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A review of the available clinical therapies for vulvodynia management and new data implicating pro-inflammatory mediators in pain elicitation

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Abstract

Localized provoked vulvodynia (LPV) is a common, chronic, and disabling condition; patients experience profound pain and a diminished quality of life. The etiologic origins of vulvodynia are poorly understood, yet recent evidence suggests a link to site-specific inflammatory responses. Fibroblasts isolated from the vestibule of LPV patients are sensitive to pro-inflammatory stimuli and copiously produce pain-associated pro-inflammatory mediators (IL-6 and PGE_2). Although LPV is a multifactorial disorder, understanding vulvar inflammation and targeting the inflammatory response should lead to treatment advances, especially for patients exhibiting signs of inflammation. NFkB (already targeted clinically) or other inflammatory components may be suitable therapeutic targets.

Keywords

fibroblast; vulvodynia; vulvar pain; vestibulitis; inflammation; Dectin-1; NFkB; IL-6; PGE_2

Introduction

Vulvodynia is a prevalent form of chronic vulvar pain, affecting as many as 28% of women within their lifetime[1]. Population studies estimate roughly 8% of women in the United States currently suffer from vulvodynia[2,3]. Recognized in 1987 as “vulvar vestibulitis,” vulvodynia is now defined as persistent vulvar pain in the absence of any obvious disease pathology, such as active microbial infection or dermatological conditions[4]. This represents a chief

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obstacle in diagnosing and treating vulvodynia. Vulvodynia can be sub-classified into "localized" or "generalized", the former affecting at least a portion of the vulvar vestibule or the clitoris, and the latter affecting the vulva as a whole[5]. The pain, often described as "knife-like," burning, stinging, rawness, irritation, or itching can be provoked by touch (e.g. during tampon insertion or sexual intercourse), can be unprovoked, or mixed[6]. Localized provoked vulvodynia (LPV) is most common, especially in premenopausal women[6,7], while generalized vulvodynia is more common in peri- and postmenopausal women[7]. Here, we will focus on LPV, which is more prevalent and has received greater attention in the literature.

The elusive origins of vulvodynia and the unsurprising treatment shortcomings

Overview

Although many theories have been proposed to explain the occurrence of vulvodynia, including gene polymorphisms[8,9], psychological disorders[10], inflammation/dysregulation of inflammatory pathways[11-17], histories of yeast[18,19] or human papilloma virus (HPV) infection[20], sexual/childhood abuse[21,22], and childbirth/pelvic floor muscle dysfunction[23,24], there is no consensus regarding the precise cause(s) of disease. It is now generally accepted that vulvodynia is a multifactorial disorder influenced by several contributing factors; multidisciplinary therapies have been most effective in reducing/managing chronic vulvar pain and are currently the recommended line of treatment[5,25].

Topical Therapies

Treatment failures stem from a limited understanding of the disease pathology and the factors that precipitate pain[5]. Current treatment strategies follow a "trial and error" approach guided mainly by expert opinion rather than an evidence-based approach from randomized clinical trials (RCTs)[26]. Under this strategy, the degree of therapeutic intervention increases as symptoms fail to remit or worsen. Initial intervention involves minimizing environmental irritants to the vulva, such as the cessation of detergent use, wearing exclusively cotton underwear, and refraining from wearing tight clothing[5]. These measures are often followed by or combined with the use of topical agents to relieve pain, namely anesthetics (e.g. lidocaine) applied nightly or immediately prior to intercourse[5]. Other topical therapies (with questionable efficacy) include estrogen[7], fibroblast lysates[27], moisturizers, muscle relaxers (e.g. baclofen)[28], capsaicin[29,30], and topical tricyclic antidepressants (e.g. amitriptyline)[31] or anticonvulsants (e.g. gabapentin)[32].

