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REVIEW

The Role of Mast Cells in the Development and Advancement of Endometriosis

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ABSTRACT

Endometriosis is a medical condition identified by the presence of endometrium-like tissue outside the uterus. This condition is known to result in symptoms such as frequent pelvic pain, infertility, and irregularities in the menstrual cycle. The development of endometriosis is complex and, involving abnormal body responses, hormonal imbalances, and genetic predispositions. Although endometriosis is common and affects quality of life, its mechanisms of development and progression are not fully understood. Mast cells (MCs), a type of immune cell, are renowned for their involvement in allergic and inflammatory responses. These cells are essential in the modulation of the immune system and the inflammatory process through the secretion of different mediators like histamine, cytokines, and proteases. In recent years, MCs have been shown to play a role in the pathogenesis of many diseases, including endometriosis. This article explores the relationship between MCs and endometriosis, including disease development, pain perception, angiogenesis, and other important processes. It elucidates how MCs, via their mediators, actively participate in the pathogenesis of endometriosis and the associated inflammatory environment. Moreover, the research emphasizes the potential of targeting MCs as a therapeutic approach for treating endometriosis. Insight into the interplay between endometriosis and MCs holds promise for developing innovative therapeutic strategies to manage this condition effectively.

1 | Normal Physiology of Endometrium

The menstrual cycle consists of several phases: proliferative, secretory, menstrual, and regenerative. Throughout this cycle, the morphology of the endometrium, the proliferation and differentiation of its cellular components, and the movement of immune cell populations change significantly [1]. These changes are primarily influenced by ovarian-derived estradiol and progesterone, along with potential interactions with other endometrial cellular components [2]. Structurally, the human endometrium is composed of two layers: the basalis and the functionalis. The functionalis layer is shed during menstruation and regenerated when pregnancy does not occur [3]. Most immune cells in the endometrium are tissue-resident, although some migrate from the peripheral circulation. These cells are scattered throughout the stromal compartment, positioned between epithelial cells in the functionalis layer, and found in lymphoid aggregates within the basalis [4]. Given the dynamic role of the endometrial immune niche in endometrial function, pregnancy establishment, tolerance of the semi-allogenic fetus, and overall tissue homeostasis, abnormalities in this niche can lead to significant consequences [5].

2 | Endometriosis

2.1 | Overview

Endometriosis is a gynecological condition that affects 7%–10% of women of reproductive age. It is marked by persistent inflammation and pain, which is influenced by estrogen [6–9]. Endometriosis occurs when endometrial tissue, consisting of glands and stroma, is found outside the uterus. This tissue can be located in various areas such as the peritoneal wall, ovaries, colon, bladder, kidneys, lymph nodes, and even in extra-pelvic structures like surgical scars, the abdominal wall, pericardium, liver, pancreas, and rarely, the umbilicus, pleura, lungs, or brain [6, 7, 10–12]. Endometriosis lesions may also be accompanied by reactive fibrosis and extrauterine muscle metaplasia [9]. Depending on the location of the ectopic disease, endometriosis can be categorized into subtypes such as ovarian cysts (endometriomas), superficial peritoneal lesions, deep endometriosis, and rare extra-pelvic lesions [7, 13, 14]. Although it is more common in women of reproductive age, postmenopausal women can also develop endometriosis, with a global prevalence rate of 2%–4% [15]. Certain populations have higher prevalence rates, with two-thirds of young women experiencing pelvic pain and 30%–45% requiring surgery due to pregnancy and complications such as fibrinoid, pelvic pain, or ovarian issues [16].

2.2 | Symptoms

Endometriosis is linked to various symptoms, including abdominal pain, menstrual irregularities, dysmenorrhea, dyspareunia, fatigue, and infertility (up to 25%–35%) [7, 14, 17–19]. Pain is the primary symptom, and about 33% of women experiencing pelvic pain are diagnosed with endometriosis [17]. Moreover, 78.7% of women with endometriosis experience secondary dysmenorrhea, characterized by pain before or during menstruation [9]. Other symptoms of endometriosis may include an abdominal mass, acute abdominal pain, gastrointestinal and urological symptoms (such as dysuria and dyschezia), depression, and anxiety. It is important to note that some individuals with endometriosis may not show any symptoms [9, 14, 20]. Endometriosis is classified as a benign morphological disease, but it shares characteristics with malignant tumors, including invasive seeding, invasive growth, and distant metastasis [18]. The recurrence rate of endometriosis is significant; 20.5% of patients report pain within 3 years, and 43.5% report pain within 5 years [20]. These symptoms affect women's quality of life and productivity [14].

