Pro-inflammatory mediators exceed regulatory brakes—including IL-10, TGF-β, IL-1Ra, SOCS, and A20 (TNFAIP3)—to drive a self-sustaining neutrophil-rich loop and epithelial barrier disruption. (Created with BioRender). Note: VECs: Vaginal Epithelial Cells; VVC: Vulvovaginal candidiasis; CXCL1/2/5: C-X-C Motif Chemokine Ligands 1, 2 and 5; Th17/Th22 polarisation: Differentiation of recruited T cells towards T Helper 17 and T Helper 22 lineages; Pra1p: pH-Regulated Antigen 1 Protein of *C. albicans*; IL-1Ra: Interleukin-1 Receptor Antagonist; A20/TNFAIP3: Tumour Necrosis Factor Alpha-Induced Protein 3.

5.2 IL-8 (Chemokine (C-X-C Motif) Ligand 8) and Neutrophil Chemotaxis

IL-8 (CXCL8) is a prototypical CXC chemokine and is one of the most abundant chemokines secreted by VECs in response to *C. albicans* [13,28]. IL-8 acts as an effective chemoattractant for neutrophils (*figure 2B*) where it is bound to receptors CXCR1 and CXCR2 on neutrophil surface, causing actin polymerisation, directional migration, and extravasation to the infected tissue [102–104]. The production of IL-8 in VECs is dependent on NF-κB and MAPK signalling, where hyphal forms of *C. albicans* and candidalysin are effective inducers [15,28]. Time-course experiments show the peak of IL-8 secretion at 6–24 h upon hyphae exposure to epithelial cells, concomitant with the appearance of neutrophils in the vaginal lumen [5,28]. Despite the critical role of IL-8 in orchestrating neutrophil recruitment, one of the neutrophil paradoxes in women with VVC is that these recruited neutrophils are functionally anergic in the vaginal microenvironment, failing to eliminate *C. albicans* while promoting tissue destruction through the release of reactive oxygen species, myeloperoxidase, and proteases [23,105]. There is a positive correlation between high levels of IL-8 in the vagina of affected patients and severity of symptoms, highlighting the importance of IL-8 as a biomarker and pathogenic mediator of VVC immunopathology [5,21,106].

5.3 S100 Alarmins (S100A8, S100A9, S100A8/A9)

S100 calcium-binding proteins, in particular S100A8 (calgranulin A; MRP8), S100A9 (calgranulin B; MRP14), and the S100A8/A9 heterodimer (calprotectin) are some of the most dramatically upregulated proteins in symptomatic VVC, and are key alarmins bridging epithelial damage and neutrophil-mediated immunopathology [21,107,108]. S100A8 and S100A9 are constitutively and abundantly expressed in neutrophils and monocytes, where they comprise approximately 40–45% of cytosolic protein [109,110]. These proteins can be induced in VECs and other non-myeloid cells in response to inflammatory stimuli and *C. albicans* infection through NF-κB and MAPK-dependent signalling pathways. Upon cellular damage or stress (e.g., candidalysin exposure), S100A8/A9 is released into the

extracellular space, where it acts as a DAMP [107,111]. Extracellular S100A8/A9 activates TLR4 and RAGE (*figure 2B*) on neutrophils, macrophages, and epithelial cells, driving proinflammatory signalling in a feed-forward manner, which results in further cytokine production [107,112]. In the vagina, S100A8/A9 also has antimicrobial effects due to metal sequestration primarily chelation of zinc and manganese, with calcium-dependent iron chelation, depriving *C. albicans* of needed nutrients [113,114]. However, despite these antimicrobial properties, the predominant effect of S100A8/A9 in VVC is pathogenic, with high levels strongly associated with neutrophil infiltration, mucosal inflammation, and clinical symptoms [21]. Importantly, S100A8/A9 is the most robust biomarker distinguishing symptomatic VVC from asymptomatic colonisation, with levels several orders of magnitude higher in the vagina of symptomatic women [21,23,115].