Oral Medications

When these lines of defense show no appreciable change, oral medications may be prescribed, which fall into two general categories: antidepressants and anticonvulsants[5]. Tricyclic antidepressants (TCAs), such as amitriptyline, nortriptyline, and desipramine target pain and depression (associated with vulvodynia)[33,34], while TCAs also have proven neuropathic pain relieving effects[35]. However, a recent placebo-controlled RCT found that desipramine alone or in combination with lidocaine performed no better than placebo[36].

Other antidepressants, such as serotonin reuptake inhibitors, are also largely ineffective for vulvodynia[26]. Although early theories suggested that unexplained vulvar pain represents a strictly psychological disorder[10], depression, hypervigilence, and catastrophizing are now regarded as evolving as the chronic pain state persists[5]. Nevertheless, many patients report symptom improvement when receiving treatment that targets the psychological sequelae of vulvodynia, such as cognitive behavioral therapy[5,6,25]. Another option is the use of oral anticonvulsants (e.g. gabapentin), which may be especially useful for patients with pelvic floor dysfunction[37-40]. However, pelvic floor dysfunction is likely secondary to and not the cause of vulvodynia[1,6]. Nonetheless, gabapentin has other indications for use; double-blind placebo-controlled studies indicate gabapentin is effective in relieving neuropathic pain[26]. Currently, the first multicenter RCT is underway to examine the efficacy of oral gabapentin[38]. Prior studies suggest that gabapentin may improve self-reported symptoms, but these investigations lacked placebo controls[39,40]. Another confounding factor is that several studies have shown a significant improvement in vulvodynia symptoms with placebo[6,36]. The degree of placebo effect is correlated with the level of desire to get better and the strength of belief that the proposed treatment may be effective[6].

Physical Therapy

Physical therapy and biofeedback have also shown some success[5,6]. These techniques can be applied to the treatment of both localized and generalized vulvodynia and can be particularly effective when there is concomitant vaginismus, a physical/psychological pain condition that may reflect hypertonicity of the pelvic floor muscles[23,24]. Physical therapy is aimed at improving pelvic floor tone and increasing the patient's awareness of her pelvic floor muscles to ease reflex guarding and muscle spasm[6]. Biofeedback also focuses on developing self-awareness to control or minimize vulvar pain and typically involves the use of an electromyography (EMG) unit that is inserted into the vagina, which allows the patient to measure the force of her pelvic floor contractions through the use of Kegel-like exercises[41,42].

Psychological Approaches

Psychological, sexual, and behavioral therapies have also been reported to be successful in reducing pain[5]. However, few RCTs have investigated the impact of such therapies; only one RCT has demonstrated that psychological and cognitive behavioral therapies (CBT) are effective treatments for vulvodynia[43]. Although it is now generally accepted that psychological distress and depression are secondary to vulvodynia, the literature supports the use of psychological, sexual, and behavioral therapy to treat vulvodynia symptoms[6]. Nonetheless, these therapies generally do not address the underlying disease mechanisms. Childhood/sexual abuse may be a risk factor for vulvodynia development and adjunctive counseling may be indicated, if discovered[21,22]. Because psychological distress and depression can arise either following past traumatic experience, such as sexual abuse, or secondary to the chronic pain of vulvodynia itself, the literature supports the adjunctive use of psychological, sexual, and behavioral therapy to treat vulvodynia symptoms[6]. Nonetheless, these therapies generally do not address the underlying peripheral disease mechanisms.

Injectable Agents

When the aforementioned approaches do not appreciably improve symptoms, some women may try injected agents[6]. Such therapies are less applicable to generalized vulvodynia, as the injection site(s) is usually limited to the vulvar vestibule and areas immediately surrounding the introitus[37,44-46]. Botulinum toxin A has been most extensively investigated as a possible injectable treatment for vulvodynia[37,44-47]. Botulinum toxin is a neurotoxin derived from bacterial pathogen, *Clostridium botulinum*[37]. In addition to reduction of superimposed pelvic floor muscle spasm, botulinum toxin may also possess efficacy for vulvodynia due to its ability to inhibit substance P release, a neurotransmitter associated with inflammation and pain[47]. Despite promising results in case studies, the only RCT examining the efficacy of botulinum toxin A failed to show a significant improvement in symptoms versus placebo[46]. Injected corticosteroids may also improve pain profiles in women with vulvodynia, which has been attributed to their potential anti-inflammatory effects[26]. However, further investigation is necessary to confirm their effectiveness.

