



Immunopathology of Recurrent Vulvovaginal Infections: New Aspects and Research Directions

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Recurrent vulvovaginal infections (RVVI), a devastating group of mucosal infection, are severely affecting women's quality of life. Our understanding of the vaginal defense mechanisms have broadened recently with studies uncovering the inflammatory nature of bacterial vaginosis, inflammatory responses against novel virulence factors, innate Type 17 cells/IL-17 axis, neutrophils mediated killing of pathogens by a novel mechanism, and oxidative stress during vaginal infections. However, the pathogens have fine mechanisms to subvert or manipulate the host immune responses, hijack them and use them for their own advantage. The odds of hijacking increases, due to impaired immune responses, the net magnitude of which is the result of numerous genetic variations, present in multiple host genes, detailed in this review. Thus, by underlining the role of the host immune responses in disease etiology, modern research has clarified a major hypothesis shift in the pathophysiology of RVVI. This knowledge can further be used to develop efficient immune-based diagnosis and treatment strategies for this enigmatic disease conditions. As for instance, plasma-derived MBL replacement, adoptive T-cell, and antibody-based therapies have been reported to be safe and efficacious in infectious diseases. Therefore, these emerging immune-therapies could possibly be the future therapeutic options for RVVI.

Keywords: adaptive immunity, innate immunity, oxidative stress, evasion, single nucleotide polymorphisms (SNPs), pattern recognition receptors (PRRs), infectious diseases

INTRODUCTION

Vulvovaginal infections (VVI) are the commonly reported microbiological syndrome affecting millions of women globally in all strata of society. An abnormal vaginal discharge is the key trait and first sign of VVI that women seeking health care frequently complaint to gynecologist. About a quarter of all adult women complain about abnormal vaginal discharge, more commonly by those belonging to Indian subcontinent i.e., South Asia (1). Moreover, the repeated experiences of common vaginal infections collectively known as recurrent VVI (RVVI) are emerging and are the major concern for researcher these days. The three common RVVI are Bacterial Vaginosis (BV), Vulvovaginal Candidiasis (VVC), and Trichomoniasis (TV) (2). The recurrence rate of BV (RBV) is as high as 30–50% within 3 months while ≥ 4 repetitive episodes of VVC in 12-months are referred as recurrent VVC (RVVC) (3). Similarly, cases of recurring TV (RTV) have also been reported with recurrence rates as high as 5–8% within 2 months of initial diagnosis (4). The milieu conditions of vagina during one VVI type create a niche for the pathogenesis of other VVI, leading to Mixed

Infections (MI) and co-infections (5, 6). These VVI, left untreated, will not only affect the female reproductive health, but may also result in many foster infections/diseases and adverse pregnancy outcomes (7–9).

The literature regarding RVVI pathogenesis has suggested that “a vaginal microbiota (VMB) dominated with *Lactobacilli* is healthier than a diverse VMB.” This diversity in VMB causes dysbiosis characterized by fall in number of *Lactobacilli* and overgrowth of opportunistic pathogens that are either normally present in human VMB in lower quantity or sexually transmitted, resulting in RVVI (10). However, the decades of research failed to find a single pathogen responsible for causing common RVVI. This is because 20–30% of healthy (asymptomatic) women were found to have VMB same as that of VVI women (11). Also, some *Lactobacilli* strains, i.e., *L. iners* and *L. jensenii*, were found to be pathogenic and associated with VMB instability in pregnant women, pre-term birth, and BV (12, 13). Therefore, the present scenario doesn't satisfy the Koch's postulates, according to which the causative agent is essential for causing disease and it should not be present in population without disease (14). Due to this reason, accurate definition of vaginal health and vaginal infections is still lacking till date. Besides this, there are other local risk factors that have also been suggested to create favorable conditions for the development of RVVI (15). However, development of RVVI in women lacking any of these recognized disposing factors, suggests the involvement of host immune components, instrumental in elimination of RVVI pathogens (16). Further suggesting that, it's the host immune system that determines the disease outcome and thus must be explored to get an accurate definition of vaginal health and infections.

Thus, an attempt has been made, to achieve a clear understanding of host immunity in three common RVVI. This review commences with a brief summary of what is known about immunology of human vagina. Different studies that contributed to host defenses against common RVVI were then addressed and linked. These protective immune mechanisms lead to oxidative stress that has been shown to play a major role in pathophysiology of common RVVI. The review further fine points the hijacking or exploitation of host immune responses by RVVI pathogens. A theory and related mechanism was then proposed to explain the immunopathogenesis of RVVI. Moreover, genetic variations in immune molecules have been shown to play an important role in how a woman responds to a particular RVVI challenge, as evidenced by several genetic disease association studies that are detailed in this review. Based on this comprehensive compilation, different strategies were proposed for treatment of RVVI that may prevent recurrence of these enigmatic infections.

IMMUNOLOGY OF HUMAN VAGINA

The human vagina consists of multiple levels of protection in form of innate and adaptive immunity that is further compartmentalize into various components and is under strong hormonal control. Inflammation signifies an essential immune mechanism that is meant to eliminate pathogens and repair damage caused by deleterious stimuli. Theoretically,

inflammation is a process that involves four stages, including an activating system, a sensing mechanism, signal diffusion, and the effector cells activation (17). In infectious diseases, the activating system is pathogen that has preserved biomolecular structures on its surface known as pathogen associated molecular patterns (PAMPs). These PAMPs lead to the activation of quick and non-specific innate immunity that further signals for the activation of specific adaptive immunity, with the ultimate goal of eradicating the pathogens and repairing tissue damage elicited by the noxious stimuli (17).

Innate Immunity in Human Vagina

The innate immunity of human vagina involve physical, chemical, and cellular components (18). Interactions between these components form a complex microenvironment that mediates immune responses in vagina, regulated by sex hormones and specific microbiome (19).

Physical Barriers

Mucosal lining and epithelial cells serve as gatekeepers preventing the entry of pathogens in to vagina (20). The gel like mucosal layer is produced by the mucin proteins expressed by the surface of upper layer of epithelial cells throughout the vagina (21). Besides entrapping the invasive pathogens, the vaginal mucosal layer also provides lubrication and acts as a source of nutrition for the VMB. In turn, the VMB of healthy women (dominated by *Lactobacilli*) contributes to the physical defense of vaginal mucosa against pathogens by maintaining low pH, producing lactic acid, and other antimicrobial substances (22). Thus, VMB is capable of modulating defense property of vaginal mucosa. However, many physiological processes including menstruation, conception, pregnancy, and the hormonal changes frequently modulate the vaginal mucosal immune system (23). The stratified squamous vaginal epithelium, underlying the mucosal layer, also acts as a barrier and first responder to pathogens by “sensing” the danger leading to immune cell activation and secretion of immune mediators driving inflammation and immune responses (24). The identified danger is the damage done to vaginal epithelial cells by virulence factors secreted by the pathogens. These damaged host cells derived immune mediators are called damage-associated molecular patterns (DAMPs, danger signals, or alarmins) that constitute the parts of chemical components of immune system. Beneath the epithelium is lamina propria that is composed primarily of fibroblasts, blood vessels, and a diversity of immune cells (explained under cellular components).

Chemical Components

DAMPs, PRRs, chemotactic cytokines, AMPs, and C system make the chemical components of innate immune system of vagina. Other than injured host cells, DAMPs are also released under conditions like necrosis, apoptosis, and by collapsed extracellular matrix (25). Some examples of intracellular DAMPs includes DNA, fibronectin, high mobility group box-1 (HMGB1), S-100 proteins, heat shock proteins, hyaluronic acid, formyl peptides, ATP, and collagen or elastin derived peptides (25). In order to discriminate own cells from pathogens, the vaginal

immune system employ pattern recognition receptors (PRRs), that specifically respond to various pathogens (26). Currently, PRRs are divided into five major families including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), the nucleotide-binding oligomerization domain (NOD) like receptors (NLRs), retinoic acid-inducible gene (RIG) I-like receptors (RLRs), and absent in melanoma 2 (AIM2)-like receptors (ALRs) (27). The PRRs expressed by squamous vaginal epithelial cells include TLRs i.e., TLR1-10 except TLR7, CLRs including dendritic cell-associated c-type lectin-1 (Dectin-1) and secretory mannose binding lectin (MBL) as well as NOD receptor including NOD1 (18, 28–32). The expression of TLR4 and Dectin-1 in the vaginal epithelial cells is controversial as some studies have shown their presence, while others reported their absence (28, 33, 34). Also, the MBL levels in vaginal fluid are partly contributed from plasma, as a result of transudation, though directly secreted by local vaginal epithelial cells (32). However, almost all the known human TLRs, CLRs and intracellular PRRs are expressed by immune cells of both myeloid (neutrophils, macrophages and dendritic cells) and lymphoid origin (B and T cells) present in lamina propria or in vagina due to transmigration (29, 30). Upon stimulation, either through direct contact of PAMPs or through indirect means (DAMPs or cytokines), these PRRs initiates a signaling cascade, that includes activation of transcription factors, release of antimicrobial peptides (AMPs) as well as chemotactic cytokines that further signals for the activation of adaptive immunity and subsequent amplification of innate immune responses, leading to the ultimate killing of pathogens (35).