2.3 | Etiology

The exact cause of endometriosis is not fully understood. Potential factors that may contribute to the development of the condition include genetics, epigenetics, metabolism, environmental factors, extrauterine bone-derived stem cells, hormones, endometrial implantation, retrograde menstruation, immune system dysregulation, immunodeficiency, inflammation, implantation during surgical procedures, defective embryogenesis, presence of Mullerian remnants, and the spread of endometrial tissue through the lymphatic or bloodstream [7, 12, 17–19, 21–23].

Recent studies have shown unusual changes in macrophage levels, microbial populations, gut barrier function, and epigenetic expression patterns in individuals with endometriosis. These changes can impact inflammation locally and systemically, contributing to disease progression [7]. Insufficient levels of prenatal and postnatal testosterone may increase susceptibility to endometriosis [11]. Animal studies have also identified stress as a factor that may contribute to the development and severity of endometriosis. This could be due to mechanisms such as activation of cell operators (especially mast cells [MCs]), release of inflammatory cells, and inhibition of the response of the hypothalamic-pituitary axis in the hippocampus [24, 25].

2.4 | Pathophysiology

There are several theories about the development of endometriosis, with Sampson's retrograde menstrual theory being widely accepted [12]. According to Sampson, endometriosis occurs when endometrial tissue flows back into the abdominal cavity through the fallopian tubes [14, 26]. These cells then move to other sites, attach there, and affect the intestinal lining through a combination of angiogenesis and neuronal infiltration [27, 28]. Recent research suggests that anomalies in the endometrium and immune system are key contributors to the advancement of endometriosis [23, 29]. Abdominal swelling is initiated by retrograde bleeding products, including apoptotic endometrial tissue, shed menstrual cells, ruptured red blood cells, and released iron [26]. Dysregulation of the inflammatory pathway resulting from altered cellular response to steroid hormones contributes to the progression of endometriosis by creating a pro-inflammatory environment, preventing apoptosis, neovascularization, promoting adhesion, endometrial cell proliferation, inflammation, and cell invasion [19, 22, 27, 30–32]. Other factors such as immunity, hormonal expression, genetics, environment, and vascularization also contribute to the development of endometriosis [14, 30, 33].

3 | MCs

3.1 | Introduction

MCs are long-lived secretory cells found in species with a circulatory system [34]. They contain large cytoplasmic granules and play a crucial role in the body's defense mechanisms through immune surveillance, phagocytosis, and immune activation [35]. These cells are strategically located at sites where antigens enter the body, such as mucosal tissues and the skin, where they act as a barrier against pathogens. They are absent in avascular tissues but are located beneath the epithelium in vascularized tissues, serving as sentinel cells against environmental threats [34, 36–39]. MCs can remain stationary or move to different sites within tissues [39]. Their phenotype varies depending on the surrounding microenvironments, customized for their roles in immune responses to pathogens [38]. MCs affect many physiological and pathological processes such as fibrosis, inflammation, angiogenesis, wound healing, cancer, mastocytosis, MC activation syndrome, osteoporosis, autoimmune diseases, cardiovascular and pulmonary diseases, Cancer, allergy, and protection against external threats [38, 40, 41]. Hematopoietic stem cells located in the bone marrow have the ability to transform into MC progenitors

when exposed to stem cell factors (SCFs) and cytokines, including interleukin IL-3, IL-4, IL-9, and IL-10. These immature MCs then exit the bone marrow and undergo maturation in various tissues, where they exhibit a prolonged lifespan [35, 41, 42].