5.4 *GM-CSF, TNF-α, IL-6, and Other Cytokines*

GM-CSF, also referred to as colony-stimulating factor 2, is released by VECs following exposure to *C. albicans*. This factor plays a crucial role in priming neutrophils and macrophages, as well as in the processes of epithelial repair and regeneration [5,116]. In response to *C. albicans* infection, TNF-α is produced by VECs and resident immune cells, which heightens inflammatory signalling through the activation of NF-κB and MAPK pathways via tumour necrosis factor receptors 1 and 2. Tumour necrosis factor receptor 1 can also engage apoptotic caspase signalling via TRADD/FADD/caspase-8 under specific conditions [117]. *In vitro* experiments involving human VECs co-cultured with *C. albicans* reveal detectable inflammatory cytokine responses, though IL-1 family cytokines appear to be less pronounced under similar conditions, suggesting a modulatory rather than primary role in VVC pathogenesis [118]. IL-6 is another cytokine involved in the acute-phase response (*figure 2A*) that activates STAT3, facilitates B-cell differentiation, promotes acute-phase protein synthesis, and drives T helper 17 polarisation [90,119,120].

5.5 *Antimicrobial Peptides and Defensins*

AMPs are an essential component of epithelial innate immunity, exerting direct antimicrobial activity and immunomodulatory effects [121]. In the vaginal mucosa, important AMPs include β-defensins (hBD1, hBD2, hBD3), cathelicidin (LL-37), secretory leukocyte protease inhibitor and elafin [15,122,123]. Human β-defensin 2 (hBD2) is specifically induced in VECs following exposure to *C. albicans* hyphae and candidalysin, mediated by NF-κB and MAPK signal transduction pathways [15]. hBD2 shows antifungal activity by disrupting the fungal membrane and is a chemoattractant for immature dendritic cells and memory T cells through CCR6, playing an important role in connecting innate and adaptive immunity [124,125]. Cathelicidin (LL-37) is stimulated by vitamin D and inflammatory cues and has direct candidacidal action as well as a range of immunomodulatory effects, such as augmentation of chemokine production and modulation of TLR responses [126,127]. However, the overall contribution of AMPs in limiting *Candida* in the vaginal environment is complex, as *C. albicans* has developed mechanisms to resist or evade AMP killing, such as modulation of cell-surface charge, efflux pumps, and protease-mediated degradation [128–131].

6 The NLRP3 Inflammasome in VVC Immunopathology

6.1 *Inflammasome Assembly and Activation of Caspase-1*

The NLRP3 inflammasome plays a central role in driving the immunopathology in VVC by integrating multiple signals from *C. albicans* and VEC damage [14,16,99]. NLRP3 inflammasome assembly occurs based on canonical two-signal model [62,132]. The first signal includes engagement of PRRs, including TLRs and CLRs, by *C. albicans* PAMPs. This engagement activates NF-κB, driving transcriptional upregulation of NLRP3, pro-IL-1β, and pro-IL-18. This priming step also results in post-translational modifications of NLRP3, such as deubiquitination [62,133–135].

The second signal is triggered by several different cellular stress signals such as potassium efflux, calcium influx, mitochondrial reactive oxygen species, mitochondrial DNA release, and lysosomal damage which cause NLRP3 to oligomerise and recruit the adaptor protein ASC through homotypic pyrin domain interactions [65,136]. ASC then nucleates the recruitment and activation of pro-caspase-1 by caspase recruitment domain interactions, creating a large multimeric complex. Auto-proteolytic cleavage generates active caspase-1 (p20/p10 heterotetramer) which then cleaves pro-IL-1β and pro-IL-18 into their active forms (*figure 1D*) [137,138]. In addition to cytokine maturation, active caspase-1 cleaves GSDMD at a specific aspartate residue in humans, releasing the N-terminal pore-forming domain, which forms oligomers in the plasma membrane to create large pores of approximately 10–16 nm in diameter, thereby causing pyroptosis, an inflammatory lytic cell death involving rupture of the plasma membrane with subsequent release of intracellular contents, including interleukin-1α (IL-1α), IL-1β, IL-18, S100 alarmins, and ATP [67,68,139–141].