AMPs are generally expressed by numerous cell types of vagina primarily by neutrophils and epithelial cells, with small fractions contributed by dendritic cells (DCs), macrophages, and natural killer (NK) cells (36). These AMPs have antimicrobial properties against bacteria, fungus, parasite, and virus (23, 36). Different AMPs that have been reported in lower genital tract include defensins, protease inhibitors, including serine protease inhibitors (serpins), secretory leukocyte protease inhibitor (SLPI), human epididymis protein 4 (HE4), cystatins, elafins, lysozyme, lactoferrin, and cathelicidin (LL-37). Out of these, human defensins [both alpha (α) and beta (β)] are among the most widely characterized and abundant AMPs present in lower genital tract including vagina (18, 23, 37). Besides antimicrobial properties, these AMPs can destroy target cells through modulating pH and ionic concentration gradient and also have been shown to have chemotactic activity (36). The detailed mechanisms of action for each AMP have been comprehensively reviewed elsewhere (36, 38, 39). As mentioned, all the immune and vaginal epithelial cells upon activation release chemical messengers called cytokines that create an aggressive milieu for the pathogen either by creating a network between the different immune cell types or by providing direct antimicrobial response (20). Different cytokines are released based on different stimuli and cell type. Other than this, the complement (C) system, a humoral component of the innate immune system, is actively involved in the host protection against vaginal infections (40). The C system recognizes the pathogens by utilizing three different molecules i.e., C1q, MBL (also a CLR) and C3, that

respectively trigger the classical, lectin and alternative pathways for pathogen elimination (41).

Cellular Components

Inflammatory immune cells e.g., Neutrophils, Macrophages, NK cells, and DCs, which are either resident (like epithelial cells) or transmigrated into the genital tract in response to DAMPs or chemotactic cytokines, form the cellular components of innate immune system (42). Neutrophils are the major cells that are recruited at the site of infection, mediating an inflammatory response against pathogens. Neutrophils are present throughout the female reproductive tract with pre-dominant number in fallopian tubes. However, the quantity steadily reduced from the upper genital tract to vagina (23, 42). However, upon infection, under the influence of chemotactic cytokines e.g., IL-8, abundant amounts of neutrophils penetrate from vaginal epithelium into the lumen to phagocytise the pathogens and cellular debris (43). Furthermore, the proportion of these neutrophils also increases prior to menses, due to the natural process of tissue breakdown, and during copulation for the phagocytosis of sperm (18). Other than phagocytosis, these neutrophils also respond to pathogens through production of oxidative compounds, leading to oxidative stress, by releasing AMPs and cytokines for its own stimulation or for the recruitment of other cells. Other important innate immune phagocytic cells include macrophages, DCs and NK cells that constitute 10% of the total leukocytes present in the female genital tract (18, 44). Macrophages and DCs act as professional antigen presenting cells (APCs) for inducing of adaptive immune responses (45). Moreover, only DCs in particular act as a main mediator for bridging the innate and adaptive immunity and generate life-long memory by priming naive T-cells (46). In addition, NK cells in vagina lead to macrophage activation and generate pro-inflammatory and cytotoxic T cell responses (18, 20).

Adaptive Immunity of Human Vagina

The adaptive immune system of female reproductive tract presents distinctive characteristics that are unique from the adaptive immunity of other mucosal surfaces (18). It involves immunoglobulins and various cellular components (18, 47).

Chemical Components

Different studies have documented antibody (the humoral component of adaptive immunity) responses against vaginal infections based on *in vivo* or *in vitro* experiments and suggested weak but consistent presence of IgG and IgA antibodies in vaginal secretions (47). Although both antibodies are present in genital secretions, IgG was found to be more predominant than IgA (48). These antibodies prevent colonization of pathogen by checking their adherence to vaginal epithelial cells and contribute to the neutralization and formation of Ag-Ab complexes, helping in uptake and clearance of pathogen by phagocytic cells of vagina (47, 48).

Cellular Components

The cellular components of vaginal adaptive immunity include effector B-cell, CD4⁺, and CD8⁺ T cells responses as well as

local B and T memory cells that are found throughout the female reproductive tract. The T cells in vaginal tissue are localized at the stroma/epithelial interface and are few in number (49, 50). Moreover, recent studies have also suggested the presence of T-helper 17 (Th17) cells and regulatory T (Treg) cells in vagina (51). Other than this, various immuno-histochemical studies have shown the presence of antibody-producing B cells with low prevalence in vagina, ectocervix, and fallopian tubes relative to endocervix (47). However, during inflammation the number of intra-epithelial lymphocyte population increases relative to non-inflamed vagina.

IMMUNOLOGICAL HOST DEFENSES AGAINST COMMON RVVI

To maintain homeostasis and minimize the risk of infection, host vagina is capable and competitive enough to generate different immune responses against different vaginal infections as given in detail below:

Immunity in BV

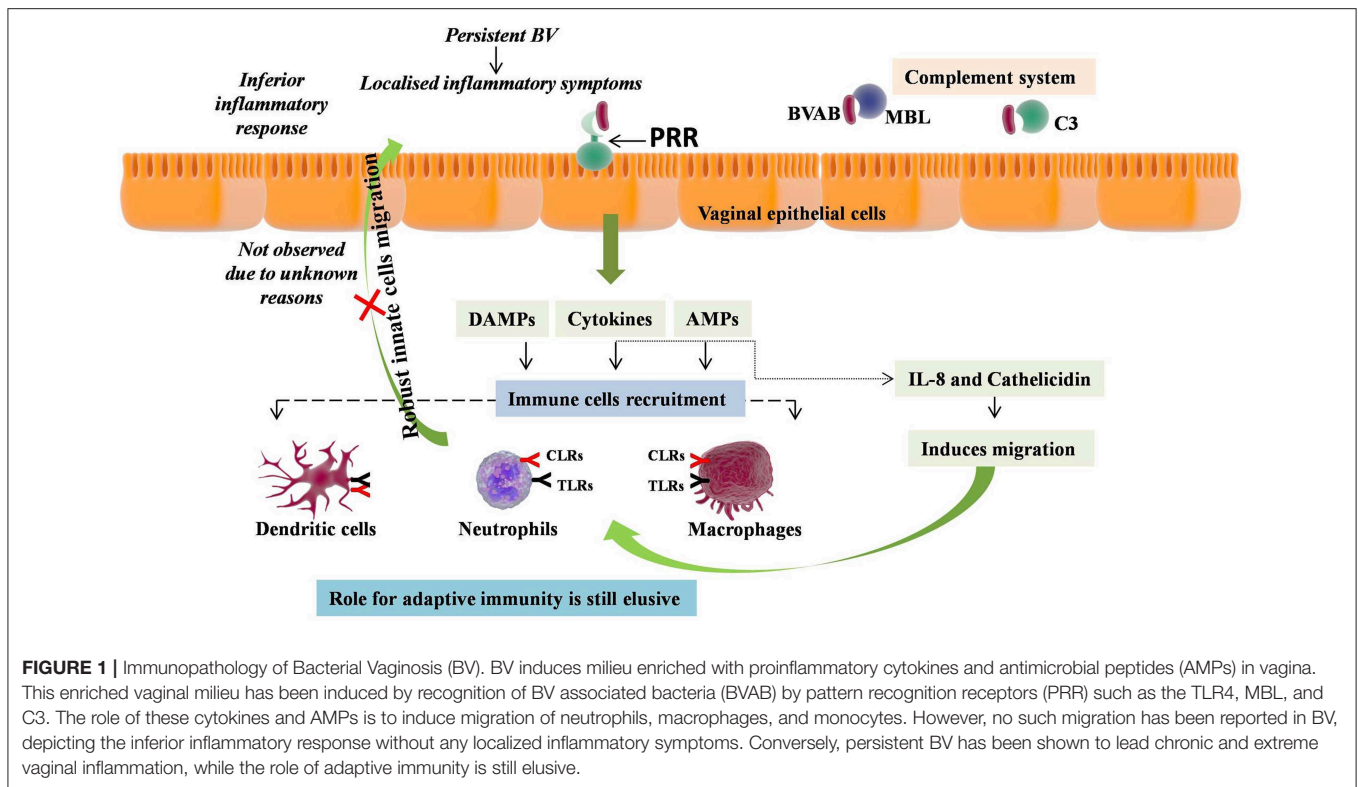
Studies based on transcriptional profiling and markers assessment in vaginal secretions and serum has indicated the major involvement of host immunity in BV (**Figure 1**). Assessment of vaginal secretions in BV women has shown the stimulation of nuclear factor- κ B (NF- κ B) in various cell types, which is the characteristic factor involved in proinflammatory signaling pathways of many TLRs (52). However, the major TLR found to be involved in BV pathology is TLR4, whose expression in monocytes is shown to be strikingly increased on exposure to lavage samples of BV women (53). Moreover, it was shown that sensing of BV associated bacteria is facilitated *in situ via* TLR4 signaling, through NF- κ B pathway leading to lymphocytes enrolment by cytokines secretion, thus causing genital inflammation (54). Other than this, immunofluorescence analysis of clue cells from BV patients revealed the presence of MBL and C3 on clue cells suggesting their direct role in recognition of BV associated bacteria (BVAB) and activation of both lectin and alternative pathways of complement system (40). Complementary evidence recommended that the chances of acquiring BV will be more in cases with insufficient sMBL levels (55). Expression of Dectin-1, another PRR, was found to increase upon stimulation with bacterial LPS relative to primarily observed low expression in freshly isolated human peripheral blood monocytes (PBMCs) and human monocytes cell line detected by both qPCR for mRNA and FACS staining for cell surface protein expression (56). In consonance, high serum Dectin-1 levels were observed in BV patients relative to controls, suggesting the active role played by Dectin-1 in defense against BV (57).