Surgical Intervention

Vestibulectomy, a surgical procedure to remove all or part of the vulvar vestibule, is currently regarded as an effective therapy for vulvodynia, yet it is typically reserved as a final measure due to its disfiguring qualities, invasive nature, and risk for both short term and long term surgical complications (e.g. unsatisfying appearance, decreased lubrication, sensitive scar tissue)[48]. The relative success of surgical intervention has been largely been evaluated using data from case reports, which suggest a roughly 90% pain improvement and satisfaction rate after vestibulectomy [48,49]. However, vestibulectomy is probably less effective for generalized vulvodynia, and a handful of cases have reported intensified post-recovery pain symptoms[48-50]. Patients receiving surgery may also experience inclusion cyst development or pain recurrence/persistence at a rate 0-13% and will therefore undergo more than one surgery[48].

As in all chronic pain conditions, long-standing vulvodynia is associated with a complex layering of neuropathology that includes supraspinal influences of depression, anxiety, hypervigilance, and catastrophization[51,52]. What is key and unique to the treatment of vulvodynia is the efficacy of targeted vestibular therapy. Clinical research support comes from a number of directions. First, a recent systematic review of vulvodynia treatment has shown a “complete relief of vulvodynia pain” effect size of 67% for surgical excision of the vestibule[53]. This clearly surpasses other published therapeutic modalities. Second, one of the few, well designed RCTs compared the therapeutic effectiveness of three modalities: surgical excision of the vestibule, cognitive behavioral therapy (which theoretically targets supraspinal neuropathology), and pelvic floor physiotherapy (targeting pelvic floor musculature)[50]. Although all treatments reduced vulvodynia pain and dysfunction, surgical excision was demonstrated to be most effective. The fact that removal of the vestibular tissue is effective in reducing pain suggests that inherent factors associated with the vulvar vestibule influence disease; the vulvar vestibule is derived from a different embryonic origin compared to the exterior vulva and vagina[54]. To place in perspective, this does not conclude that surgical excision of the vestibular tissue is the only effective future approach. Rather,

medically-targeted intracellular intervention to the unexcised vestibule is both feasible and likely to correct pain in a majority of vulvodynia cases.

Summary

Although a number of vulvodynia causes have been theorized, no definitive mechanism has been defined and no therapy is effective in permanently eliminating all patient-reported symptoms. Current evidence suggests that several contributing factors and potentially overlapping mechanisms/etiologies are involved in generating chronic vulvar pain. Therefore, there is an urgent need to develop improved treatment strategies. Using both basic and clinical research strategies to better elucidate the origins of disease should lead to vast improvements in the available therapeutic tools, enabling clinicians to target the underlying causes of vulvodynia, directing our efforts toward primary prevention.

Inflammation revisited: evidence that vulvodynia may have an inflammatory basis

History of terminology

The original term vestibulitis eludes to the potential inflammatory origins of the disease; “itis” typically denotes an inflammatory condition[55]. The use of this term was supported by evidence that inflammatory cell infiltrates (e.g. mast cells) and inflammatory mediators were present in the vestibular tissue of women with vulvodynia[56,57]. However, inflammatory cells are also present in “healthy” women, indicating that this may be a normal state not associated with disease pathology[58]. Therefore, this condition was reclassified as vulvodynia in 2003, effectively removing the inflammatory classification and placing emphasis on allodynia (pain to light touch)[55]. However, recent studies have revisited the potential inflammatory origins and suggest that a less classical inflammatory presentation may contribute to chronic vulvar pain[11-17].