6.2 *Candidalysin for NLRP3 Activation*

Candidalysin has also been shown to be involved in activating the NLRP3 inflammasome in VECs during *C. albicans* infection [9,16,97]. Mechanistically, candidalysin creates pores in the epithelial cell membranes, causing ionic dysregulation, namely K^+ efflux and Ca^{2+} influx, both strongly activates NLRP3 [16,65,142]. Candidalysin-induced membrane damage also leads to mitochondrial stress, such as mitochondrial depolarisation, mitochondrial fragmentation, generation of mitochondrial reactive oxygen species, and release of mitochondrial DNA to the cytosol, where it can act as inflammasome activator [16,143,144].

Experiments based on candidalysin-deficient *C. albicans* strains (ece1Δ/Δ or ece1Δ/Δ + ECE1Δ184–279) demonstrate dramatically reduced IL-1β secretion, caspase-1 activation, and pyroptosis in VECs, confirming the central role of candidalysin [15,16]. *In vitro* models demonstrate that synthetic candidalysin peptide alone is sufficient to trigger activation of the NLRP3 inflammasome in primed cells, mimicking the effects of *Candida* hyphal infection [16,40].

6.3 Pyroptosis and Disruption of the Vaginal Epithelial Barrier

Pyroptosis is a caspase-1/GSDMD-dependent inflammatory cell death pathway that acts as a host defence mechanism, by removing infected cells from the body and releasing alarmins, as well as driving immunopathology, through tissue damage and uncontrolled inflammation [67,68]. In VVC, pyroptotic death of VECs exacerbates the severity of the disease. The death of these cells results in the release of mature IL-1β and IL-18, which enhance inflammatory signalling throughout the vaginal mucosa. Simultaneously, the release of IL-1α, S100 alarmins, ATP, and High Mobility Group Box 1, all classified as damage-associated molecular patterns or DAMPs, further activate the surrounding epithelial and immune cells, causing a self-perpetuating inflammatory cascade. Pyroptosis also affects the integrity of epithelial barriers, which promotes deeper penetration of fungi and augments the cycle of infection and inflammation [9,97]. The mediators released during pyroptotic cell death lead to the recruitment and activation of neutrophils, which exacerbates immunopathology [105,145]. Pharmacological inhibition of caspase-1 in experimental models of VVC reduces the severity, mucosal inflammation, and neutrophil infiltration, without substantially reducing fungal clearance [14,99].

7 The Neutrophil Paradox in VVC

7.1 Neutrophil Recruitment and Functional Anergy

A hallmark of symptomatic VVC is massive neutrophil infiltration into the vaginal lumen (*figure 2B*), driven by epithelial-derived chemokines (IL-8) and alarmins (S100A8/A9, IL-1 family) [105]. However, despite overwhelming neutrophil recruitment, these cells exhibit functional anergy (*figure 2C*), characterised by impaired candidacidal activity and reduced antifungal effector functions, resulting in ineffective clearance of *C. albicans* [23,105]. This neutrophil paradox explains why high fungal burdens persist despite intense inflammation. Several vaginal microenvironmental factors have been attributed to this functional impairment. Mechanistic investigations indicate that neutrophil anergy in VVC is, in part, influenced by the disruption of macrophage antigen-1 (CD11b/CD18), a β2 integrin essential for recognising and adhering to fungi and facilitating phagocytosis. Components within vaginal fluid, including perinuclear anti-neutrophil cytoplasmic antibodies and soluble heparan sulfate, act via distinct mechanisms: heparan sulfate acts as a competitive ligand (*figure 2C*) that occupies macrophage antigen-1 binding site, directly blocking the interaction of macrophage antigen-1 on neutrophils with *C. albicans* surface protein Pra1p and thereby preventing Pra1-mediated fungal killing while perinuclear anti-neutrophil cytoplasmic antibodies independently impair candidacidal activity [23,105]. This interference impairs neutrophil-*Candida* interactions and compromises antifungal effector functions, ultimately rendering neutrophils functionally inactive despite significant recruitment. As a result, neutrophils primarily contribute to tissue inflammation rather than effective fungal clearance [23,105]. Hormonal influences, particularly oestrogen, modulate the vaginal immune environment and are associated with altered host defence responses, which may contribute to reduced antifungal activity during VVC [146]. Metabolic constraints imposed by the lactate-rich vaginal fluid may limit the glycolytic capacity of neutrophils, though this requires further investigation. Also, chronic exposure to elevated concentrations of S100 alarmins, specifically S100A8/A9, may induce TLR tolerance or neutrophil exhaustion [23]. Functionally anergic neutrophils still release inflammatory mediators including reactive oxygen species, myeloperoxidase, elastase, and matrix metalloproteases that contribute to epithelial damage, barrier disruption, and symptom generation without effectively eliminating *C. albicans* [105,145]. This dissociation between neutrophil recruitment and antifungal efficacy represents a critical target for therapeutic intervention in VVC.

