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What is special about the vulvar vestibule?

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Abstract

The pathological underpinnings of localized provoked vulvodynia (LPV), the most prevalent cause of vulvar pain that is frequently comorbid with other variants of chronic pelvic pain, have evaded clinicians and scientists for decades. This commentary describes the background and implications of the findings presented by Foster et al. [6] in this issue. An emphasis is on reasons why the vulvar vestibule—an embryologically distinct band of tissue demarcating the internal female reproductive tract and external vulva—should exhibit a propensity for fibroblast-mediated proinflammatory responses to commonly encountered yeast in healthy women, as well as women with LPV. Foster and colleagues' findings have the potential to advance the clinical assessment of women with LPV, facilitate the identification of mechanistically distinct comorbid pelvic pain conditions, and guide future animal model development to optimize their clinical relevance.

Keywords

localized provoked vulvodynia; vulvar pain; inflammation; fibroblast

The reproductive machinery is evolutionarily precious. As a result, physiological mechanisms evolved to protect reproductive organs from common environmental threats. Ongoing exposure to potentially pathogenic fungi, bacteria, and viruses has made the female lower reproductive tract a veritable battleground for immune defense. The external vulva and vaginal canal express a unique immune profile that differs from other mucosal sites and elsewhere in the periphery, and this specialization is preserved across species [10]. It therefore follows that pain induced by inflammation may also show vulvovaginal-specific properties.

The elegant work presented by Foster and colleagues [6] expands our understanding of the complex relationship between pain and immune function with the novel observation that the vulvar vestibule—a thin band of tissue demarcating the entrance to the vagina—exhibits a highly localized and tissue-specific pro-inflammatory response in healthy women. This response is further amplified in women with localized provoked vulvodynia (LPV), a common type of chronic pelvic pain that afflicts 9–16% of premenopausal women [8]. LPV is characterized by sharp, burning pain localized to the vulvar vestibule in response to light

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CONFLICT OF INTEREST
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pressure (i.e., mechanical allodynia) and is accompanied by enhanced vulvar pain perception (i.e., mechanical hyperalgesia) and continued pain that is temporally dissociated from its stimulus (i.e., “after sensation”). The mechanisms underlying LPV remain unknown, despite equivocal evidence for low-grade vulvar inflammation, altered peptidergic vulvar innervation, and genetic susceptibilities that contribute to abnormal inflammatory cascades.

Candida albicans is a known inflammogen across species and is implicated in over 90% of vulvovaginal yeast infections in women. The high incidence of recurrent yeast infections in women with LPV prompted the hypothesis that yeast-induced vulvovaginal inflammation may underlie peripheral (and potentially central) sensitization of primary afferent nerve endings at the vestibule. This hypothesis allows for experience-dependent inflammatory insults to play a role in the initiation and/or maintenance of LPV (supported by direct activation of nociceptors by pathogenic bacteria, see [3]), as well as genetic polymorphisms that are frequently identified in this population [2]. The former point is supported by an experimental mouse model of LPV that confirmed that repeated vulvovaginal infections with *C. albicans* are sufficient to cause chronic vulvar pain behavior and increased vulvar peptidergic innervation, a finding that parallels observations in the clinical literature [2,4]. Furthermore, some women with chronic vulvar pain may be exceptionally vulnerable to *C. albicans* exposure, as indicated by enhanced contact sensitivity to intradermal *C. albicans* injections and increased fibroblast-mediated cytokine production [7,11]. The question remains, how does the vestibule uniquely mediate these symptoms, and how can we differentiate normal vulvar nociceptive processes from pathological ones?