New evidence implicating inflammation in vulvodynia

Although both LPV patients and healthy women show signs of infiltrating inflammatory cells, the relative abundance and organization of these cells may differ between patients and controls. A recent paper demonstrated that women with LPV have higher densities of immune cells in the vulvar vestibule[16]. LPV patients presented with greater numbers of B lymphocytes and mature mucosal IgA-plasma cells, while B and T cells were arranged into germinal centers in cases that were absent in controls[16]. However, similar to much earlier observations, cases and controls both showed the presence of antigen-presenting dendritic cells, macrophages, and mast cells, which were of roughly equivalent abundance[16,58]. In addition, LPV patients may have elevated levels of CD4 positive T cells, which are often recruited by allergic or infectious triggers[17]. Overall, the vestibular area appears to have a localized immune system that contributes to inflammation. Therefore, targeting inflammation may represent a valuable resource for the development of more efficacious therapies for vulvodynia, although, as for any therapy, it may not be equally effective for all LPV patients, based on individual disease profiles.

There is an established link between pain and inflammation; inflammation and pro-inflammatory mediators have been long associated with allodynia[12,59-67]. Allodynia is generally indistinguishable from neural pain fiber (nociceptor) sensitization and is often stimulated by the release of intradermal or subcutaneous pro-inflammatory factors, including IL-6 and prostaglandin E_2 (PGE_2)[60,61]. Such factors are frequently elevated in chronic pain conditions[62,64], and elevated expression of PGE_2 and IL-6 provokes allodynia in both human and animal studies[59,66], while suppression of these pro-inflammatory mediators alleviates allodynia[68,69]. We have determined that human fibroblasts isolated from painful vulvar sites produce elevated levels of IL-6 and PGE_2 compared to fibroblasts isolated from non-painful sites[12,13]. Furthermore, pro-inflammatory mediator production is elevated in fibroblasts isolated from vulvodynia patients compared to those isolated from "healthy" controls.

Other research groups have also shown that pro-inflammatory mediators are present/elevated in the vestibule of women with vulvodynia. One recent report examining pro-inflammatory mediator expression in the vestibular tissue of cases and controls detected tumor necrosis factor-α (TNF-α; a pro-inflammatory mediator) more readily in women with vulvodynia[15], which is consistent with previous findings indicating that TNF-α and IL1-β are elevated in vulvodynia patients[70]. This study provides histological evidence suggesting that pro-inflammatory mediator production is elevated in the vestibule of vulvodynia patients[15], which agrees with findings from our group that indicate vestibular fibroblasts from cases produce elevated levels of pro-inflammatory mediators[11-13].

Clinically pain mapping the vulva of an affected patient finds that a mere 3 cm distance separates painful vestibular sites from the non-painful exterior vulva[13]. Despite the proximity to the external vulva, the vestibular tissue is derived from the endoderm,[54] and this tissue likely holds distinct immunologic properties[11-13]. Furthermore, the vestibule of women with vulvodynia may also be hyperinnervated compared to pain-free controls[71,72]. However, hyperinnervation may lack specificity for vulvodynia, because it has been associated with itching in atopic dermatitis[73], and neuropathic pain is usually linked to nerve loss, rather than increased nerve density[74]. We propose that hyperinnervation likely does not represent the pathophysiological foundation of vulvodynia, although it may play a role in this condition. Specifically, there may be an important relationship between hyperinnvervation and the inflammatory response; nerve fibers express receptors for recognizing inflammatory stimuli and produce pro-inflammatory mediators, while inflammatory stimuli may promote nerve growth (demonstrated in a mouse model of vulvodynia), and increased nerve density can exacerbate the inflammatory response[18,75-77].