7.2 NETosis and Extracellular Traps

Neutrophil extracellular traps (NETs) are web-like structures composed of decondensed chromatin (DNA and histones) decorated with antimicrobial proteins, including myeloperoxidase, elastase, and cathepsin G, released by activated neutrophils through the process of NETosis. *In vitro*, NETs can trap and kill *C. albicans*, including immobilising fungal hyphae [147,148]. However, in the vaginal environment, NET formation can be attenuated or dysfunctional, consistent with the functionally anergic phenotype of VVC-associated neutrophils [23]. Moreover, excessive and/or dysregulated NETosis may contribute to tissue damage and chronic inflammation, through the release of histones and proteases that directly damage VECs [149,150]. The role of NETs in VVC pathogenesis whether protective, neutral, pathogenic, or context-dependent remains to be elucidated [151].

8 Hormonal Regulation of Epithelial Immunity

8.1 Oestrogen and Epithelial Activation Thresholds

17β-oestradiol (E2) is a critical hormonal regulator of VEC physiology and immune responsiveness, and fluctuations in oestrogen levels are strongly associated with VVC susceptibility [146]. Elevated oestrogen such as during pregnancy, oral contraceptive use, or during the follicular phase of the menstrual cycle enhances glycogen deposition in VECs, which is processed by

Lactobacillus spp. amylases into fermentable oligomers that are then used to produce lactic acid, maintaining acidic pH [152–154]. Paradoxically, glycogen can also serve as a nutrient source for *C. albicans*, supporting fungal proliferation [152]. This dual effect creates a microenvironment that simultaneously maintains vaginal health through acidification while providing substrates that can promote fungal growth under certain conditions.

Beyond metabolic effects, oestrogen directly modulates epithelial immune signalling. Oestrogen binds to intracellular oestrogen receptors (ERα and ERβ), which translocate to the nucleus and regulate transcription of genes involved in barrier function, cytokine production, and PRR expression [146,155]. The role of oestrogen in the inflammatory response to *C. albicans* is complex: oestrogen signalling via ERα in VECs appears to suppress baseline IL-1β and IL-8 expression, yet the oestrogenised state maintains *Candida* colonisation and the conditions required which include glycogen availability which support hyphal growth and ultimately the cascading inflammatory response [146,155]. Ovariectomised mice treated with oestrogen receptor antagonists show reduced VVC susceptibility [155]. The mechanisms by which oestrogen amplifies epithelial cytokine signalling likely involve enhanced PRR expression including TLR2 and Dectin-1 and potentiation of NF-κB and MAPK pathways. Whether oestrogen directly upregulates inflammasome components such as NLRP3 in VECs remains to be elucidated and warrants further investigation. Additionally, altered epithelial barrier under oestrogen influence may also facilitate fungal adherence and invasion and contribute to the increased susceptibility to VVC during high oestrogen states.