3.2 | MC Receptors and Mediators

MCs have several receptors that interact with cells and different molecules, some activating and some inhibiting their activity [42]. Table 1 provides a list of MCs activating and inhibitory receptors. They also have adhesion receptors that enable them to bind to different cells and surfaces. MCs may be activated via IgE (Immunoglobulin E)-dependent or IgE-independent receptors like pattern recognition receptors and the IL-33 receptor [41]. Each MC contains approximately 500 000 particles containing a wide range of molecules [24, 38, 43]. Table 1 shows the main molecules produced by MC in response to stimulatory factors [38, 43]. Factors such as SCF, IL-33, and substance P (SP) can increase MC count. SP induces the secretion of vascular endothelial growth factor (VEGF) and works as a "cellular damage sensor" [24]. MC mediators are divided into pre-stored granular mediators and newly synthesized mediators [35, 38, 43–45]. MCs can also release exosomes, which transport proteins, enzymes, RNA, and miRNA to nearby or distant cells [41]. This transfer of mediators can significantly impact nearby tissues, triggering immune and inflammatory responses. This process can also contribute to cellular hyperplasia, angiogenesis, and tumorigenesis, highlighting their possible involvement in the development of certain illnesses [45]. MCs rapidly react to stimuli by secreting secretory granules through exocytosis, releasing preformed mediators like histamine, proteases, and heparin. Additionally, MCs can generate and release new mediators hours after activation [38, 43].

3.3 | MC Heterogeneity

Different classifications of MCs have been established based on their role, location, staining potency, major proteases, and mechanisms that release mediators in response to specific secreted molecules [34, 44]. In humans, different MC subpopulations are characterized by their protease composition, including trypsin-like (MCT), trypsin-like and chymase production (MCTC), and chymase (MCC) production. These subtypes, which include mucosal MC (MMC) and connective tissue MC (CTMC), differ in distribution, mediator properties, and sensitivity to secreted molecules [37, 41]. MCs can also be categorized based on their resident or inducible nature, inflammatory (iMC), or pro- or anti-tumor (MC1 or MC2) properties. MC receptors and mediators act differently in different tissues, and there are significant differences even within tissues [41].

3.4 | Mechanisms That Influence the Migration of MCs

The movement of MC progenitors in the bloodstream and their entry into tissues for development is influenced by local factors. The exact mechanisms that control this migration are not fully understood, but they are known to be tissue-specific. MC population increases in inflamed areas, such as those affected by allergic rhinitis and asthma, likely due to increased proliferation, migration, survival, and the development of recruited progenitors in response to chemoattractants [41].

3.5 | MCs in the Normal Uterus

MCs are involved in various physiological activities in women, such as reproduction, pregnancy, and birth. These cells are found in greater numbers in the myometrium compared to the endometrium in the human uterus. The MC numbers are stable throughout the proliferative and secretory phases of the menstrual cycle. However, they decrease in the premenstrual endometrium, resulting in their degranulation. Before pregnancy, activated MCs in the endometrium promote endometrial shedding by inducing arterial ischemic spasm and stimulating stromal cells to produce matrix metalloproteinase (MMPs) [40, 51]. Tryptase-containing MCs are mainly distributed in the active layer, while chymase, tryptase, cathepsin G-like protease, and carboxypeptidase-containing MCs are mainly distributed in the myometrium and basal layer [52]. Basal endometrial MCs contribute to postmenstrual tissue regeneration by producing heparin and other essential components. Additionally, MCs are involved in angiogenesis and wound healing in various tissues [40, 51]. Tryptase and chymase play a crucial role in initiating the MMP cascade, which is essential during pregnancy. MCs produce histamine, heparin, arachidonic acid products, cytokines, and growth factors, impacting endothelial cell function and causing local edema [52].

4 | The Association of Endometriosis and MCs

4.1 | Role of MC in Endometriosis

There is increasing evidence supporting the involvement of MCs in inflammatory and autoimmune conditions by influencing vascular permeability, immunity, and fibrosis [26, 53, 54]. Moreover, MCs are linked to cell proliferation, angiogenesis, endometriosis, and pain symptoms [6]. The exact role of MCs in endometriosis development is still debated, with some studies suggesting a closer relationship between MCs and lesion progression [6, 16, 55]. Endometriotic lesions show elevated levels of MCs, which are responsible for releasing various inflammatory mediators, including histamine, TNF-α, NGF (nerve growth factor), and IL-6. Studies have also demonstrated that SCF and MC tryptase levels in the peritoneal fluid of women diagnosed with endometriosis are higher than in healthy individuals [6, 26, 27, 53, 54, 56–59]. In addition, SCF and growth factors increase in endometriotic cells and promote MC recruitment and differentiation [57, 60, 61]. One study found extensive MC infiltration in stromal lesions in endometriosis cases, which was rare in normal uterine serosa and eutopic endometrium. This indicates a connection between endometriosis and an abnormal immune response, especially hypersensitivity [62]. Decreased MC numbers also led to reduced VEGF levels, a cytokine typically produced by MCs during inflammation, emphasizing their importance in disease development [31]. Single-cell RNA sequencing analysis revealed two distinct subtypes of MCs in the peritoneal fluid of individuals with endometriosis. Cluster 13 is characterized as activated MCs,

TABLE 1 | MC mediators and receptors.

