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Review Article

The Immune System and its Role in the Generation of Pain in Women with Endometriosis

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Abstract

Endometriosis is a benign, oestrogen dependant gynaecological disorder defined by the growth of endometrial-like tissue resembling the endometrium in sites outside the uterus often causing pain and Infertility. The prevalence of endometriosis is 10-15% of women of reproductive age and up to 47% of infertile women. Although the majority of affected women are of reproductive age, however, it has also been documented in pre-menarchal girls and post-menopausal women and in adolescents. Endometriosis is an inflammatory disorder, with signs of increased leukocyte recruitment and activation within, and in close vicinity to endometriotic lesions. The complex interactions of the immune system appear to be lightly regulated during the normal menstrual cycle and variations to these cyclical patterns at local and systemic levels are likely to be involved in pathological states such as endometriosis.

Keywords: Endometriosis; Immune; Leukocytes; Mitochondrial; Pain; Oxidative

Introduction

Endometriosis is a complex hormonal and immunological disease affecting girls and women during their reproductive years [1,2]. Characterised by the presence of lesions, histologically similar to the glands, stroma of endometrium and outside the uterus [3,4]. It has been estimated that 5-15% of women in their reproductive years within the general population suffer from endometriosis [1,4,5]. The reported prevalence among women presenting for investigations of pelvic pain (such as dysmenorrhoea) is as high as 50% and in women with infertility it is estimated to be 40-50% [1,6]. Although the majority of women with endometriosis are of child-bearing age, reports have also described infrequent endometriosis in pre-menarchal girls and postmenopausal women [5,7].

Currently, the 'gold-standard' for the diagnosis of endometriosis is laparoscopy by an experienced gynaecological endoscopist [2,8]. The clinical diagnosis of endometriosis is made by the visual conformation of endometriotic lesions within the pelvis with or without prior histological confirmation. Ideally, histological confirmation to support the clinical diagnosis by biopsy of the ectopic endometriotic lesions is preferable, especially in circumstances of uncertainty in observation of non-pigmented lesions on serosal surfaces of pelvic organs [9].

Immune System Role in Pain Generation

The immune system consists of a network of cells and molecules that work together to provide a response to pathogens [10]. They also provide a defence mechanism and maintain homeostasis and the general wellbeing of the organism [11]. The immune response can be facilitated through innate and adaptive immune components. An innate immune response can be considered as the early line of defence to invading pathogens. On the other hand, an adaptive immune response is more specific to a specific pathogen and also has the ability to preserve memory of such pathogenic constituents [12]. Immune responses are facilitated mainly through immune cell populations (leukocytes) and through mediators that are synthesized and secreted by these cells [13].

Interaction between the immune system and nervous system

Neuroimmune interactions play a critical role both in the initiation and proliferation of peripheral inflammation [14]. The nervous system influences the immune system through hormonal and neuronal pathways. The hormonal pathway mainly involves the Hypothalamic-Pituitary-Adrenal Axis (HPAA) and Hypothalamic-Pituitary-Gonadal axis (HPGA) [15,16]. Glucocorticoids are the end products of HPAA and cause suppression of the immune system. End products of HPGA pathway are estrogens in females and androgens in males. Estrogens prompt and androgens suppress immune responses. Experimental studies have shown that suppression of different types of immune cells can reduce the chronic pain [17]. Therefore, the prevalence of inflammatory, chronic pain and autoimmune disorders are higher in females [18,19].

The neuronal pathway involves the nerves ability to influence the immune system through autonomous nervous system. Catecholamines, which are neurotransmitters, cause anti-inflammatory effect through the promotion of Th2 immune response. In addition, the existence of Beta-2 adrenergic receptor on lymphocytes further validates

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this direct interaction [20]. Other evidence is the inhibitory effect of the parasympathetic system and acetylcholine through nicotinic receptors on macrophage production of pro-inflammatory cytokines [21]. Therefore, pain and inflammation can interact with each other in complex and multi-dimensional ways which are associated with multiple outcomes and lead to an array of 'difficult to manage' pathologies [14].

Peripheral nociceptor sensitization during inflammation

Reports in the literature are that neurons are not the only element that plays a role in the formation and maintenance of most clinical pain states [22]. The immune system comes into action in most cases of chronic pain [17]. In inflammatory responses, the circulation and local leukocytes produce proalgesic mediators that prompt the pain through the stimulation of specific afferent nerve ending called nociceptors [23]. Nociceptors are found on unmyelinated A and C fibers which transduce and propagate noxious stimuli to the brain. With several neurotransmitters modulating these signals at the level of the spinal cord and at supraspinal sites and together with environmental and cognitive factors sensation of pain occur [23].