8.2 Progesterone and Immunomodulation

Progesterone, whose levels peak during the luteal phase and are sustained during pregnancy, exerts immunosuppressive and anti-inflammatory effects on mucosal immunity, and generally opposes oestrogen's pro-inflammatory actions [156,157]. Progesterone modulates immune-related gene expression through progesterone receptor signalling [146]. Functionally, progesterone reduces epithelial cytokine production including IL-8 and TNF-α, suppresses neutrophil recruitment and activation, and enhances regulatory T cell activity, promoting immune tolerance. Progesterone may also influence vaginal microbiome composition, though the relationship is complex: combined elevated oestrogen and progesterone, as during pregnancy, is associated with increased *Lactobacillus* dominance, whereas progestin-only contraceptives may reduce *Lactobacillus* abundance [146,157]. The balance between oestrogen and progesterone signalling thus determines the net inflammatory milieu in the vaginal mucosa and influences susceptibility to VVC [146,157].

9 Microbiome and Immunological Cross-Talk

9.1 Lactobacillus and Colonisation Resistance

The healthy vaginal microbiome is typically dominated by Lactobacillus species (e.g., *L. crispatus*, *L. iners*, *L. jensenii*, and *L. gasseri*), which provide colonisation resistance against *C. albicans* through multiple mechanisms [158,159]. Key protective mechanisms include lactic acid production, which maintains acidic pH (4.0–4.5), inhibiting fungal growth and hyphal morphogenesis [154,160,161]. *Lactobacillus* species also provide competitive exclusion by occupying epithelial binding sites and consuming nutrients and produce antimicrobial compounds including hydrogen peroxide, bacteriocins, and biosurfactants [152,162], and immunomodulation where lactobacilli dampen epithelial inflammatory responses, reducing excessive cytokine production and maintaining immune homeostasis [163]. Disruption of Lactobacillus dominance due to antibiotics, douching, or dysbiosis removes these protective barriers, permitting *C. albicans* overgrowth and increasing VVC risk [120,164].

9.2 Bacterial Vaginosis (BV) and Fungal Co-Infection

Bacterial vaginosis (BV), characterised by depletion of Lactobacillus and overgrowth of anaerobic bacteria (e.g., *Gardnerella vaginalis*, *Prevotella* sp., *Fannyhessea vaginae*), is associated with increased susceptibility to *C. albicans* colonisation, though the relationship between BV and VVC is complex and bidirectional [2,158,165]. BV-associated bacteria produce metabolites (e.g., short-chain fatty acids and biogenic amines) that alter vaginal pH and immune tolerance, potentially promoting fungal growth [165,166]. Conversely, antifungal treatments may disrupt residual lactobacilli, increasing BV risk [2].

9.3 Microbial Metabolites and PRR Modulation

Emerging research suggests that microbial metabolites, including lactate, short-chain fatty acids, tryptophan derivatives, and quorum-sensing molecules, can directly influence epithelial PRR signalling and inflammatory responses [167–169]. For instance, lactate generated by lactobacilli may activate G protein-coupled receptor 81 on epithelial cells, which in turn can attenuate NF-κB activation and decrease the production of pro-inflammatory cytokines, a mechanism that resembles that of the intestinal epithelium [170,171]. Also, indole metabolites produced by Lactobacillus species, notably indole-3-aldehyde, stimulate the aryl hydrocarbon receptor, driving aryl hydrocarbon receptor-dependent IL-22 transcription that provides colonisation resistance to *C. albicans* and mucosal protection from inflammation; short-chain fatty acids can reduce fungal filamentation and colonisation [167,172,173].

10 Colonisation Versus Disease: Determinants and Thresholds

10.1 Fungal Factors: Strain Variation and Candidalysin Expression

Not all *C. albicans* strains are equally virulent or capable of causing symptomatic VVC. Strain-specific differences in candidalysin expression, hyphal morphogenesis, adhesin repertoires, and SAP production influence disease outcomes [9,15]. Clinical isolates from

symptomatic VVC patients exhibit higher candidalysin expression and greater capacity for epithelial damage compared to commensal isolates [9]. Moreover, mutations or polymorphisms in ECE1 that reduce candidalysin production are associated with asymptomatic colonisation [9]. These findings support a virulence threshold model (*figure 2D*), wherein high candidalysin-expressing strains exceed epithelial tolerance thresholds, triggering inflammasome activation, which in turn triggers excessive cytokine production [9,15,174].