Important mediators of MCs [46, 47]		
Early phase mediators	**Late phase mediators**	**Extracellular vesicles (exosomes)**
Cytokines (TNF-α-IL-4)	Cytokines (IL-1, IL-3, IL-5, IL-6, IL-8, IL-10, IL-18, IL-33, TNF-α, SCF, TGB-β)	Proteins
Amines (Histamine-serotonin)	Chemokines (MCP-1, RANTES, TARC, CCL2, CCL5)	Enzymes
Proteoglycans (heparin)	Neuropeptides (CRH, VIP)	RNA, miRNA
Proteases (tryptase, chymase, MMPs)	Lipid derivatives (LTC4, LTD4, LTE4, PGD2, PAF)	—
Growth factors (bFGF-VEGF-NGF, PDGF)	Growth factors (VEGF, bFGF, NGF, GM-CFS, M-CFS)	—

Important receptors of MCs [48–50]			
Activating receptors		**Inhibitory receptors**	
Receptor	Ligand	Receptor	Ligand
FCεR1	IgE	FCγRIIB	IgG
TLRs	Various	PIR-B	MHC I
RLRs	ssRNA, dsRNA, ssDNA, dsDNA	CD300	Phosphatidyle serine
NLRs	Various	Gp49B1	Integrin αvβ3
C-type lectin receptors	Various	CD200R	CD200
C3a, C5a receptors	C3a, C5a	Siglecs	Various
CXCR1-4 receptors	Chemokines	CD305	Collagen type XVII
CD47	Amyloid ß peptides	CD172a	CD47
KIT	Stem cell factor (KIT-ligand)	Allergin-1	Unknown
CD226	Nectin-2	PECAM-1	Integrin αvβ3
CD300	Eosinophilic cationic protein	MAFA	Unknown
CRHR-1, 2 receptors	Corticotropin-releasing hormone, urocortin	CD72	CD100
Cysteinyl receptor 1 and 2	Leukotrienes	IL-10R	IL-10
Endothelin receptors types A, B	Endothelin 1, 3	Cannabinoid CB2	Anandamide
Histamine H1- H2- H4 receptors	Histamine	Glyceraldehyde-3-phosphate dehydrogenase	Lactoferrin
IL-1R type 1	IL-1β	Interleukin 1 receptor accessory protein like 1	Il-37
IL-4R	IL-4	Nucleotide converting ectoenzyme E-NPP3	ATP
IL-6R	IL-6	Peroxisome proliferator-activated receptor gamma	15-Deoxy-Δ12,14-Prostaglandin J2 (a metabolite of PGD2)
IL-17R	IL-17	Sialic acid binding Ig-like lectin 9	Sialic acid binding Ig-like lectin 9 ligand
IL_18R	IL-18		
IL-33R	IL-33		

(Continues)

TABLE 1 | (Continued)

Important receptors of MCs [48–50]		
Activating receptors		**Inhibitory receptors**
Low-density lipoprotein-, Very low-density lipoprotein-receptors	Apolipoprotein E	
Neurotrophic receptor tyrosine Kinase 1	NGF	
Tachykinin receptor 1, 2	SP	
Neurotensin receptor 1,2	Neurotensin	
MRGPRX2 receptor	Opioid peptides	
F2R Like Trypsin Receptor 1	Proteases	
P2Y-, P2X-purinoceptors	ATP	
S1P1- S1P2-receptors	S1P	
TGF-βR1-3	TGF-β1, TGF-β2	
Somatostatin receptor 2	Somatostatin	

Abbreviations: LTC4, leukotriene C4; MCP-1, monocyte chemoattractant protein 1; MCs, mast cells; MMPs, matrix metalloproteinase; NGF, nerve growth factor; SP, substance P; TLR, toll-like receptor.

while Cluster 16 is suggested to be in a transitional phase, possibly originating from basophils [63].