In addition, cytokines have been shown to directly contribute to BV pathology, as, BV was found to induce milieu enriched with proinflammatory cytokines in the lower genital tract. These include IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-1 β , IL-1 α , TNF- α , IFN- γ , FMS-like tyrosine kinase 3 ligand, chemokine C-C motif ligand 5 (CCL5), and SLPI [compiled in 58 and

currently reported in Jespers et al. (58) and Lennard et al. (59)]. These studies supported the concept that BV triggers the innate immune responses, which was also assessed independently for individual bacterial species present in VMB of BV patients. For example, *A. vaginae* was found to induce expression of IL-1 β , IL-6, IL-8, CCL20, human β defensin-2 (HBD-2), and TNF- α via NF- κ B, TLR2, and MyD88 signaling pathways; *G. vaginalis* was found to induces IL-1 β , IL-18, IL-6, IL-8, and TNF- α ; *Mobiluncis curtisii* and *Prevotella bivia* induced IL6, IL8, G-CSF, IP-10, MIP-1 β , RANTES, and Gro- α (60–64).

Of all the associated pro-inflammatory cytokines, IL-1 β was consistently been linked with BV, with four to over 10-fold higher levels than controls, validated both by earlier as well as current studies (58, 65–75). Moreover, successful treatment of BV has been shown to normalize the elevated pro-inflammatory cytokines levels (76). IL-1 β , a pro-inflammatory cytokine produced by innate immune cells, is a key mediator of the inflammatory response and is essential for the host-response and resistance to pathogens (77). IL-1 β has a special role in the altering production of pro-inflammatory cytokines such as IL-8, IL-6, and TNF- α and found to be positively correlated with their levels and cell surface expression of TLR4 in human epithelial cells (78). This suggests that the secondary pro-inflammatory cytokines should also increase with increase in IL-1 β levels during BV. This was further confirmed by studies that have found higher levels of IL-8 in women with BV (67, 72). In contrast, inconsistent but elevated expression of IL-1 α was also found to be associated with BV (65, 79, 80).

Other than cytokines, AMPs, particularly defensins, were found to be associated with BV, though their role in pathogenesis is not clear due to inconsistencies in the results obtained. Elevated expression of human α -defensins, mainly formed by neutrophils and epithelial cells, were observed in BV with intermediate flora (81). Furthermore, a study has also shown increased expression of HBD-2 in vaginal epithelial cells elicited by BVAB, while no such association was found by another study (63, 82). Expression of other AMPs including SLPI and HE4 was also found to be associated with BV organisms, but their negative association were also reported (63, 83). The high levels of AMPs, including S100A8 and calprotectin, were found in lavage samples of BV cases (84). These proteins bind manganese, leading to decrease in availability of free manganese which is an absolute requirement for *lactobacilli* to grow, thus inhibiting their proliferation and creating milieu for BVAB to grow (85). Another AMP i.e., cathelicidin was also observed at high levels in BV women, acting as a pore-forming toxin to disrupt membrane of pathogenic bacteria (86, 87). Cathelicidin also induces the migration of neutrophils, macrophages, and monocytes, ultimately leading to inflammatory response against infection (88). Recently, high levels of lactoferrin, an iron binding AMP, which is predominantly produced by neutrophils, were also reported in BV women (89). Iron sequestering ability of lactoferrin leads to depletion of free iron that is required for the growth by BVAB. The elevated levels of α -defensins, lactoferrin, and cathelicidin in BV suggest the possibility of high neutrophils levels in BV, however, no such elevation has been observed (69, 90).



On the other hand, DCs maturation has been shown to be induced by lavage samples from women with BV leading to DC-surface expression of CD83 and CD86 markers, reduced internalization ability, improved antigen presentation to T cells, thereby modulating T cell responses (91). The same profile of activation and maturation of DCs and T cells has been reported recently but found to occur only at the highest *G. vaginalis* concentration (92). No heightened neutrophils levels and maturation of DCs only at high bacterial concentration depicts the uncharacteristic and poor inflammatory response without any localized inflammatory symptoms, perhaps the reason why BV is not called bacterial vaginitis. However, very recently a longitudinal study has shown occurrence of chronic and extreme vaginal inflammation due to persistent BV (59). Overall, these studies confirm the inflammatory nature of BV. Absence of local inflammatory responses can be attributed to evasion of BVAB or perhaps the presence of genetic polymorphisms in inflammatory genes modifying the inflammatory responses.

Immunity in VVC

Unlike BV, where the host immediately recognize and generate immune responses against BV associated bacteria, which are the different entities from the normally present *Lactobacilli*, VVC involves the same entity *Candida*, present both as commensal as well as responsible for pathogenesis. The pathogenic activity of *Candida* is determined by its morphology, where the yeast form is associated with commensalism, and hyphal form with pathogenicity. The detection and elimination of *Candida* pathogenic form is mediated by vaginal epithelial cells, the first

barrier encountered by pathogen (93). Vaginal epithelial cells “sense” the danger constituted by the pathogen and respond by immune cell activation, secretion of inflammatory immune mediators and by generating immune responses. The danger can be attributed to virulence factors secreted by *Candida* hyphae e.g., secreted aspartic proteases (Saps). Saps can directly lead to neutrophils recruitment at the site of infection (94). However, a new protease, namely Candidalysin, has recently been proposed to be secreted by *Candida* hyphae (95). This protease is the first protein toxin recognized in any human fungal pathogen that damages the epithelial cells and thus triggers host immune responses. Candidalysin has recently been proposed as a key hypha-associated virulence factor responsible for immunopathogenesis of VVC (96). By sensing candidalysin activity, vaginal epithelial cells respond to pathogenic *C. albicans* through activation of two signaling pathways i.e., p38/c-Fos and MKP1 pathways (95, 96). The same pathways have been suggested as common mechanism facilitating different human epithelial cells for differentiating pathogenic *Candida* from non-pathogenic yeast form and to coordinate innate immune responses (93, 97). The receptors employed by epithelial cells to sense candidalysin activity are still pending to be elucidated. The resulted activation of p38/c-Fos and MKP1 signaling pathways persuades expression of pro-inflammatory cytokines and AMPs including IL-1 α , IL-1 β , IL-8, G-CSF, GM-CSF, β -defensin 3, CCL20, S100A8, and S100A9 from vaginal epithelial cells, which are instrumental for innate immune cells recruitment (95–97). Vaginal epithelial cells were shown to produce calcium-binding proteins namely S100A8 and S100A9 in response to *C. albicans*

that lead to robust neutrophils migration during VVC (98, 99). However, their involvement was not found to be crucial for driving the neutrophils response in VVC (100).

Neutrophils and macrophages are the first innate immune cells that recruit at the site of infection in response to affected epithelial cells derived immune mediators. The neutrophils further release TNF- α that consequently up-regulates TLR4 expression on epithelial cells (101). Independent to these virulence factors and cytokines response, direct contact mediated recognition of *C. albicans* sugar moieties such as mannan and β -glucan is mediated by neutrophils, macrophages, and dendritic cells via surface PRRs including TLRs (including TLR 2, 4, and 9) and CLRs (including MBL, Dectin-1, Dectin-2, DC-SIGN, and Mincle) (40, 102, 103). Ligation of PRRs further stimulate downstream MAPK and Syk signaling, production of NF- κ B, and pro-inflammatory cytokines. The activated immune cells form a loop of positive feedback that amplifies the inflammatory process, leading to ultimate effectors functions. Other than this, immunofluorescence analysis of the *Candida* hyphae from VVC patients showed the presence of C3 and pH dependent binding of MBL suggesting their direct role in *Candida* recognition and activation of alternative as well as lectin complement pathways (40, 102). In addition, MBL have been shown to cause agglutination of *Candida* upon hyphae generation independent of direct/indirect opsonophagocytosis and complement activation (104). In consonance, two different studies have reported high MBL levels in women with VVC than healthy women, suggesting the active role of MBL in the defense against VVC (105, 106). Other complementary evidences have shown that low MBL levels in women predispose them to VVC (55, 107, 108).

Moreover, neutrophils, through direct contact via PRRs particularly CLRs, mediate killing of *Candida* with short hyphae intracellularly and those with long hyphae extracellularly. The intracellular killing is mediated by phagocytosis while, extracellular killing is mediated by NETosis i.e., development of neutrophils extracellular traps (NETs). Both mechanisms involve oxidative burst due to reactive oxygen species (ROS) production (109–113). Additionally, autophagy, fibronectin, release of granular enzymes, AMPs including calprotectin and Dectin-1 signaling has also been shown to be involved in NETosis (109, 110, 112, 114, 115). In contrast, some other studies suggested that β -glucan mediated NETosis occurs through complement receptor 3 (CD11b/CD18) and not through Dectin-1 signaling or ROS mechanism, indicating their controversial role in NETosis (111, 114). Furthermore, recruitment of polymorphonuclear neutrophils (PMN) into vagina was observed to be associated with vaginal inflammatory symptoms when volunteer women were challenged with live *C. albicans* (116). This vaginal inflammation was observed to decrease with diminution of PMNs (117, 118). Robust response by neutrophils recruitment correlates well with local vaginal inflammation similar to high vaginal *Candida* burden for causing VVC. However, a mechanism explaining PMN dysfunction at the vaginal mucosa remained a mystery. The most current information relative the mechanism(s) of the VVC immunopathogenesis where a strong inflammatory condition occurs (via candidalysin and

hyphal morphology transition), but fail to reduce the *Candida* load and thus the persistence of infections has been proposed (119). This has recently been termed as “neutrophil anergy” and involves vaginal factors that inhibit the ability of the PMN to bind to *Candida* for effective killing (119). Unlike neutrophils, macrophages mediate only intracellular killing of *Candida* but both through ROS and RNS mechanisms (120).