10.2 Host Factors: Genetic, Hormonal, and Immune Determinants

Host vulnerability to VVC is influenced by a combination of genetic, hormonal, and immune factors. Variations in genes related to inflammasome components like NLRP3 [175] have been linked to susceptibility to RVVC, while the NLRP3 variable number tandem repeat polymorphism (12/9 genotype) is associated with elevated vaginal IL-1β production. Among PRR genes, the most established association with RVVC is a non-synonymous polymorphism in TLR2 (Pro631His, rs5743704), which increases susceptibility nearly threefold [176]. Mannose-binding lectin 2 polymorphisms have also been consistently linked to RVVC where these genetic abnormalities impact the activation of epithelial inflammasomes, cytokine production, and neutrophil activity [55,175,177].

Elevated oestrogen promotes VVC susceptibility principally through metabolic and physical epithelial conditioning (i.e., glycogen deposition, epithelial thickening, and facilitation of fungal adherence and hyphal growth) rather than through direct upregulation of inflammatory cytokines [155]. Also, baseline priming of epithelial cells, microbiome composition, and the functional ability of neutrophils further influence disease outcomes [105]. Together, fungal virulence, host genetic makeup, hormonal environment, immune response capabilities, and microbiome health ultimately determine whether colonisation leads to symptomatic VVC (*figure 2D*).

11 Therapeutic Implications and Future Directions

11.1 Limitations of Conventional Antifungal Therapy

Current standard treatment for VVC involves topical or oral azole antifungals (e.g., fluconazole and clotrimazole) that target fungal ergosterol biosynthesis [2,178]. While generally effective for acute episodes, antifungal therapy has several important limitations. Less than half of women with recurrent VVC remained disease-free at 12 months after stopping antifungal therapy, indicating that the majority experienced recurrence [179]. A clinical trial demonstrated that 57.1% of patients relapsed by 12 months, and real-world cohort studies reporting relapse rates of 60–80% [180]. Fungal resistance is increasing with azole resistance [166,181]. Microbiome disruption: antifungal treatments may further deplete protective Lactobacillus species, perpetuating dysbiosis and potentially compromising vaginal microbial balance [182]. There is a failure to address immunopathology, since antifungals reduce fungal burden but do not modulate the dysregulated epithelial inflammatory response that drives the symptoms [15].

11.2 Immunomodulatory Strategies

Given the immunopathological basis of VVC, immunomodulatory therapies targeting epithelial cytokine signalling represent promising adjunctive or alternative approaches. IL-1 blockade via inhibition of IL-1 signalling using anakinra, a recombinant IL-1 receptor antagonist or canakinumab, an anti–IL-1β monoclonal antibody may reduce inflammasome-driven immunopathology without impairing fungal clearance [92]. Pre-clinical studies in VVC models support this approach [99]. NLRP3 inflammasome inhibitors, including small-molecule compounds such as MCC950, a potent, selective diarylsulfonylurea inhibitor that targets the NLRP3 NACHT domain and blocks both canonical and non-canonical inflammasome activation [183] represent a further promising preclinical strategy. Their applicability to VVC is supported by the established role of NLRP3 in VVC-associated immunopathology where NLRP3 inhibition reduces disease severity without impairing fungal clearance in murine models [14,99,184].

11.3 Microbiome-Based Therapies

Restoration and maintenance of a protective Lactobacillus-dominated vaginal microbiome represent a rational, mechanism-based therapeutic strategy. Oral or intravaginal administration of *L. crispatus* (a vaginal-native dominant species) and/or *L. rhamnosus* GR-1 together with *L. reuteri* RC-14 (an established probiotic combination with randomised controlled trial-level adjunctive evidence in VVC [185]) may restore colonisation resistance and dampen epithelial inflammation [158,186]. Vaginal Microbiome Transplantation represents an emerging approach analogous to faecal microbiota transplantation, though safety, efficacy, and standardisation require further investigation [158]. Supplementation with vaginal glycogen, lactic acid, or lactate receptor agonists may promote lactobacilli and modulate epithelial immune tone [187].