Studies of endometriosis found that black peritoneal lesions had higher MC concentration than red lesions. This suggests that MCs may be involved in the development of peritoneal endometriosis [64, 65]. Paula Jr. et al. found a higher presence of MCs in endocervical smears of women with dysmenorrhea compared to those without dysmenorrhea [66]. Additionally, research on abdominal wall endometriomas indicated that the coexpression of MC chymase and the ANXA1 (Annexin A1 gene)-FPR1 (Formyl peptide receptor 1) system in ectopic endometrium may play a role in forming endometriotic lesions [67]. The research conducted by Fusco et al. revealed that abnormal expression of the Fpr1 gene leads to the regression of endometriotic lesions in an autologous mouse model of surgically induced endometriosis [31].

4.2 | Interaction of Steroid Hormones and MCs

The interaction between the immune system, steroid hormones, and angiogenic pathways is crucial in controlling cellular processes in endometriosis [26, 68]. Studies have demonstrated that estrogen not only increases degranulation when IgE allergens are cross-linked but also directly activates MCs in endometriosis. MCs express estrogen (ERα, Erβ, and GPR30) and progesterone (PR-A and PR-B) receptors, which influence their cell count, distribution, and function in various tissues [11, 60, 69–71]. Endometriotic lesions secrete elevated amounts of estrogen, which results in MC recruitment, maturation, and degranulation [6, 9, 11, 27, 53]. The activation of this process may lead to the release of inflammatory mediators, stimulate local angiogenesis, and contribute to chronic pelvic pain, thereby facilitating the progression of endometriosis [6, 11].

The research conducted by ZU et al. showed that estrogen can regulate the estrogen response element (ERE) through ERα, which subsequently affects the function of MCs in endometriosis [70]. Among estrogen receptors, GPR30 is responsible for the negative effects of estrogen, such as granule release from MCs [11]. However, it is currently unclear whether estrogen affects MC activity via GPR30 in endometriosis. Zhao's study found that estrogen in endometriosis activates MCs through nonclassical estrogen receptors via the MEK/ERK pathway [70].

4.3 | The Effects of MCs on Other Components of the Immune System in Endometriosis

Endometriosis is characterized by irregularities in the quantity and function of various immune cells in the abdominal cavity. This abnormality increases the potential for invasion and adhesion of endometrial cells by natural killer cells, monocytes/macrophages, MC, dendritic cells, B cells, and T cells, leading to implantation, proliferation, and formation of abnormal lesions [23, 29, 72, 73]. Studies have indicated that MCs play a crucial role in developing endometriosis by affecting inflammatory cells in the endometrium during pregnancy [40]. As part of the immune system, MCs have a vital function in orchestrating the immune response by eliminating pathogens and regulating the activity of other cells. Elevated levels of SCF stimulate MC to secrete tryptase, which subsequently activates protease-activated receptor 2 (PAR2), a member of the family of seven transmembrane G protein-coupled receptors, on endometriotic cells. This activation results in the proliferation of endometriotic stromal cells and an increased release of IL-6 and IL-8. Increased levels of monocyte chemoattractant protein 1 (MCP-1/CCL2) and IL-8 in peritoneal fluid indicate a significant association with the severity of endometriosis [74, 75].

Increasing evidence supports the view that MCs participate in the regulation of inflammatory processes by regulating T cell function and stimulating T cell activation, recruitment, proliferation, and cytokine release on a specific antigen (autoantigen) in endometriosis [11]. The analysis revealed a rise in plasma cells, a change in the Th1/Th2 ratio, and an elevation of Th2

levels associated with endometriosis. This elevation subsequently leads to an increase in MCs due to increased SCF levels [61]. When pro-inflammatory factors stimulate normal endometrial cells, they activate complement factor 3 (C3). This process leads to the activation of MCs in endometriosis lesions, which causes the release of inflammatory factors. As a result, a bacterial microenvironment is created where MCs are significantly involved [29].

A recent study found a possible link between endometriosis and type 1 hypersensitivity due to a higher incidence of asthma, allergies, and immune system disorders in endometriosis patients [6]. IL-25 is an important cytokine secreted by MCs and Th2 cells. Studies have shown that endometriosis patients have more IL-25 in their peritoneal fluid compared to healthy people. This suggests that MC and Th2 cells play a role in endometriosis [76]. Considering this problem, IL-25 shows promise as a diagnostic marker for endometriosis [77].