Neurotrophins and immune system

The possibility of interaction between neurotrophins and lymphocytes was first stated by Dean et al., who observed that the blastogenic response of mouse spleen cells was increased by Nerve Growth Factor (NGF) [24]. This observation has been followed by several other studies that validated each lymphocyte subset produced and expressed different neurotrophins and their receptors [25-27]. As for neurotrophin production, these studies have revealed that B cells produce NGF and NT-3 [25,26,28]. Activated T and B cells also produce Brain-Derived Neurotrophic Factor (BDNF) [29]. In addition, it was suggested that NGF is involved in the survival of B-cell as it has the ability to rescue these cells from stimulated apoptosis [30]. These studies led to the suggestion that there might be autocrine and paracrine activities of neurotrophins and their receptors on immune cells [31].

Neuronal guidance molecules and immune system

Neuronal guidance molecules have gained much interest in the field of immunology and there is an increased focus on the Semaphorin family and their respecters Plxins. Although only a limited number of family members have been comprehensively investigated, they actively contribute to different aspects of the immune system activities [32]. Studies of Semaphorin and Plxins have indicated that some members of these families play crucial roles in immune cell interactions, which in return impact the immune response [33]. In addition, the discovery that lymphocytes expressing semaphorins is a significant breakthrough, as it suggests the involvement of these molecules in both the nervous system and immune system [34]. The current knowledge about these molecules is summarized in (Table 1).

Endometriosis and Immune System

Research into immune system changes in endometriosis has mainly been on local changes in immune cell expression and activity within the peritoneal cavity and ectopic endometriotic lesions [35-37]. Only a few studies have explored the immunological changes at the uterine level [38-41]. These studies have suggested that the immune system plays a crucial role in both the initiation and development of the [42-45]. More specifically, immune cells like T and B lymphocytes and natural killer cells appear to play essential roles in determining either acceptance or rejection survival, implantation, proliferation of endometrial and endometriotic cells [46,47].

Altered leukocytes in eutopic endometrium of women with endometriosis

Evidence suggests that there were alterations in the activity and the number of uterine T-lymphocytes in women with endometriosis in comparison to women without the disease. A study by Mettler et al., showed a reduction in $CD3^+$ T-cells, during the early proliferative phase in the eutopic endometrium of women with endometriosis [48]. This diminution could be caused by the migration and localization of T-cells at the site of ectopic disease [49,50]. Moreover, the number of total T lymphocytes as well as that of activated T lymphocytes was shown to have decreased in eutopic endometrium compared to ectopic endometrium [51,52]. However, a study by Fernandez-Shaw et al., failed to show any difference in the number of T-cells in the endometrium from women with endometriosis compared to women without the disease [53]. On the other hand, studies have demonstrated significant increases in the number of $CD4^+$ T helper cells, expressing IL-2 and γδT cells in eutopic endometrium compared to ectopic endometrium [54,55].

B-lymphocyte populations have illustrated alterations in women with endometriosis. The mean density of endometrial B-cells ($CD20^+$) was higher in women with endometriosis compared to women without the disease. On the other hand, numbers of activated B-lymphocytes ($CD20^+$ and $HLA\text{-}DR^+$) and B-1 cells ($CD5^+$ and $CD20^+$) showed no difference between the two groups [54]. These findings have indicated that there are functional alterations in the activation of B-lymphocytes which modify antigen response and dysregulation of the immune response in women with endometriosis [56]. Previous studies showed no differences between endometrial NK cells in women with and without the disease [51,53,57,58]. However, studies have indicated that eutopic endometrial cells of women with endometriosis release increased levels of Natural Killer (NK) inhibitory substances and shown a reduction in endometrial NK cells cytotoxicity [56,58-61]. This in return prompts the ability of endometrial cells to survive and implant at ectopic sites [62].