Stimuli associated with the development of vulvodynia

Another problem in linking LPV to inflammation is that the identification of precursors to vulvodynia onset has been subject to patient recall and represents a major hurtle in elucidating the origins of disease[6,78,79]. Patient interviews have generated long lists of possible catalysts, reflecting the complex etiology of LPV, which include childbirth, pregnancy, stress, diet, vulvovaginal infections, sexual/physical abuse, and injury, many of which have not been reliably associated with the onset of vulvar pain[6,78,79]. However, one

consistent precipitating stimulus has been cited in greater than 70% of vulvodynia patients, which is a history of recurrent yeast infections[80]. The empirical evidence linking yeast infection to vulvodynia is limited, although in a mouse model, repeated vulvovaginal infection with *Candida albicans*, a common etiological agent of vulvovaginal yeast infection, results in contact hypersensitivity and pain, even after infection clearance[18]. Furthermore, a study in humans showed that vulvodynia patients are more likely to react to a patch test with *C. albicans* than "healthy" women[19]. Nonetheless, one important caveat to consider is that in most cases yeast infection is self-diagnosed and treated with topical over-the-counter preparations, offering the potential for misdiagnosis; self-reported yeast infection could represent other gynecological conditions or infections[81]. Therefore, it is plausible that additional organisms may play a role in this inflammatory response, while there is a clear role for *Candida* species. Mucous membranes are particularly vulnerable to microbial infection and utilize a number of often overlapping defense systems for responding to noxious stimuli including, fungi, bacteria, and viruses[82].

Critics of the infectious origins theory have noted that women with vulvodynia do not present with yeast infection[1,5,26]. Furthermore, treatment with antifungals does not resolve the symptoms of vulvodynia[83], although previous recurrent infection may be sufficient to elicit chronic pain[18]. However, patient vestibular fibroblasts respond to very low doses of *C. albicans* (less than 100 yeast cells), while pain-free external vulvar cells fail to respond[11]. Such a low dose of yeast is unlikely to be detected by our current clinical diagnostic methods (e.g. culture or DNA probe) and is typically not associated with active infection[84]. This may explain why women with vulvodynia do not present with yeast infection. Doses required to elicit a response in control fibroblasts and in the external vulvar fibroblasts of LPV patients were roughly 1000-fold greater, more consistent with infectious loads[11]. These findings suggest that the vulvar vestibule of women with vulvodynia is inherently sensitive to yeast; subclinical infection with *C. albicans* may be sensed by these fibroblasts to generate a maladaptive immune response. We propose that this represents dysregulation of a normally beneficial response that would typically help to maintain a healthy vulvovaginal flora.

Mechanisms for vulvar inflammation

Research into the mechanisms that might govern inflammation led our group focus on Dectin-1, a well-characterized yeast responsive pattern recognition receptor (PRR) that recognizes fungal β-glucan[11,85]. The current literature suggests that β-glucan is abundant during chronic infection[86,87], while it is also probable that fibroblasts would be able to sense β-glucan during infection, because *C. albicans* debrides the epithelium through protease secretion and invasion[88,89]. In turn, the underlying fibroblasts should be exposed to invading yeast and their products. We found that vestibular fibroblasts from vulvodynia patients express slightly elevated protein levels of Dectin-1 compared to controls[11]. At the same time, Dectin-1 is modestly elevated in vestibular versus external vulvar fibroblasts. Although we have not yet definitively demonstrated that increased receptor abundance accounts for heightened sensitivity, this is a plausible explanation we plan to investigate further. However, additional receptors (e.g. TLR-2, TLR-4; Figure 1) may also be involved in the heightened response to yeast or other microbial triggers, as we identified other active PRRs on

vestibular fibroblasts. PRRs have been implicated in host recognition of a wide range pathogen-associated molecular patterns (PAMPs) expressed by yeast and even bacterial and viral species[85,90]. We suspect that the combined abundance and activity of these receptors influences the production of pro-inflammatory mediators, ultimately determining the overall pain profile.