11.4 Vaccines and Adaptive Immunity

Despite decades of research, no licensed or approved *Candida* vaccine exists for VVC, though the ALS3-based vaccine NDV-3A has completed Phase 2 clinical trials and demonstrated significant protection against RVVC, with anti-ALS3 immunoglobulin G2 antibody titres identified as a biomarker of efficacy [188,189]. Challenges include the complex role of adaptive immunity, specifically T helper 17 responses, in vaginal mucosal immunity [17,18]. Rational vaccine design requires careful consideration of antigen selection i.e., ALS3 and Hyr1, while candidalysin is an emerging target for passive immunisation (both anti-candidalysin nanobodies and monoclonal antibodies targeting candidalysin and Hyr1 have demonstrated pre-clinical VVC protection in murine models) [190,191]. Though

active vaccination strategies targeting *Candida* virulence factors such as candidalysin remain under development, immunisation to elicit protective mucosal immunity without exacerbating immunopathology has yet to be discovered [189].

11.5 Personalised Medicine Approaches

Integration of host genetic profiling (e.g., inflammasome, cytokine, and PRR variants), microbiome characterisation, and fungal strain typing may enable personalised risk stratification and tailored therapeutic strategies [15,175]. Patients with hyperactive inflammasome signatures may potentially benefit from IL-1 blockade, those with dysbiotic microbiomes from microbiome restoration strategies, and those with azole-resistant strains from targeted antifungal or immunomodulatory approaches. Such precision medicine strategies remain largely aspirational but represent a future direction in VVC management [15,175].

11.6 Translational Prospects and Challenges

Immunomodulatory strategies such as IL-1 blockade and NLRP3 inhibition hold considerable promise based on preclinical evidence, yet their translation into clinical practice faces substantive hurdles. These include the intricate and contextually variable immunoregulatory environment of the vaginal mucosa, the risk of off-target immunosuppressive effects, interindividual variability in host response, and the requirement for adequately powered, well-designed clinical trials to confirm both safety and efficacy. Microbiome-targeted approaches and personalised medicine strategies similarly demand rigorous evaluation across diverse patient populations. Passive immunisation strategies targeting candidalysin and Hyr1 which are supported by published preclinical murine data, represent an emerging paradigm that bridges immunopathological understanding with novel therapeutic design [190,191]. The development of candidalysin-targeting vaccines, neutralising antibodies, and small-molecule inflammasome inhibitors must be guided by careful benefit-risk assessment in order to deliver meaningful therapeutic advances without compromising mucosal immune defence. Overcoming these translational barriers will be essential to convert current mechanistic insights into effective clinical treatments for VVC and RVVC.

12 Conclusions

Vulvovaginal candidiasis exemplifies a mucosal immunopathology in which epithelial inflammatory signalling rather than fungal burden drives symptomatic disease. VECs function as sophisticated immune sentinels, deploying an array of PRRs, intracellular signalling modules such as NF-κB, MAPK/activator protein 1, and JAK-STAT, and inflammasome pathways to detect and respond to *C. albicans* infection. The hypha-specific toxin candidalysin has emerged as the central virulence determinant and proximal trigger for epithelial damage, together with NLRP3 inflammasome activation, and pyroptotic cell death. The resulting cytokine storm dominated by IL-1 family cytokines and S100 alarmins orchestrates massive neutrophil recruitment. However, these neutrophils exhibit functional anergy in the vaginal microenvironment, failing to eliminate fungi while exacerbating tissue damage. Understanding VVC as an immunopathological condition fundamentally shifts therapeutic paradigms away from purely antifungal approaches toward immunomodulatory, microbiome-based, and personalised strategies, including targeted vaccines and neutralising antibodies. By integrating molecular, cellular, systems-level, and clinical insights, the field is poised to transform VVC management, improving outcomes for the millions of women affected by this common yet inadequately addressed condition.

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