Altered circulating leukocytes of women with endometriosis

In addition to local immunological alterations within the eutopic endometrium, there are immunological changes present in the peripheral blood of these women. T-lymphocyte numbers in circulating peripheral blood in women with endometriosis have shown contradictory results. Whilst, some studies have demonstrated no differences in the levels of peripheral $CD3^+$, $CD4^+$ and $CD8^+$ T-lymphocytes in women with endometriosis [63,64]. Another study has reported that the total number of $CD3^+$ T-lymphocytes was reduced in the circulating peripheral blood of women with endometriosis [65]. Wu et al., also looked at the T-lymphocytes activity though the investigation of $CD3^{+/}CD69^+$ and $CD3^+/CD25^+$ lymphocytes [65]. Whilst, CD69 on T-lymphocytes are associated with a higher production of inflammatory mediators TNFα and IL-2, CD25 expression is associated with protecting T-lymphocytes against apoptosis [66-68]. The study has shown a decrease in the numbers of T-lymphocytes expressing these antigens. The result is suggestive of changes in the systemic activity and an increased sensitivity of T-cells to apoptosis in women with endometriosis. In addition, there is also a contradiction to their results in the ratio of helper T-lymphocytes which simulate the immune response to suppressor T-lymphocytes, which in turn reduces the

immune response. Whilst one study has illustrated a higher ratio of helper T-lymphocytes to suppressor T-lymphocytes in the circulating blood of women with endometriosis compared to women without the disease, another investigation into the expression of these peripheral lymphocytes has failed to demonstrate any difference in the ratios of the circulating peripheral blood of women with early- or late-stage endometriosis [69,70]. High helper T-cells in relation to suppressor T-cells maybe indicative of a higher stimulation of immunological responses in endometriosis, with a reduction in the suppression of the immune system. This is suggestive of a dysfunction in the immune response in women with endometriosis and a possible link between endometriosis and autoimmune disease [71-74].

There is also controversy regarding the numbers of B-lymphocytes in the circulating peripheral blood of women with endometriosis. Studies have revealed both higher and lower numbers of $CD20^+$ B-lymphocytes in circulating peripheral blood of women with endometriosis compared to women without the disease [64,69]. Moreover, other studies have reported no differences in the numbers of $CD20^+$ B-lymphocytes in circulating peripheral blood of women with endometriosis compared to women without the disease [70]. In regards to B-lymphocytes activity, a study examined the expression of $CD20^+$, $CD20^+/CD5^+$ and $CD20^+/HLA\text{-}DR^+$ B-lymphocytes in women with endometriosis [70]. CD5 being involved in antigen recognition and HLA-DR involved in antigen presentation. This study has indicated that there are no differences in the ability of peripheral B-cells to recognize and present antigens in women with and without endometriosis [54,75-79].

Studies have demonstrated no differences in the numbers of NK-cells in circulating peripheral blood in women with and without endometriosis [64,80,81]. On the other hand, other studies have found higher and lower circulating NK cell numbers in women with endometriosis compared to women without the disease [82-84]. The activity of circulating NK cells has been shown to be reduced in women with endometriosis. Tanaka et al., reported in a cell-culture, that NK-cell activity was reduced in a dose-dependent manner when cells were exposed to blood sera of women with endometriosis [85]. In addition, NK-cell cytotoxicity was reduced in severe endometriosis, which suggested the association of reduced activity of peripheral NK cells in women with endometriosis with the severity of the disease [86]. It is important to mention that there was a significant reduction in the ability of overall circulating lymphocytes to proliferate and initiate cytotoxic activity against autologous and heterologous endometrium *in vitro* in endometriosis [87]. This result suggests that the ability of peripheral blood lymphocytes to initiate successful immunological response against endometrial cells in culture is considered to be a reflection of the lymphocytes inability to target displaced endometrial fragments in endometriosis.

Interaction between the immune system and nervous system in women with endometriosis

As previously described, the complex interactions between the immune and nervous systems are important factors in the initiation and maintenance of chronic pain [17,22]. Previous studies have investigated the possible role of macrophages in maintenance and growth of nerve fibres in peritoneal endometriotic lesions. These studies demonstrated that Vascular Endothelial Growth Factor (VEGF), produced by macrophages, can act as a neurotrophic factor maintaining and stimulating the growth of nerve fibres and VEGF was higher in the PF from women with endometriosis in comparison to women without the disease [88,89]. However, the role of lymphocytes in pain generation has never been investigated and the role of the immune system in pain generation in endometriosis remains poorly understood.