At present, this PRR-mediated response (summarized in Figure 2) is the only intracellular mechanism described for vulvodynia[11]. We acknowledge that more investigation will be required to completely elucidate the mechanisms of disease and definitively demonstrate that inflammation plays a causative role in vulvodynia. However, our research has uncovered potential targets for the development of additional LPV therapeutics. Not only have we shown that Dectin-1 is more abundant on fibroblasts isolated from painful areas, but the activity of Dectin-1 contributes to the production of pro-inflammatory mediators; blocking the function or expression of Dectin-1 results in a significant decrease in IL-6 and PGE_2 production[11]. Dectin-1 can signal through the NFkB pathway, a key pathway triggered during inflammation, which activates the transcription of pro-inflammatory mediators (e.g. IL-6 and Cox-2, involved in PGE_2 production)[91-93]. Although NFkB activation has not been previously investigated in vulvar fibroblasts, our recent work demonstrates that the NFkB pathway is activated in cells stimulated with zymosan or live yeast[11]. Furthermore, inhibiting NFkB essentially abrogates pro-inflammatory mediator secretion in vulvar fibroblasts[11]. Therefore, we have already identified at least two potential targets for the development of new therapeutics: Dectin-1 and NFkB. We expect our current line of investigation to identify other potentially more specific and selective targets.

Towards better therapeutics

Vulvodynia is a prevalent condition with severe consequences for afflicted women and their partners. However, treatments for vulvodynia fall short, and patients may not receive adequate relief, or symptoms may recur, even after undergoing invasive treatment (e.g. vestibulectomy)[48-50]. Multidisciplinary approaches have been most effective and all available evidence suggests these will continue to be[5,6,25]. However, taking into account the limited number of RCTs and the placebo effect, it is difficult to discern what the overall best course of treatment will be for a given woman[26,36,38]. This results in multiple visits to various physicians and therapists, during which time the patient may perceive that her situation is hopeless or is not being adequately addressed[5,6]. This only serves to augment the psychosomatic components of the disease[33,34].

The monetary cost of vulvodynia care in the United States is greater than $8000/patient for a six-month course of treatment and bears with it an annual national burden in excess of $31 billion[94]. The sudden onset and crippling effects of vulvodynia, combined with its prevalence, translates to countless women willing to try nearly any therapy, regardless of cost or proven efficacy[6]. However, some measures taken by patients to “wash away” symptoms may only exacerbate them[6]. Therefore, it is imperative that we carefully examine the underlying mechanisms of disease and develop improved rationales for new therapies or enhanced formulations of current therapies. It is not our viewpoint that the current treatment modalities are invalid; most clinically implemented therapies do have at least some empiric

evidence to support their use[5,6,26]. However, we envision a future where these therapies can be better implemented, along with new therapies targeting the inflammatory origins of disease. We believe that recent evidence is sufficient to implicate an inflammatory mechanism that serves a role in generating or amplifying vulvar pain. Therefore, the addition of strategies aimed at modulating this response will likely improve pain symptoms in women with vulvodynia.

Conclusion

By accepting inflammation as a possible contributing factor to the occurrence of vulvodynia, we open a new set of possibilities for the treatment and management of this disabling condition. Although we do not advocate for a terminology change (a return to vestibulitis) or drastic changes to how practitioners treat vulvodynia, we contend that researchers and clinicians alike should be aware that inflammation likely plays a role in this condition. Further investigation into how inflammation may influence LPV could lead to the development of new therapeutics or even the improved application of currently accepted and utilized therapies.

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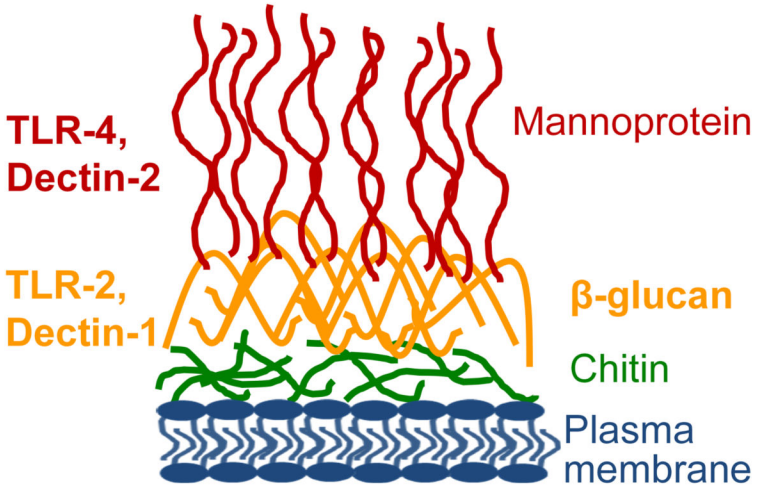