To address these questions, Foster et al. [6] evaluated women with and without chronic vulvar pain with vulvar quantitative sensory testing (QST) and examined vulvar tissue variability in fibroblast-mediated cytokine release. Women were assessed for alterations in pain perception associated with vulvar mechanical allodynia (via algometry) and hyperalgesia (via the cotton swab test). Mechanical pain threshold and suprathreshold levels were measured at the vestibule and an adjacent vulvar control site, and tissue biopsies were obtained from the same regions. In normal vulvar tissue of healthy women, fibroblast exposure to Candida and non-Candida yeast elicited modest fibroblast-mediated inflammation, as measured by interleukin-6 (IL-6) and prostglandin E2 (PGE2) levels. Importantly, a robust increase in the magnitude of this pro-inflammatory response was evident at the vestibule, compared to adjacent vulvar tissue. These observations strongly support the vulvar vestibule as immunologically unique tissue that exhibits enhanced inflammatory responsiveness to multiple genera of fungi, mediated in part by specialized fibroblasts. In women with LPV, exaggerated IL-6 and PGE2 levels were observed at both vulvar sites following Candida exposures. Vestibule fibroblasts, in particular, induced a profound increase of pro-inflammatory mediators in response to all yeast stimuli. Therefore the vulvar tissue of women with and without LPV were differentiated by the degree of naturally occurring inflammation.

Given the increasing focus on peripheral and central immune factors underlying acute and chronic pain, this work is a timely and topical advance in our understanding of site-specific mucosal immunity. The unique inflammatory properties of the vestibule appear to facilitate the rapid detection of pathogens at a critical anatomical gateway to the reproductive tract. It

is feasible that other structures derived from the endoderm, including the bladder and anterior urethral wall, may also exhibit unique immune properties. Notably, the high incidence of comorbid vulvar and bladder pain in young women, in some cases, may reflect vulnerabilities of endoderm-derived tissue [1,5]. These possibilities require a shift in our understanding of inflammation as it relates to pain pathology, a sort of immunopathological relativism: the clinical significance of inflammation depends on its anatomical context. For instance, the magnitude of a pro-inflammatory response—rather than its presence alone—may be critical in differentiating pelvic pain populations from healthy individuals, and from one another. Long after the original nociceptive stimuli are gone, *in vivo* and *in vitro* pathogen/irritant challenges that evoke pro-inflammatory responses can provide an ideal diagnostic strategy for examining such responses.

Clinically, the correlations between self-reported vulvar pain sensitivity and distinct fibroblast-mediated pro-inflammatory factors reported by Foster et al. [6] provides some tantalizing results. Matching such specialized immune mechanisms to clinical symptoms is the closest the field has come to identifying an objective marker of pathology of LPV. This finding in part reflects the authors' painstaking efforts to obtain tissue from patient-identified sites of vulvar pain. Furthermore, the data presented in Tables 2 and 3 raise the possibility that levels of IL-6 and PGE2 are associated with distinct sensory aspects of LPV. Fibroblast-mediated IL-6 levels appear to uniquely relate to pain threshold and, by extension, mechanical allodynia, whereas PGE2 production tended to preferentially reflect suprathreshold pain evoked during the cotton swab test (8/10 mean pain rating in this sample). These speculations, as well as other novel hypotheses raised by the authors, would require larger samples of women with LPV who are carefully phenotyped. The likely existence of distinct subtypes of LPV suggests that a principle components analysis would be needed to identify women who show sensitized inflammatory responses, as any clinical sample may contain mechanistically distinct variants of LPV (see [9]). Furthermore, the use of zymosan as an inflammatory stimulus can be applied across laboratories without the need for biohazard safety measures required for handling Candida. This convenience facilitates its use in animal model development to better understand the acute and chronic impact of vulvovaginal yeast versus bacterial exposure, the genetic mediation of this impact, as well as the prevention and treatment of resulting vulvar pain behavior.

Without mincing words, I believe that Foster and colleagues' proof of concept is one of the most significant advances in vulvodynia research over the past 20 years. Their work answers longstanding questions about the significance of vulvar inflammation in women with and without LPV pain, establishes tissue-specific fibroblasts as sufficient and sensitive mediators of cytokine release, and relates fibroblast-mediated cytokine levels with clinically meaningful behavioral outcomes used in the assessment and diagnosis of LPV. This work is the closest we have come to identifying objective and quantifiable indicators of peripheral pathology underlying persistent vulvar pain. Moving forward, it will be important to integrate these findings with information on peripheral afferent sensitization, spinally-mediated central sensitization, and supraspinal processes underlying emotional learning of the chronic pain state.

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