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Inflammation and nerve fiber interaction in endometriotic pain

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Endometriosis is an extremely prevalent estrogen-dependent condition characterized by the growth of ectopic endometrial tissue outside the uterine cavity, and is often presented with severe pain. Although the relationship between lesion and pain remains unclear, nerve fibers found in close proximity to endometriotic lesions may be related to pain. Also, women with endometriosis pain develop central sensitization. Endometriosis creates an inflammatory environment and recent research is beginning to elucidate the role of inflammation in stimulating peripheral nerve sensitization. In this review, we discuss endometriosis-associated inflammation, peripheral nerve fibers, and assess their potential mechanism of interaction. We propose that an interaction between lesions and nerve fibers, mediated by inflammation, may be important in endometriosis-associated pain.

Endometriosis and the enigma of pain

Endometriosis (see Glossary) is characterized by the presence of endometrial epithelial and stromal cells outside the uterine cavity. It is extremely prevalent, occurring in up to 10% of reproductive age women [1], significantly impacts quality of life, and places a large burden on the healthcare system [2]. The pathogenesis of endometriosis is not entirely clear, although retrograde menstruation is the most commonly accepted theory (Box 1). It is a remarkably heterogeneous disease, broadly separated into peritoneal, ovarian, and deeply infiltrating endometriosis (DIE) [3]. It is also associated with a multitude of painful symptoms which vary from person to person [4]. There is little direct relationship between the physical presentation of the endometriotic lesions and the pain reported [5].

Endometriotic lesion growth stimulates an increase in the concentration of proinflammatory cytokines [6–8], chemokines [9–11], and growth factors [12] in the peritoneal cavity (Table 1). It is speculated that inflammation is associated with neuropathic pain, and recent evidence from animal models using dorsal root ganglia (DRG) neuronal cultures are beginning to elucidate the mechanisms by which inflammation may stimulate peripheral nerve sensitization [13,14].

Emerging research that shows women with endometriosis and chronic pain have permanent alterations in the central nervous system [15] is beginning to validate the notion that the nervous system may have a role in endometriotic pain, although it is still unclear how these lesions engage the nervous system. A spatial relationship has been proposed, as some lesions infiltrate nerve fibers and produce hyperalgesia [16], and a pilot study found that nerve fiber proximity to a lesion is indicative of increased pain [17]. Conversely, no correlation between the presence of nerve fibers and pain has been reported [18,19].

Glossary

Central sensitization: an enhanced excitability of the central nervous system leading to an exaggerated response.
Deep infiltrating endometriosis (DIE): the presence of endometrial epithelial and stromal cells that infiltrate more than 5 mm under the peritoneum.
Dorsal root ganglia (DRG): a cluster of cell bodies that contain the sensory neurons that innervate the peritoneal cavity.
Dysmenorrhea: abdominal pain during the menstrual cycle.
Dyspareunia: painful sexual intercourse due to a medical condition.
Endometriosis: the growth of endometrial epithelial and stromal cells outside the uterine cavity.
Gonadotropin-releasing hormone agonist (GnRHa): a synthetic compound designed to bind to the gonadotropin-releasing hormone receptor in the pituitary and used in the treatment of endometriosis due to its ability to create a hypoestrogenic state.
Hyperalgesia: a condition that is characterized by the application of a stimulus that elicits a painful response that would not normally.
Neuropathic pain: is pain caused by damage or dysfunction of the peripheral nerve that is mediated by a sensitization or ectopic firing of afferent nerve that induces nociceptive signaling in the central nervous system.
Peripheral sensitization: amplification in the responsiveness of peripheral nerve terminals to simulation or injury manifested by a reduction in the thresholds of activation.
Peritoneal fluid (PF): fluid contained within the peritoneal cavity that reduces friction produced by the movements between organs.
Purinergic receptors: are a family of ligand-gated cation channels that are activated by ATP and are involved in the effects of chronic pain.
Rectovaginal septum (RVS): a layer of strong connective tissue between the rectum and vagina, referred to sometimes as the rectovaginal fascia.
Retrograde menstruation: the reflux of viable endometrial and stromal cells into the peritoneal cavity during menstruation.
Transient receptor potential vanilloid 1 (TRPV1): is a member of the TRP superfamily and is a nonselective cation channel that is expressed in neuronal and non-neuronal cells and functions in the recognition of noxious stimuli. It is upregulated in various human disease states.
Voltage-gated sodium channels (Na_v): voltage-gated sodium channels are a family of ion channels that initiate action potentials in nerve muscle and other excitable cells. The genes for these proteins are referred to as SCN1A–SCN11A.

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Box 1. The pathogenesis of endometriosis and the associated inflammation

Originally proposed in 1927, Sampson's theory of retrograde menstruation asserts that, during menstruation, endometrial tissue is refluxed back through the fallopian tubes and into the peritoneal cavity. Viable epithelial and stromal cells can attach to the wall of the peritoneum and structures therein [85].