Just like surface PRRs, the intracellular PRR i.e., NLRs of innate immune cells are also activated by DAMPs or through direct contact of internalized pathogenic fungal components that activate NLRP3 inflammasome, consequently leading to release of proinflammatory cytokines including IL-1 β and IL-18 (121). This inflammasome activation also led to programmed host cell death known as pyroptosis, which is employed as one of the evasion strategies by virulent *Candida* for escaping macrophages (122, 123). Owing to this reason, the macrophages mediated killing of intracellular *C. albicans* is shown to be of lower efficiency than neutrophils (103, 121). However, the fungal triggers activating the inflammasome mediated pyroptosis are still not known. Finally, IL-1 β and IL-18 release through inflammasome activation by innate immune cells promote adaptive T helper 17 (Th17) and Th1 responses respectively, thus linking innate with adaptive immunity (124). Moreover, both *in vitro* and *in vivo* studies have shown that Dectin-1-Syk-CARD9 signaling couple innate and adaptive immunity independently of TLR signals and induce differentiation of adaptive Th-17 and Th-1 cells (125, 126).

Carvalho and group showed that Dectin-1 is necessary for controlling vaginal infections (127). The study evaluated two genetically distinct strains of mice with vaginal candidiasis for Dectin-1 deficiency and showed that the role of Dectin-1 in antifungal immunity lies ahead of Th17 cell activation and is significantly dependent on host genetic milieu. The study found that Dectin-1 was required for appropriate control of vaginal candidiasis in mice strain C57BL/6, but not in BALB/c mice. The former Dectin-1 deficient strain of mice was found to be vulnerable to infection, with defective production of cytokines including IL-17A as well as IL-22 and adaptive Th1 responses, relative to reverse effect observed in latter strain. However, this depiction of two tremendously contradictory phenotypes, have been attributed to differential expression of functionally distinct Dectin-1 isoforms by two strains (128). Thus, the study clearly depicts that Dectin-1 essentially contributes to the stability of Th1, Th17, Treg CD4⁺ T-cell populations during infection, as its deficiency lead to defective release of Th17 cells in C57BL/6 mice and both Th1 as well as Treg cells in BALB/c mice after infection. This suggests the contribution of Dectin-1 in differentiation of T helper cells and its relative ability to control the vaginal infection. In consonance to this, another study highlighted the specific role of Dectin-1 in VVC in four women from Netherlands, affected either by onychomycosis or RVVC (129). The Dectin-1 expression in these women was found to be poor with defective β -glucan binding, defective Th17 responses, and defective production of cytokines including IL-6, TNF- α , and IL-17. Another study has shown increased intracellular expression of Dectin-1 in response to opsonised *Candida albicans* through recognition of β -1,3-glucan (130).

In consonance, a recent study found significantly high serum Dectin-1 levels in VVC cases relative to controls suggesting the active role played by Dectin-1 in defense against VVC (57). Thus, Dectin-1 is certainly a formidable PRR for providing systemic immune defense against the infection however, its role as a mucosal defense marker is still ambiguous due to inconclusive literature regarding its normal expression on vaginal mucosa as aforementioned. Therefore, caution should be taken regarding these interpretations. Moreover, two studies based on different animal models (rat and mouse) of VVC, have depicted the controversial role of dendritic cells following infection with no definite conclusion (131, 132).

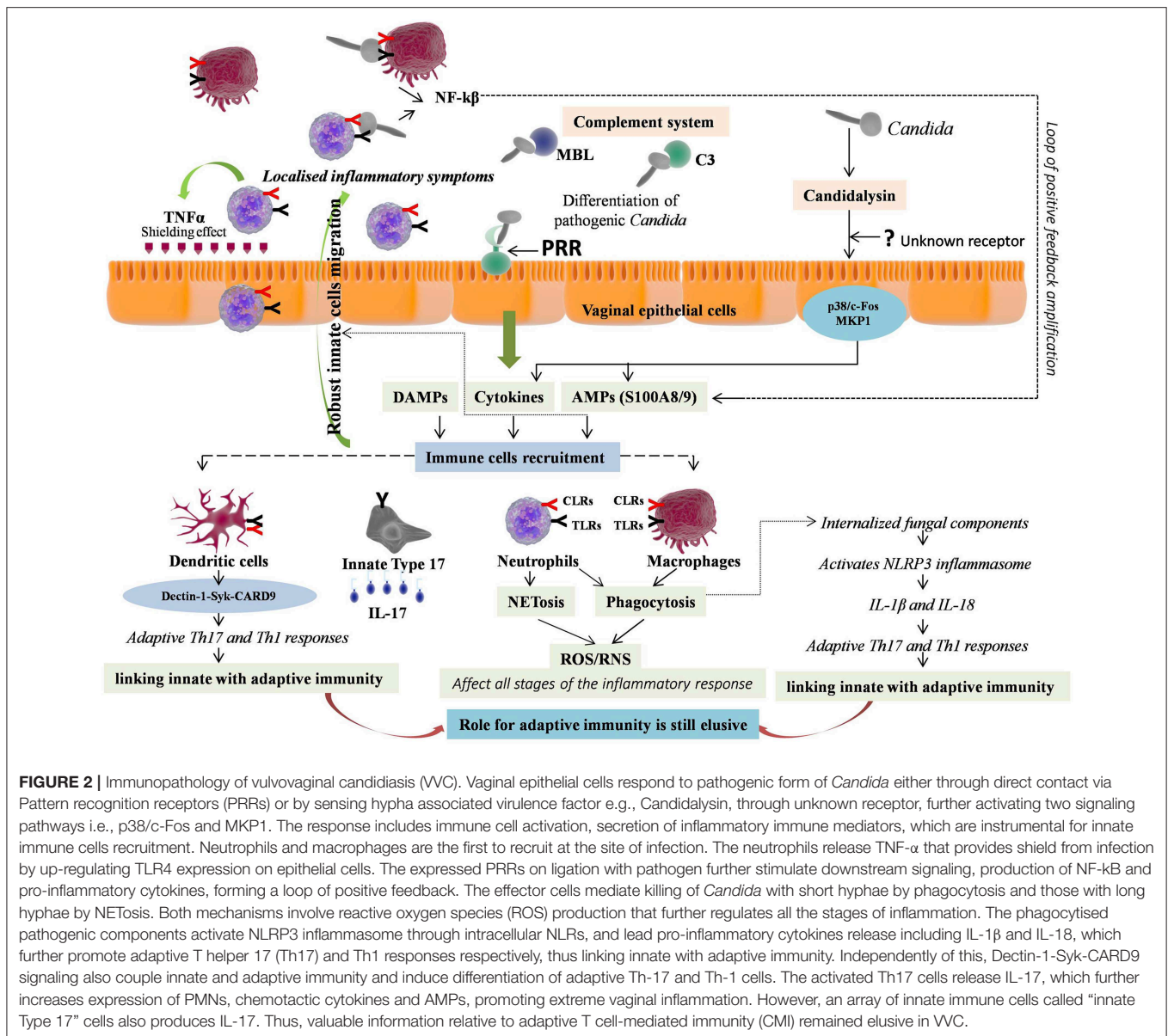
The activated Th17 cells release IL-17, a multifunctional pro-inflammatory cytokine, that further increases expression of PMNs, chemotactic cytokines and AMPs (HBD-2/3, histatins), promoting effective inflammatory response (133–135). Studies have shown that inhibition of Th17 cells differentiation led to considerable decrease in production of IL-17 and HBD-2 with consequent exacerbation of VVC (136–138). However, some studies have suggested that inflammatory response during VVC occurs independently of Th17 cell lineage (99, 139, 140). Hence, valuable information relative to adaptive T cell-mediated immunity (CMI) remained elusive as almost equal number of studies are recommending and contrasting its role in VVC. Additionally, studies have also established the link between acquired antibody mediated humoral immunity (HI) with CMI against VVC, suggesting the existence of protective antibodies but at lower concentrations with no appreciable protection (141–143). A common misbelieve regarding IL-17 is that, it is only produced by adaptive Th17 cells and thus function mainly in the adaptive immunity. However, an array of innate immune cells called “innate Type 17” cells also produces IL-17. These cells include innate lymphoid cell type 3 (ILC3), natural killer T (NKT) cells, $\gamma\delta$ T cells, and TCR β^+ “natural” Th17 cells (nTh17) (144–146). Furthermore, contrasting data regarding neutrophils as a source of IL-17 has also been documented (147, 148). However, as aforementioned, CARD9, an adapter that mediates Dectin-1 signaling, is essential for adaptive IL-17 response but this adaptor was not shown to be involved in innate IL-17 responses (126). Recently, a study reported Candidalysin mediated innate IL-17 response in murine model of oral candidiasis (149). However, the role of IL-17 production by innate type 17 cells in VVC is largely uncharted. Overall, these studies highlight the role of innate immunity that work in concurrence with vaginal epithelial cells against VVC, while, the role of adaptive immunity is still elusive (Figure 2).