Reactive Oxygen Species an Oxidative Stress Role in Pain

Reactive oxygen species an oxidative stress

Oxidative stress is defined as the imbalance between the production of reactive species, including Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), and the system's ability to neutralize and eliminate them [90-93]. ROS are by-products of Aerobic metabolism and include Superoxide anion (O_2^-), Hydrogen peroxide (H_2O_2) and Hydroxyl radicals (OH) [94]. ROS have the ability to react and oxidize any molecule they come in contact with and cause modification such as functional alterations and impair cellular processes. These modifications are dependent on the tissue concentration they can either exert beneficial physiologic effects or pathological damage to cellular components, including lipids, proteins and nucleic acids [95,96].

Reactive oxygen species and regulation of inflammation and pain

ROS generated by mitochondria are important in normal innate and adaptive immunity through the activation of immune cells [97,98]. However, increased levels of ROS within immune cells can lead to hyperactivation of these cells and induce inflammatory responses, resulting in tissue damage and pathology [99,100]. High level ROS can induce pain indirectly through oxidative stress-associated inflammation, which is a key component of pain [101-104]. In addition, ROS induces pain directly through sensitizing the nociceptive neurons including myelinated Aδfibers or non-myelinated C fibers that transmit the signals to cerebral sensory cortex and perceive as feeling of pain [104-106].

Reactive oxygen species

Mitochondria

Mitochondria are the primary source of ROS, which generate through Oxidative Phosphorylation (OXPHOS) as a by-product of ATP synthesis [107]. The OXPHOS system consists of around 90 proteins with a dual genetic origin. The subunits are either encoded by nuclear genes or encoded by mtDNA [108]. ROS generation in mitochondria is regulated by a number of factors, including oxygen concentration, efficiency of Electron Transport Chain (ETC), availability of electron donors including NADH and FADH2, activity of Uncoupling Proteins (UCPs) and cytokines [109-111]. In addition, for being a main source of ROS production, mitochondria are also affected by severe and prolonged oxidative stress [110,112]. In normal state, there is a network of mitochondrial antioxidant systems that protect the mitochondria from oxidative damage [113]. This network includes superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase and also a number of low molecular weight antioxidants including α-tocopherol and ubiquinol [114]. However, these antioxidant systems are not perfect [115]. Hydrogen peroxide produced by superoxide dismutase is relatively unreactive, but in the presence of ferrous ion, it can form high reactive hydroxyl radicals through Fenton chemistry. These radicals can induce lipid peroxidation in mitochondrial membranes [113,116]. Accumulative oxidative damages to mitochondria, caused by endogenous metabolic processes and/or exogenous oxidative influences, cause mitochondria to progressively become less efficient. As mitochondria progressively lose their functional integrity, ever-greater proportions of oxygen molecules reaching them are converted to ROS [117].

Plexin/semaphorin	Expression	Binding partner	Activities
Plexin-A1	DCs, plasmacytoid DCs	Semaphorin-6D, Semaphorin-3E	DC activation, movement and lymph node trafficking
Plexin-A4	T cells, DCs, Macrophages	Class 6 Semaphorins	Inhibition of T cell activation Enhancing TLR signaling
Plexin-B1		Semaphorin-4D	
Plexin-B2	GCB cells, macrophages	Semaphorin-4A Semaphorin-4D	Marks Germinal Centers, controls macrophage movement, T cell activation
Plexin-D1	Double positive thymocytes, Activated B cells	Semaphorin-4A and -3E	Thymocyte trafficking Germinal Center B cell development
Semaphorin-3A	T cells	Plexin-A family	Inhibits T-cell activation and monocyte migration, DC movement
Semaphorin-3E	Thymic epithelial cells	Plexin D1	Double positive thymocyte migration and movement, T cell development
Semaphorin-4A	DCs, activated T cells, Th1 cells	Plexin-D1, Plexin-B2, Tim-2	T-cell activation and monocyte migration
Semaphorin-4D	T cells, activated B cells, DCs	CD72	B-cell activation and homeostasis, DC activation, mast cell responses
Semaphorin-6D	T cells, B cells, NK cells	Plexin-A1	DC activation and production of type1 interferon, late-phase T cell proliferation
Semaphorin-7A	Activated T cells	Integrin α1β1	Monocyte/macrophage activation

Table 1: Expression and activities of plexin and semaphorin family members in the immune system [33].