Endometriosis cases, however, have been documented in men [86] and women with Mayer–Rokitansky–Küster–Hauser syndrome, who are missing a uterus [87], suggesting other mechanisms may be involved. Therefore, other theories have been proposed, including coelomic metaplasia, lymphatic spread, and adult stem cells that play a role in the endometrial self-renewal process. In addition, recent genome-wide association studies have found a consistent alteration in certain regions of the genome that are associated with endometriosis [88], indicating a genetic component to the disease. Although the significant heterogeneity of endometriosis suggests that ultimately a number of these factors may combine to produce the endometriotic lesions, retrograde menstruation remains the most commonly accepted theory.

As this inflammatory environment has been considered a pivotal point in the pathogenesis of endometriosis, much research has focused on characterizing the main components that are differentially regulated in women with endometriosis. It is hoped that this will not only result in a better understanding of the pathogenesis of the disease but also identify potentially useful diagnostic biomarkers. The concentrations of numerous compounds are significantly increased in the PF of endometriotic women, and a summary of the more pertinent cytokines is listed in Table 1 in the main text.

A direct innervation of endometriotic lesions occurs in surgical-induced endometriosis rodent models [20], which led to the proposal that a two-way communication between the lesions and the nervous system may contribute to the variable association between the lesion and pain [21]. Recently, another reciprocal relationship has also been identified that may facilitate the pain experienced, specifically the influence of efferent signals from the sensory nerve on lesion progression [22]. Coupled with the recognition that endometriotic-related pain stimulates permanent changes in the central nervous system [15], it is timely to question if endometriotic lesions interact with peripheral nerves at the disease site.

In this article, we identify inflammatory molecules that are both upregulated in endometriosis and are related to pain, discuss the data supporting the presence of nerve fibers in endometriotic lesions, and speculate on the potential mechanisms by which endometriosis lesions and nerve fibers, through inflammation, might interact. We propose that endometriosis-associated inflammation may interact with sensory nerve fibers, and that this interaction could lead to peripheral sensitization and potentially chronic pain symptoms.

Endometriosis-associated inflammation

Numerous molecules are present in and contribute to the inflammatory milieu observed in the peritoneal fluid (PF) of women with endometriosis (Table 1), and regulation of this milieu is associated with the pain reported. Expression of peroxisome proliferator-activating receptor-γ (PPAR-γ), a nuclear transcription factor that regulates cytokine production, in epithelial and stromal cells of peritoneal endometriotic lesions, is positively correlated with both dyspareunia and dysmenorrhea, in women with peritoneal endometriosis [23]. Furthermore, the reduction in the levels of IL-8, pregnancy-associated plasma protein A (PAPP-A), progestagen-associated endometrial protein (PAEP), and midkine (MK) in the PF of endometriotic women treated with gonadotropin-releasing hormone analog (GnRHa) [24] is associated with a reduction in painful symptoms [25].

The specific molecules that may mediate these painful sensations have been more difficult to identify. The proinflammatory cytokines tumor necrosis factor α (TNFα) and IL-1β play essential roles in initiating the cascade of cytokine production in the inflammatory response. TNFα concentrations are significantly increased in the PF of women with endometriosis [26] and are positively correlated with menstrual pain [27]. IL-1β is also significantly increased in the PF of women [28] and is significantly higher in women with endometriosis who also report chronic pelvic pain [29].

Chemokines may also play an important role in neuroinflammation. Monocyte chemoattractant protein 1 (MCP1) is a secreted protein that binds to the C–C chemokine receptor type 2 (CCR2) and is involved in the infiltration of monocytes in sites of inflammation. MCP1 concentrations are significantly higher in the PF of women with endometriosis, compared with women without [30], as are the chemokine regulated on activation normal T cell expressed and secreted (RANTES) [10], and IL-8 [9]. A direct correlation between these chemokines and endometriotic pain has not yet been reported; however, several chemokines interact with sensory neurons. RANTES increases Ca^{2+} channel currents in DRG neurons isolated from Holtzman rats [13], and MCP1 and its receptor CCR2 (Figure 1) are upregulated in chronically compressed DRG from Sprague–Dawley rats, which serves as a model of neuropathic pain [31].

Nerve growth factor (NGF) is a member of the neurotrophin neuronal growth factor family and binds to both the high-affinity tropomyosin receptor kinase A (TrkA) and the low-affinity p75 neurotrophin receptor (p75NTR) (Figure 1). NGF and TrkA are expressed in endometriotic lesions of various locations [32] with a particularly strong expression in DIE lesions [33], with both NGF and TrkA expression in epithelial and stromal cells [34]. The PF of women with peritoneal endometriotic lesions has a significantly higher NGF concentration, compared with women without endometriosis [35]. TNFα and IL-1β treatment of human endometrial epithelial cells (hEECs) also induces NGF secretion [36]. However, NGF mRNA expression in whole endometrioma lesions and pain are not correlated [37], although women with severe pain were more likely to have high PF NGF concentrations [32]. Furthermore, inhibition of NGF via siRNA in a surgically induced rat model of endometriosis inhibited both endometriotic lesion growth and nerve fiber density, and reduced hyperalgesia [38]. Thus, whether NGF is related to endometriosis pain is not clear and the question warrants further investigation.

Non-traditional cytokines are also increased in the inflammatory response to endometriosis and may also play a role in the pain experienced. PAEP is a glycoprotein produced by epithelial cells of the endometrium in the late luteal phase. Evidence suggests that PAEP PF