Immunity in TV

The innate immunity against *T. vaginalis* involves PRRs stimulation, phagocytes recruitment in vagina and complement activation (150–154). The first barrier of innate immunity encountered by pathogens is vaginal epithelial cells, that lead to immune response generation by TLRs (TLR2, TLR4, and TLR9) expression via p38 MAPK signaling pathway, consequently leading to IL-8 and TNF- α release from vaginal epithelium (155, 156). However, ligands of *T. vaginalis* that bind to these TLRs have not been identified till date. Alternatively,

independent of these TLRs expression, the lipophosphoglycan (LPG), a major component of *T. vaginalis* membrane, also induces inflammatory response by release of pro-inflammatory cytokines after contacting human vaginal epithelial cells (157). In addition, galectin-1 and galectin-3 expressed by vaginal epithelial cells were reported as receptors for *T. vaginalis* LPG (158, 159). Galectin-3 was accounted for pro-inflammatory cytokines (IL-8 and MIP-3 α) release whereas galectin-1 was shown to play immunosuppressive role that might help in parasites evasion. Both, IL-8 and MIP-3 α cytokines show chemotactic activity, promote migration of immune cells particularly neutrophils and other phagocytes across the endothelium, while, MIP-3 α also induces dendritic cell maturation (146). Moreover, *T. vaginalis* also releases leukotriene B4 (LTB4), an endogenous lipid, which leads to inflammation in women infected with *T. vaginalis* due to its leukocytes chemotactic activity (160, 161). This lipid mediator induces the release of IL-8, ROS, and AMPs including β -defensin-3 and cathelicidin (LL-37) through binding to its receptors BLT1 and BLT2 on immune cells (162). The immune cells that are predominantly found in the vaginal secretions of *T. vaginalis* infected patients are neutrophils (163). In response to *T. vaginalis* stimulation, immune cells release pro-inflammatory cytokines including IL-1 β , IL-6, IL-8, and TNF- α , leading to neutrophils recruitment, explaining its predominant accumulation for mediating initial inflammatory response following TV (161, 164, 165). These neutrophils achieve *T. vaginalis* killing by phagocytosis and by novel mechanism i.e., taking *T. vaginalis* “bites” prior to parasite death, using trogocytosis (166). Immune-fluorescence analysis of the *T. vaginalis* revealed binding of MBL to its surface carbohydrates i.e., unmodified N-glycans (153). MBL binding to *T. vaginalis* have shown to cause self-aggregation of parasites, lowering their motility and division rate (153). *T. vaginalis* also leads to the activation of complement system, encouraging killing through neutrophil-mediated endocytosis (150, 151, 153). Furthermore, SLPI, an AMP, has also shown to be associated with TV (167).

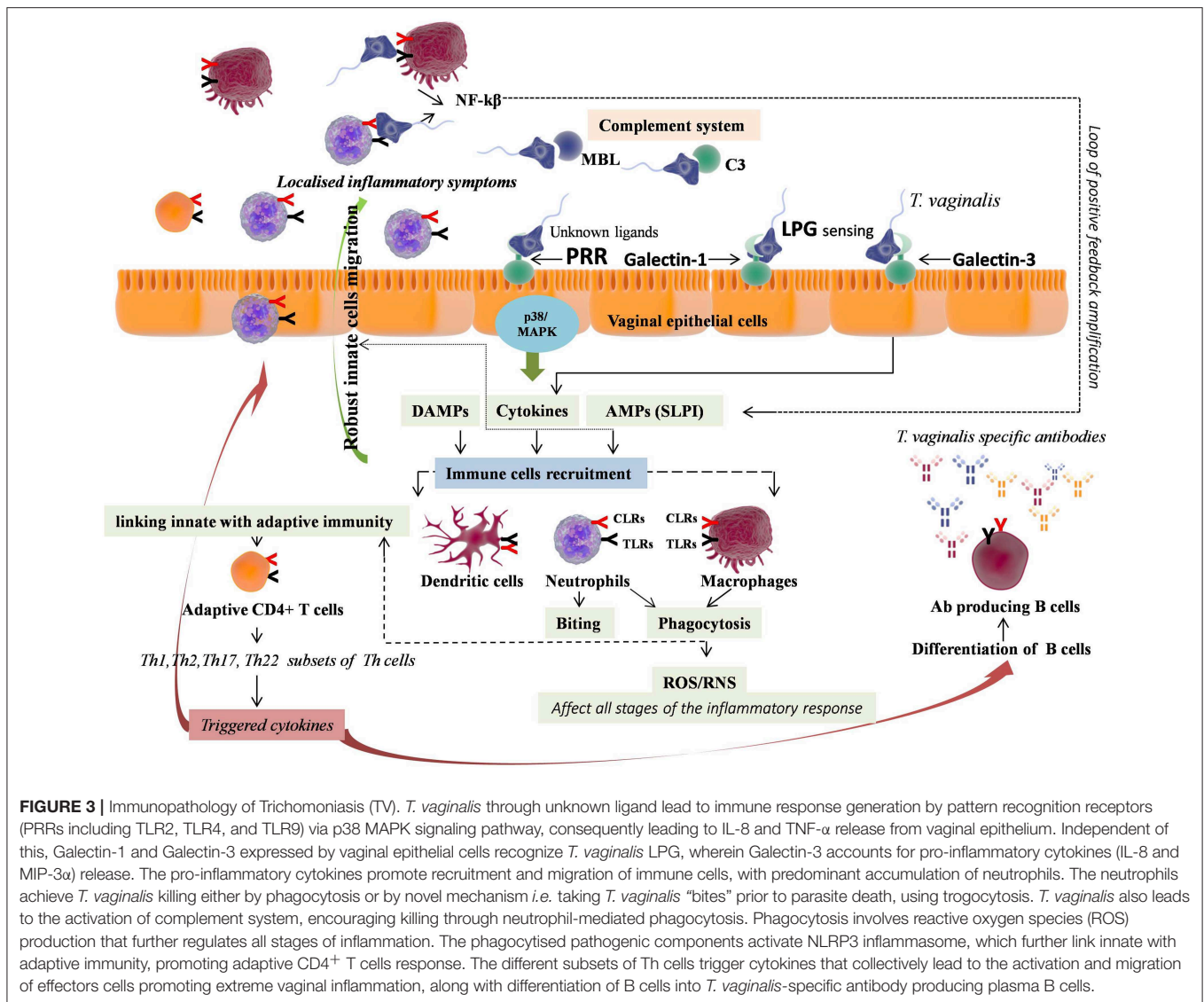
Moreover, TV was found to induce CD4⁺ T cells penetration in vaginal tissues indicating the role of T-cell mediated adaptive immunity in defense against TV (168). In support of this, a study reported the involvement of Th1 triggered cytokines (IL-2 and IFN- γ) in maintaining low burden of *T. vaginalis* infection (169). Similarly, the elevated levels of Th17 triggered IL-17 and Th22 triggered IL-22 were found in women with Trichomoniasis (170). Furthermore, elevated expression of cytokines including IL-6 and TNF- α , that induces the differentiation of Th22 cells, were reported in *T. vaginalis* activated macrophages (165). Both, IL-22 and IL-17 share common functional aspects and were shown to collaboratively induce and up-regulate production of an AMP named cathelicidin (LL-37) (170–172). All these cytokines produced by different subsets of Th cells collectively lead to the activation and migration of effectors cells including neutrophils, macrophages, cytotoxic T lymphocytes, natural killer cells, along with differentiation of B cells into antibody producing plasma B cells (173). However, the exact role of these different subtypes of Th cells in TV is still remains to be elucidated. *T. vaginalis* infection also leads to the induction



of high concentration of *T. vaginalis* specific IgG, IgM, IgA, and IgG subclass antibodies, along with induction of low concentration of IgE antibodies, in vaginal secretions and serum of *T. vaginalis*-infected subjects (152, 154, 174–177). However, the protective role of these antibodies during *T. vaginalis* infection remains obscure due to their short-lived effects caused by degradation of these antibodies by *T. vaginalis* secreted cysteine proteases (178, 179). Moreover, recently a study has reported direct association between the effective metronidazole based therapy of TV with diminution of specific anti-*T. vaginalis* IgG antibody in serum (177). Thus, just like other VVIs both innate and adaptive immune responses are activated during *T. vaginalis* infection (Figure 3). However, the role of adaptive immunity is still not clear, though elucidated better than VVC and BV.

HOST DEFENSE AGAINST RWVI LEADS TO OXIDATIVE STRESS

A wide range of substances, known as reactive oxidants, consisting of free radicals and other non-radical oxygen derivatives, are constantly generated as an essential part of metabolism. These reactive oxidants are further neutralized by an array of protective antioxidant mechanisms occurring in human system and thus maintains redox homeostasis (180). An imbalance between oxidants and antioxidants, due to an excess oxidants production, leads to oxidative stress that disrupts redox homeostasis (180). From the past decade, evidences have emerged that suggested, reactive oxidants also generate as an integral part of defense mechanism, leading to the state of oxidative stress with significant biological consequences and



thus contributing to the pathophysiology of diseases (181). These reactive oxidants are divided in to two main types including reactive oxygen species (ROS) and the reactive nitrogen species (RNS) (182). The former includes primary ROS namely superoxide anion radical (O_2^-) and secondary ROS including hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH\cdot$) generated by the action of enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) that exists in different isoforms (183). The latter includes nitrogen oxide free radical ($NO\cdot$), the parent molecule of all RNS, generated by the action of enzyme NO synthase (NOS) that catalyse the conversion of L-arginine to L-citrulline in a five-electron oxidative reaction. The NOS exist in three different isoforms that includes type I-neuronal NOS (nNOS), type II-inducible NOS (iNOS), and type III-endothelial NOS (eNOS). In which iNOS is expressed only upon cell stimulation by pro-inflammatory cytokines, by pathogen and pathogen associated molecules (as given below) while nNOS and eNOS express constitutively (184).