Figure 1. The fungal cell wall and its paradigm receptors

This illustration depicts the *C. albicans* cell wall, which is comprised of four major components: mannoprotein, β-glucan, chitin, and the plasma membrane. Although, the mannoprotein layer is primarily exposed, β-glucan and chitin are accessible at bud scars during cell division, and β-glucan is actively secreted by *C. albicans* during chronic infection. We have focused on receptors involved in mannoprotein and glucan recognition (listed on the left), as they are major components of zymosan, which has also been established to elicit a strong response in human vulvar fibroblasts.

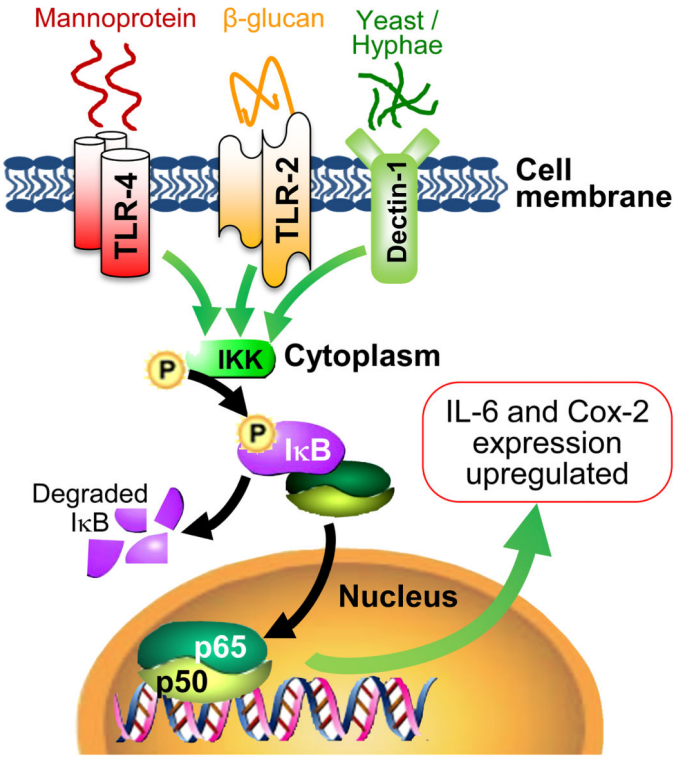

Figure 2. Inflammatory PPR-mediated mechanisms implicated in vulvodynia

This illustration depicts the transcriptional activation of pro-inflammatory mediators when Dectin-1 and other PRRs (e.g. TLR-2 and TLR-4) signal through the NFkB pathway. Dectin-1 senses live yeast and zymosan to elicit the production and release of pro-inflammatory mediators (IL-6 and PGE_2). Signaling through Dectin-1 results in phosphorylation of NFkB inhibitors, which are subsequently degraded via proteolysis to allow NFkB subunits (associated with canonical pathway) to translocate to the nucleus to activate transcription of IL-6 and Cox-2 (rate-limiting enzyme in PGE_2 synthesis). We have discovered the presence of TLR-2 and TLR-4 on vulvar fibroblasts; these PRRs have been shown to signal through NFkB in other cells types, although their function in vulvar fibroblasts has not been confirmed. We are investigating the role of these and other PRRs in sensing and responding to subclinical levels of yeast and other stimuli that may contribute to chronic vestibular inflammation.