Mitochondrial DNA

Mitochondria have their own double-stranded DNA molecule of 16.6 kb and encode 11 messenger RNAs (mRNAs), which is translated to 13 proteins, 2 ribosomal RNAs (rRNAs) and 22 tRNAs [108]. The Displacement Loop (D-loop) is the only noncoding region of the mitochondrial genome and mutations at a higher frequency and is accumulated in this region more than any other region [118]. It is a hot spot for mtDNA alterations and contains two hypervariable regions. The D-loop includes important components for replication and transcription of mtDNA which may alert the overall mitochondrial function and cellular ROS generation [119]. Mitochondrial DNA is transmitted exclusively through the female germ line [120].

A number of mutations have accumulated in the mtDNA during evolution to facilitate adaption to the different global environments [121]. According to these mutations, human populations have been divided into a number of discrete, region specific, mitochondrial haplogroups [107]. MtDNA haplogroups are defined as patterns of specific Single Nucleotide Polymorphisms (SNPs) scattered throughout the mitochondrial genome, that tend to occur together within individuals and could cause functional changes and alert rates of replication and transcription of the mtDNA [107,122]. In populations of European ancestry, which most studies have focused on, nine such haplogroups with frequencies of at least 1% have been described which include mtDNA haplogroups H, I, J, K, T, U, V and W [122,123]. In addition, Africans are characterized by super haplogroup L, whilst, Asian are characterized by haplogroup M [123,124]. It has been proposed that different mtDNA haplogroups could influence OXPHOS capacity and the production of ROS, which are signalling elements for pathways, can affect cellular behaviours [122,125,126].

Given that mitochondria are involved in ROS formation, and energy production required for the activation and proliferation of peripheral lymphocytes, it has been suggested that mtDNA variants are involved in the pathogenesis of endometriosis [90]. Kao et al., identified novel 5335 bp deletion of mtDNA in endometriotic tissue [127]. A study of women with endometriosis from a South Indian population revealed somatic and germline mtDNA variations in endometrial tissue, suggesting a strong association between mtDNA variations and endometriosis risk [128]. This study was also the first to investigate the association of haplogroups with endometriosis risk and revealed a strong association between haplogroup M5 and endometriosis risk in a South Indian population. Another study on South Indian women with endometriosis investigated the association between D-loop alternations with endometriosis, this was suggestive that mitochondrial D-loop alterations could be an inheritable risk factor for endometriosis [129]. All previous studies have suggested a possible association between mtDNA and endometriosis, although further investigations are required for a clearer understanding of inheritable mtDNA role in endometriosis.

Oxidative stress and endometriosis

Oxidative stress has been involved in endometriosis and develops when there is an imbalance between the ROS and RNS production and scavenging capacity of antioxidants in the reproductive tract [130]. Endometrial tissue of women with endometriosis has shown a higher endogenous oxidative stress with increased ROS generation and alterations in ROS detoxification mechanisms [131]. It's been suggested that the peritoneal protective mechanisms in women with endometriosis might be defective by menstrual reflux. The peritoneal fluid of women with endometriosis has been shown to have increased ROS generation by activated peritoneal macrophages [132]. In addition, women with endometriosis showed a higher iron expression, which can act as a catalyst of free radicals' generation and contribute to oxidative stress, in the peritoneal cavity including peritoneal fluid, ectopic endometrial tissue and peritoneum adjacent to lesions and macrophages as a result of lysis of pelvic red blood cells [130,133]. Yamaguchi et al., reported that high free iron in the contents of endometriotic cysts was found to be strongly associated with oxidative stress and frequent DNA mutations [134]. As a result, the iron-rich environment may impair the functionality of immune cells, thereby contributing to the development of the disease. In addition, Ota et al., revealed that there were high expressions of xanthine oxidase, an enzyme producing ROS, in the endometrium of women with endometriosis throughout the cycle compared to women without endometriosis [135]. This study also indicated that the expression enzymes

associated with free radicals were expressed in the glandular epithelium of endometrium, at levels which were noticeable in endometriosis [135]. Moreover, the expression of 8-hydroxy 1-deoxyguanosine, an oxidative stress marker and lipid peroxide were 6-fold higher compared with normal endometrial tissue [136]. These findings were indicative of the abnormal metabolic activity of free radicals in women with endometriosis [130]. However, the role of oxidative stress and ROS in pain generation in women with endometriosis is still poorly understood.

Conclusion

An improved understanding of the immune system and its relationship between innervation and clinical characteristics may elucidate aspects of pain mechanisms in endometriosis and facilitate the development of novel therapeutic approaches.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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