These reactive oxidants affect all the stages of the inflammatory immune response, starting from the release of DAMPs, their sensing by PRRs, activation of signaling pathways, release of immune mediators, and initiation of the innate and adaptive cellular responses to the ultimate killing of pathogens by effectors phagocytic cells as validated by different studies mentioned above and below.

Oxidative stress plays an important role in release of DAMPs such as HMGB1 in external surroundings (185–187). In turn, HMGB1 itself leads to ROS and RNS generation by stimulating cellular responses and up-regulating genes encoding iNOS via TLR4 activation (188, 189). Moreover, these oxidants also promote cells surface expression of PRRs (190, 191). In turn, activated TLR and CLR-dependent pro-inflammatory signaling, is coupled with ROS generation and up-regulated NOXs and iNOS expression (130, 185, 192, 193). Thus, TLRs and CLRs activation results into both oxidative and nitroxidative stress. These oxidants further leads to TLR engagement and activation

resulting in a round of magnification, designated as the “TLR-radical cycle,” which ultimately causes chronic inflammatory response (193). Moreover, the responses generated by PRRs activation are mainly communicated through activation of NF- κ B, a redox sensitive transcription factor, which is also activated by ROS. In turn, NF- κ B controls the expression of genes involved in innate immunity that leads to ROS generation (194). In addition, ROS generation have also been implicated for NLRP3 activation that generate adaptive immune responses through inflammasome and also leads to further ROS generation (195, 196).

Overall, these studies suggest that both oxidative stress and inflammation stimulate each other and thus create a nasty cycle that leads to the amplification and dissemination of inflammatory response and respiratory/oxidative burst (the production of ROS). The latter is a crucial reaction that occurs in activated inflammatory cells especially neutrophils and macrophages to degrade and kill internalized pathogen by phagocytosis. That is why oxidative burst has long been recognized as a typical consequence of immune cell stimulation coupled with both chronic and acute states of inflammation (182, 197). All these inflammatory stages that lead to ROS generation are shown to be actively involved in RVVI, discussed above, suggesting the major role of oxidative stress in pathophysiology of RVVI and its contribution in vaginal immunity as an integral part of defense mechanism.

Moreover, studies have documented the ROS production by neutrophils in response to pathogenic bacteria, *C. albicans* and *T. vaginalis* infection (43, 130, 163, 198–200). Studies also documented the release of high levels of ROS by neutrophils in response to *Candida* species such as *C. glabrata* and *C. dubliniensis* (201, 202). The concentration of ROS in the vaginal discharge of BV patients was found to be significantly higher than that from healthy women (203). *Candida* species isolated from VVC patients induce ROS production in neutrophils (204). Reduced vaginal concentrations of NO metabolites were shown to increase susceptibility to recurrent episodes of VVC (205). Likewise, reduced serum concentration of ROS has been shown to increase susceptibility to RVVI (206). Other than neutrophils, macrophages were also shown to release cytotoxic NO products against *T. vaginalis* with increased iNOS expression (165, 207). In addition, high levels of cytotoxic NO products and increased iNOS expression was found in WBCs and vaginal lavages of *T. vaginalis* infected asymptomatic women relative to symptomatic women (208, 209). Thus, high ROS production plays an important role in maintaining low burden of infections, as observed in asymptomatic women depicting a strong relationship between oxidative stress and vaginal inflammation caused by RVVI.

HIJACKING OR EXPLOITATION OF HOST IMMUNE RESPONSES BY RVVI PATHOGENS

As discussed above, inflammation signifies an essential immune mechanism which is meant to eliminate pathogens and

repair the damage caused by deleterious stimuli. However, there are conditions in which such refurbishment may not occur effectively, resulting in constant pushy cellular stress, disseminating, and magnifying the inflammatory response. In these situations, the process becomes defective, leading considerable variations in tissue functions, with persistent and systemic derangements of homeostasis (182, 210). These conditions usually occur when pathogen becomes capable of evading and subverting host immune responses, creating a niche that allows its replication and leading to continuous stimulation and thus amplification of inflammatory immune responses. Generally, the evasion mechanisms counteract different events in the entire RVVI pathogenesis, but this review will focus on the mechanisms by which pathogens subvert or manipulate the host immune responses, hijack it and use it for its own advantage.

In BV, the biota related to BV was found to inhibit the release of secondary pro-inflammatory cytokine i.e., IL-8 (69). As IL-8 endorses neutrophils migration, its absence does not allow neutrophils to enter the vagina because of which local inflammation does not occur, allowing pathogen survival. Also BVAB were shown to release a combination of short chain fatty acids, including butyrate and succinate, which modulate the host immune responses by negatively affecting neutrophils and monocytes migration in vagina and their endocytic activity (211). Moreover, lavages from women with BV as well as *G. vaginalis* separately found to reduce internalization ability of dendritic cells (DC) (91, 92). Additionally, BVAB has been shown to mask itself from host's immune responses by incorporating host sialic acid produced as a result of chopping of vaginal mucosal layer by bacteria (212–214).

Similarly in VVC, *C. albicans* was found to down-regulate TLR4 expression on epithelial cells, thus restraining TLR4 mediated stimulation of immune responses and increasing *C. albicans* infection (101). *Candida* species has the ability to shield its β -glucan (the popular ligand of Dectin-1) with the help of its cell wall components, thus preventing its recognition by Dectin-1 and inhibiting Dectin-1 mediated immune responses (215). As mentioned above, *C. albicans* leads to the activation of complement (C) system and thus generate host immune responses against pathogens. However, the pathogen employs different strategies to evade the classical and alternative pathways of C system. The first strategy includes degradation of host complement components including C3b, C4b, and C5 (216). Second involves surface acquisition of host complement inhibitors or regulators involving plasminogen-binding surface protein, factor H, C4b-binding protein (C4BP), and FHL-1. These surface attached inhibitors sustain their regulatory property and inactivate respective host C proteins (217–219). The third strategy includes direct and indirect C inhibition by self secreting inhibitory protein including pH-regulated Ag 1 (Pra1). This protein either directly blocks the activation and conversion of C3 or indirectly inhibits C system by binding to the host C inhibitor proteins (factor H and C4BP) (220–222). *Candida* also inhibits the terminal complement complex (TCC) formation by secreting Saps proteins (216).

Alternatively, *C. albicans* was shown to inhibit phagolysosomes formation, which is an important step in

the process of killing of a pathogen (223). Moreover, pyroptosis is a host antimicrobial response mechanism that involves death of host cells infected with intracellular pathogens. This mechanism has been shown to be hijacked by highly virulent *Candida* strain, for escaping the host immune cells, particularly macrophages, thus mediating its own survival and host cell killing (122, 123, 224, 225). As afore-discussed oxidative stress plays a fundamental role in host defense against RVVI. However, *Candida* has strategies to neutralize and evade the oxidative stress. *C. albicans* expresses superoxide dismutase (SODs) and other antioxidant enzymes on the cell surface. These extracellular SODs also have vital roles in the detoxification of superoxide radicals generated by phagocytes and hence prevent massive ROS accumulation (226, 227). In addition *C. albicans* catalase and vacuole (fungal organelle) formation has been suggested to counteract oxidative stress (228–230). Moreover, *C. albicans* also exploit host cytokine production for its own benefit by inhibiting host IL-12, IL-17, and IFN γ production (231–234). These cytokines are critical for host innate and adaptive immunity as studied above.

Similarly, *T. vaginalis* uses DCs and macrophages for its own advantage by modulating their immune responses leading to reduced synthesis of IL-12 and increase synthesis of IL-10 and TGF- β (235, 236). Furthermore, NF- κ B was also shown to be inhibited by *T. vaginalis*, further suppressing the expression of pro-inflammatory genes including IL-12, suggesting the modulation of the host cytokines milieu as an effective immune evasion strategy followed by *T. vaginalis* (235). Other than this, cysteine proteases secreted by *T. vaginalis* helps in evasion of host's immune responses by degrading its various components that includes subclasses of host antibodies (IgG and IgA), C3 opsonin and secretory leukocyte protease inhibitor (SLPI), an antimicrobial peptide (178, 179, 237–239). The cysteine proteases also contribute to cytotoxicity particularly against B cells (240, 241). Killing of B cells and phagocytosis of human peripheral blood mononuclear cells (PBMCs) through contact dependent manner by *T. vaginalis* have also been reported (242, 243). This parasite neutralize specific host antibodies by secreting numerous immunogenic soluble antigens, thereby evading host immune responses (244–246). Additionally, *T. vaginalis* has been suggested to incorporate host serum proteins in its surface, masking itself from host's immune responses (247). Taking this into consideration, recently it was proposed that *T. vaginalis* acquire CD59 from host cells, e.g., red blood cells (RBCs), thereby evading itself from host complement mediated killing (248).

As mentioned above, galectin-1 and galectin-3 receptors expressed on vaginal epithelial cells surface, bind to LPG core of *T. vaginalis* (158, 159). The binding of *T. vaginalis* to galectin-1 plays an immunosuppressive role by inhibiting the releases of IL-8, MIP-3 α , and RANTES, the chemokines that connect innate and adaptive immunity and facilitate the recruitment of phagocytes, an another important evasion strategy by the pathogen (159). This suggests that in response to *T. vaginalis* infection, the two molecules of same family play contrasting role. However, in general, galectin-1 can also play immunostimulatory role while galectin-3 is also capable of down-regulating the inflammation (249, 250). The possible explanation

behind this inconsistency could be recognition of self ligands on host cell surface by galectins, the reason behind why galectins are still not strictly considered as PRRs, because PRRs recognize only highly conserved pathogen associated structure that are not present in host (251). This obvious contradiction divulges our incomplete understanding regarding the structural and biophysical features of ligand binding preferences displayed by galectins and genuine variety in identification of the host galectin range (252). However, the details of this topic are outside the scope of this review. Moreover, *T. vaginalis* can leads to apoptosis of neutrophils and macrophages by reducing expression of the anti-apoptotic proteins and by activating caspase-3, which is a pro-apoptotic marker (253, 254). Other than this, like many other parasites, *T. vaginalis* also releases extracellular vesicles, for instance exosomes, which can also modulate the host immune responses by diminishing vaginal IL-17 concentration and up-regulating IL-10 expression in macrophages (255). Besides this, the surface immunogens of *T. vaginalis*, involving P230 and P270 go through conformational changes that prevent the epitope accessibility for binding of host antibodies that allows parasite to evade host humoral immune responses (256, 257). Thus, understanding the molecular mechanisms employed by pathogens to exploit the host immune response for its own benefits is of crucial importance for the management of these devastating infections.

IMMUNOPATHOGENESIS OF RVVI: PROPOSED THEORY

Vaginal innate immunity is the first line of defense system that responds to the pathogens and activates the adaptive immunity. In turn, activation of adaptive immune responses also support the function of innate immunity consequently forming a loop of positive feedback, leading to amplified inflammatory responses and augmented effectors functions for the ultimate killing of the pathogens. This emphasize on the pivotal role of innate immunity, whose impairment can leads to adaptive immune dysfunction and increased susceptibility to infections. Women inspite of having disturbances in vaginal milieu represent different clinical outcomes. Asymptomatic cases of RVVI is due to proper functioning of both innate and adaptive immune system, that have successfully coped up with the infection in spite of different evasion strategies followed by the pathogens and thus asymptomatic cases should be considered as healthy individuals. While symptomatic cases are characterized by the impairment in the communication part of the innate immunity that signal for the activation of host adaptive immune responses thus, breaking the loop of feedback amplification. This increases the chances of hijacking and evasion of the immune system by the pathogen, which creates a niche for the pathogen replication, leading to continuous stimulation and violent innate immune responses. Thus, symptoms that define the infection are due to robust inflammatory immune responses and high vaginal pathogen burden—a fine interplay that determines the clinical outcome of infection. However, the presence of symptomatic RVVI is appeared to be more dependent on host factors rather

than on pathogens itself. Therefore, treatment should depend upon recognition of the impaired unit of innate immunity that do not allow adaptive immunity to respond and thus increasing susceptibility to vaginal infections. These most probable impaired innate immune units could be PRRs that signal for activation of adaptive immune responses. The genetic variations in these PRRs have been shown to play an important role in how a woman responds to a particular microbial challenge, as evidenced by several genetic disease association studies given below. Thus, looking at the women itself provided the answer to the major query suggesting that symptomatic/asymptomatic cases of RVVI are due to differences in women's immunity, conferred partially or wholly by genetic variations.

GENETIC SUSCEPTIBILITY: HOST GENOTYPE MODULATES IMMUNE RESPONSES AND VULNERABILITY TO RVVI

Genetic variations, particularly single nucleotide polymorphisms (SNPs), in genes coding various components of immune system have evidently been shown to modulate innate and acquired antimicrobial immune responses, both qualitatively and quantitatively. These SNPs affect gene expression as well as function and hence modulates individual's susceptibility to acquire diseases including RVVI, as evidence by several studies (Table 1). SNPs in genes coding cytokines, enzymes, growth factor, PRRs, and signaling adaptors were found to be associated with RVVI susceptibility. A study have shown association of dull IL-1 β response against pathogens in allele 2 IL1RN*2 carriers resulted due to polymorphism in intron 2 (IL1RN) of interleukin-1 receptor antagonist gene (*IL-1Ra*), widely known to modulates the pro-inflammatory action of IL-1 gene (258). Similarly, immunomodulatory effect of *IL1 β* polymorphisms was shown to be associated with susceptibility of acquiring BV (259, 260). Another study showed increased susceptibility to RVVC due to reduced levels of vaginal anticomicrobial factors in *IL-4* polymorphism homozygotes carriers (205). Also, polymorphisms in *IL-6* were associated with reduced cytokine responses, conferring increased risk to BV and premature deliveries (260, 261). However, *IL-8* polymorphism was shown to be associated with increased cytokine responses and decreases BV risk (260). Presence of polymorphisms in tumor necrosis factor- α (*TNF- α*) in BV women were associated with increased vaginal *TNF- α* levels and preterm deliveries (262, 263). Another study showed association of increased BV risk as well as pre-term delivery with polymorphisms in protein kinase C alpha (*PRKCA*) and fms-like tyrosine kinase 1 (*FLT1*) genes involved in the regulation of inflammatory responses (261). Corticotropin-releasing hormone (CRH) is involved in stress and regulation of inflammatory immune responses. Polymorphisms in genes coding for Corticotropin-releasing hormone binding protein (*CRH-BP*), Corticotropin-releasing hormone (*CRH*) and corticotropin-releasing hormone receptor 2 (*CRH-R2*) were found to be associated with BV (264). Functional polymorphism at position 677 in gene coding for

methylene tetrahydrofolate reductase (*MTHFR*), a rate limiting enzyme in methyl cycle, was shown to alter *MTHFR* activity and DNA methylation in human placenta, which further increases 3.5-fold risk of premature rupture of membranes in BV positive women (265).

As discussed above, PRRs are the important dictatorial components of immune system. Polymorphisms in gene encoding PRRs including TLRs (*TLR2*, *TLR4*, *TLR7*, and *TLR9*), NLR (*CIAS1*), and CLRs (*MBL2* and *CLEC7A*) have been shown to modulate immune responses and susceptibility to RVVI. Studies have shown association of *TLR2* polymorphisms with 3-fold increased risk of acquiring BV and increased colonization of BVAB (266, 268). In consonance, a non-synonymous SNP (nsSNP) in *TLR2* was linked with defective protein function, which subsequently reduced the production of pro-inflammatory cytokines and predisposition to RVVC (269). Similarly, polymorphisms in *TLR4*, *TLR7*, and *TLR9* were shown to be associated with increased risk of BV and >10-fold increased colonization of BVAB (71, 267, 268). In contrast, a study has shown decreased risk of acquiring BV with *TLR2* and *TLR7* Polymorphisms (267). Additionally, polymorphism in *NLRP3* gene, also known as cold-induced auto-inflammatory syndrome 1 (*CIAS1*) gene, which code for the inflammasome component *NLRP3*, has been shown to cause impaired *NLRP3* expression and IL-1 β production that subsequently predisposes women to RVVC (270). Moreover, polymorphisms in genes involving *MBL2* and *CLEC7A* have been shown to modulate their encoded CLRs expression and activity resulting in defective immune responses and altered susceptibility to RVVI (55, 57, 107, 108, 129, 271–273). Studies have shown an association of *MBL2* codon 54 polymorphisms with increased RVVC risk (107, 108, 271, 272). Another study has found an association of codon 54 polymorphism with increased risk of both RVVC and RBV (273). Moreover, Y/X promoter polymorphism of *MBL2* was found to predispose women to RVVI either it is BV, VVC, or MI in North Indian population (55). A study identified and explained a *CLEC7A* nsSNP i.e., Y238X (rs16910526) in antifungal defenses in onychomycosis and RVVC (129). The study showed poor expression of mutated form of Dectin-1, with defective β -glucan binding, defective Th17 responses, and defective production of cytokines including IL-6, TNF, and IL-17, alluring the cause of VVC in these patients. Moreover, Y238X variant was depicted to show gene-dose effects i.e., onset of disease at early age of 10–12 years was observed in homozygous variant daughter relative to late onset at age of 40 and 55 years in heterozygous mother and father, respectively (129). Recently, another study has reported that G allele of *CLEC7A* rs3901533 intronic variant and its homozygous carriers significantly lower the risk of developing RVVI and its types i.e., BV, VVC, or MI in North Indian population (57). Furthermore, a variation (Q295X) in *CARD9*, coding for adaptor (*CARD9*) that mediates Dectin-1 signaling, was shown to impair Dectin-1 signaling, resulting in decreased numbers of interleukin-17 producing effector Th17 cells and increased risk of RVVC (276). In addition, precision in diagnosing RVVI and subject assortment lead to variations between studies that limit the simplification of the reported findings to other populations.

TABLE 1 | Human genes conferring susceptibility to RVVI.

Genes	SNP(s) [‡]	Associated phenotype observed	RVVI	References
<i>IL-1ra</i>	IL1RN*2	Reduced IL-1 β response	Increased colonization of anaerobic Gram-negative rods, <i>Mycoplasma</i> , and <i>Peptostreptococci</i> and Decreased <i>Lactobacilli</i> colonization	(258)
<i>IL-1β</i>	-511 and +3954 +3954	- Increased cytokine response	Increased risk for BV Decreased risk for BV	(259) (260)
<i>IL-4</i>	rs2243250 (-589T/C)	Increased vaginal IL-4, reduced NO and MBL levels	Increased risk for RVVC	(205)
<i>IL-6</i>	-174 rs1800795	Reduced cytokine response -	Increased risk for BV BV and High spontaneous preterm delivery	(260) (261)
<i>IL-8</i>	-845	Increased cytokine response	Decreased risk for BV	(260)
<i>TNF-a</i>	TNF-2 (-308)	-	BV and Increased risk of spontaneous preterm birth	(262)
	-308G>A	Elevated levels of vaginal TNF- α	BV	(263)
<i>PRKCA</i>	rs1003599, rs10491202, rs11658528, rs16960112, rs17762314, and rs1990503	-	BV and High spontaneous preterm delivery	(261)
<i>FLT1</i>	rs748252	-		
<i>CRH-BP</i>	+17487	-	BV	(264)
<i>CRH</i>	+ 3362 and -1667	-	Increased risk for BV	
<i>CRH-R2</i>	+8288, + 5253, and + 4853	-	BV	
<i>MTHFR</i>	C677T	Altered MTHFR enzyme activity, Affect DNA methylation in the human placenta	BV and increased risk of premature rupture of fetal membranes	(265)
<i>TLR2</i>	rs1898830, rs1898830, rs11938228, rs3804099	- -	3 fold increased rate of BV/intermediate flora Increased colonization of endometrial anaerobic gram-negative rods. anaerobic non-pigmented Gram-negative rods, anaerobic Gram-positive cocci	(266)
	rs3804099	-	Decreased risk of BV	(267)
	rs1898830	-	Increased risk of BV	(268)
	rs5743704 (P631H)	Deleterious effects on protein function; reduces production of IL-17 and IFN γ	3-fold increased risk of RVVC	(269)
<i>TLR4</i>	896 A > G	Reduced vaginal IL-1 β and IL-1ra levels	>10-fold increased colonization of <i>Gardnerella vaginalis</i> and anaerobic Gram-negative rods, <i>Prevotella</i> , <i>Bacteroides</i> , and <i>Porphyromonas</i> .	(71)
	rs4986790	-	Increased risk of BV	(268)
<i>TLR7</i>	rs5743737 and rs1634323 rs179012	- -	Decreased risk of BV Increased risk of BV	(267)
<i>TLR9</i>	rs187084	-	Increased risk of BV	(268)
<i>CIAS1</i>	Tandem repeat in intron 4	Impaired NLRP3 expression and IL-1 β production	RVVC	(270)
<i>MBL2</i>	Codon 54 (rs1800450)	Low MBL levels in cervico-vaginal fluids	Increased risk of RVVC	(107, 108, 271, 272)
	Y/X(rs7096206)	Low sMBL levels	Increased risk of both RBV and RVVC Increased risk of RVVI either it is BV, VVC or MI	(273) (55)
	rs10824792	Low sMBL levels	Increased risk of RVVI either it is BV, VVC or MI	(274)
	rs7084554 and rs36014597	Low sMBL levels	Increased risk of RVVI either it is BV, VVC or MI	(275)
<i>CLEC7A</i>	rs16910526 (Y238X) rs3901533	Poor dectin-1 expression, defective ligand binding, defective immune responses High sdectin-1 levels	Increased risk of RVVC Decreased risk of RVVI either it is BV, VVC, or MI	(129) (57)
<i>CARD9</i>	Q295X	Decreased proportion of Th17 cells	RVVC	(276)

[‡]represented either by rs number, position or by possible allele, See text for required abbreviations.

RESEARCH DIRECTIONS

Though, understanding regarding immunopathology of recurrent vulvovaginal infections has broadened recently, still there are many key questions that are needed to be addressed.

First, unlike VVC and TV, studies have provided no relevant evidence for neutrophils elevation in BV, though evidences regarding high levels of bio-markers including cathelicidin that induces neutrophils migration in BV is present (88, 89).

Second, candidalysin has recently been proposed as a key hypha-associated virulence factor responsible for immunopathogenesis of VVC (96). However, the receptors employed by epithelial cells to sense candidalysin activity are still pending to be elucidated.

Third, pyroptosis is employed as one of the evasion strategies by virulent *Candida* for escaping macrophages (122, 123). However, the fungal triggers activating the inflammasome mediated pyroptosis are still not known.

Fourth, both *in vitro* and *in vivo* studies in VVC have shown that Dectin-1-Syk-CARD9 signaling, couple innate and adaptive immunity independently of TLR signals and induce differentiation of adaptive Th-17 and Th-1 cells (125, 126). However, no such role of Dectin-1 has been reported in BV and TV till date. Though, its role in defense and recognition of these pathogens has been revealed (277, 278). However, these pathogens do not possess β -glucans, suggesting the possibility of other ligands of Dectin-1 that are still not identified.

Fifth, an array of innate immune cells called “innate Type 17” cells have also been shown to produces IL-17 (144–146). Recently, a study reported candidalysin mediated innate IL-17 response in murine model of oral candidiasis (149). However, the role of IL-17 production by innate type 17 cells in BV, VVC, and TV is largely uncharted.

Sixth, the first barrier of innate immunity encountered by pathogens is vaginal epithelial cells that lead to immune response generation by TLRs (155, 156). However, ligands of *T. vaginalis* that bind to these TLRs have not been identified till date.

Seventh, the odds of hijacking increases, due to impaired immune responses, the net magnitude of which is the result of numerous genetic variations, present in multiple host genes, detailed in this review. However, so far, the functional consequences of genetic variations of only two genes i.e., *MBL2* and *CLEC7A* have been reported, while the role of other associated genetic polymorphisms are still pending to be elucidated.

Finally, valuable information relative to the role of adaptive immunity in RVVI is still not clear, though elucidated better in TV than VVC and BV.

TREATMENT STRATEGIES

Advancements in diagnostic tools as well as drugs, targeting the pathogens, provide temporarily relief, as the infection re-occurs because disturbance in host genetic system is still persisting that must be rectified in order to restore host homeostasis. The afore-highlighted causal factors, that modulate propensity to RVVI in

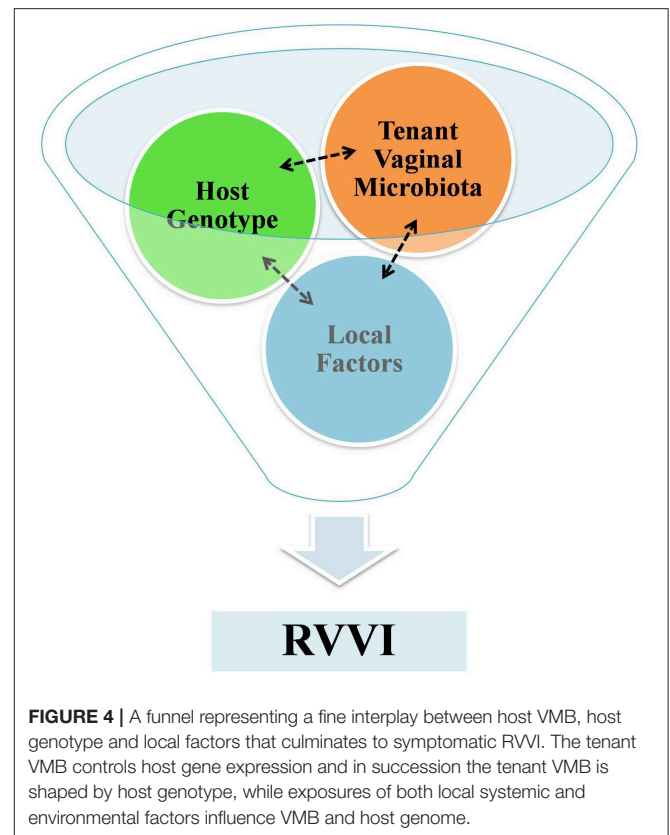


FIGURE 4 | A funnel representing a fine interplay between host VMB, host genotype and local factors that culminates to symptomatic RVVI. The tenant VMB controls host gene expression and in succession the tenant VMB is shaped by host genotype, while exposures of both local systemic and environmental factors influence VMB and host genome.

women, may further be used to develop efficient diagnosis and treatment strategies of this enigmatic disease. As for instance,

MBL Replacement Therapy

Plasma-derived MBL replacement has become a safe and efficacious therapeutic option in diseases associated with low MBL levels (279–281). Therefore, the emerging MBL substitution therapy could possibly be the future treatment strategy for RVVI (282).

Adoptive T-Cell Therapy

The use of CD8⁺, CD4⁺, and $\gamma\delta$ T cells for the treatment of infectious diseases and cancer has been reported to safe and efficacious (283). Therefore, the emerging MBL substitution adoptive T-Cell therapy could possibly be the future treatment strategy for RVVI.

Antibody-Based Therapy

Presence of many licensed monoclonal antibodies for the treatment of infectious diseases including HIV (284) outlines the prospects of this therapy for RVVI.

CONCLUSIONS

The methodical scrutiny of literature indicated RVVI as a multifarious disease, requiring a “perfect storm” to start infection. This “perfect storm” is a result of fine interplay between host VMB, host genotype and other local risk factors

that culminate into symptomatic infection (Figure 4). However, the presence of symptomatic RVVI is appeared to be more dependent on host factors rather than on pathogens itself. Thus, by underlining the role of the host immune responses in disease etiology, modern research has clarified a major hypothesis shift in the philosophy of RVVI pathogenesis. Future research in explication of highlighted critical questions may provide complete understanding of immunopathological mechanisms of RVVI. Future research in explication of the highlighted causal factors, that modulate propensity to RVVI in women, may reveal new biologicals for preventing and treating RVVI.

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AUTHOR CONTRIBUTIONS

NK collected the literature and wrote the manuscript. JS and MK designed and critically checked the manuscript.

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