According to a recent study, estrogen stimulates the expression of NLRP3 (NOD-like receptor family pyrin domain containing 3) through ERα and the ERE in MCs. This stimulation is crucial for activating the NLRP3 inflammasome and producing mature interleukin IL-1β in MCs. This event also results in the overexpression of IL1R1 in the ectopic endometrial stroma [56]. Activation of the NLRP3 inflammasome leads to the release of proinflammatory cytokines like IL-1β and IL-18 [53]. Reactive oxygen species (ROS) also affect NLRP3 activation and play a role in various diseases. Exposure to certain stimuli can trigger ROS production by MCs [26, 53]. However, the specific mechanisms by which the NLRP3 inflammasome affects ectopic endometrial development are not fully understood. The selective inhibition of NLRP3 has shown a significant ability to reduce lesion expansion and fibrous tissue growth in mouse models of endometriosis. This finding suggests that MCs contribute to the progression of endometriosis by activating the NLRP3 inflammasome [53].

The activation of the IL-1β-IL1R1 signaling pathway in stromal cells causes the production of IL-33. Subsequently, IL-33 promotes the polarization of recruited peritoneal monocytes to the M2 subtype. The M2 subtype of monocytes releases IL-1β, which induces stromal cells to secrete IL-33 within the wound environment. The incidence of endometriosis is associated with the presence of the M2 subtype and the IL-33 cytokine. This is because IL-33 reduces the phagocytic capacity of the M2 subtype. Activated monocytes may promote macrophage activation and polarization in endometriosis by creating an inflammatory microenvironment. The activated macrophages then undergo phenotypic polarization in response to microenvironmental signals, thereby promoting inflammation in endometriosis [56]. Figure 1 briefly illustrates the effects of MC on the immune system during the development of endometriosis.

The immune system in the peritoneal cavity undergoes specific changes in endometriosis. These changes include increased numbers and activation of peritoneal macrophages and MCs, decreased T-cell and NK-cell activity, and lower levels of dendritic cell maturation. These changes lead to inadequate removal of ectopic endometrial cells from the peritoneal cavity [27, 51, 78]. Previous studies have shown that alterations in regulatory T cells (Tregs) and T helper 17 (Th17) cells may contribute to the occurrence and development of ectopic endometrial implantation and accelerate the progression of endometriosis to an advanced stage [23]. Additionally, the fraction of Th17 lymphocytes is significantly higher in the lesions compared to the normal endometrium [79]. A specific population of MCs expressing aryl hydrocarbon receptor (AhR), IL-17, and IL-10 has been identified in the endometrium [76]. The simultaneous production of IL-17, IL-6, and IL-10 by MCs, along with peritoneal mesothelial cell-derived TGF-β, could cause Tregs to transform into chronic inflammatory Th17 lymphocytes [80]. Also, Th17 cells can develop from naive CD4+ T cells when exposed to TGF-β, IL-6, and IL-23. CD4+ Th17 cells express CCR6 and the RORC2 transcription factor and are known for producing IL-17. IL-17 induces the expression of PGE2, COX2, MMP3, ICAM1, and MCP-1 in target cells such as MCs, B cells, macrophages, and natural killer cells. It is important to note that IL-17A stimulates the secretion of IL-8 from endometriotic stromal cells, promotes the proliferation of these cells, and facilitates neutrophil migration, which could lead to increased inflammation. However, Th17 cells are not the only cells producing IL-17; other immune cells like neutrophils, MCs, natural killer cells, and gamma-delta T cells also produce this interleukin [40]. This underscores the complexity of the interactions among different types of immune cells in the development of endometriosis. One of the essential substances secreted by MCs is prostaglandins (PGs) [81]. PGs have the ability to amplify the actions of cytokines on different types of inflammatory cells. One way that PGs amplify cytokine actions is by promoting the expression of relevant cytokine receptors, particularly during the differentiation of Th1 cells and the expansion of Th17 cells. This process can contribute to chronic immune inflammation [82].

The research indicates no significant difference in natural killer cell levels between individuals with and without endometriosis. Natural killer cells from the peritoneal fluid of women with endometriosis exhibit lower cytotoxicity [79]. Endometriotic endometrial stromal cells, macrophages, MCs, Tregs, and platelets produce anti-inflammatory cytokines IL-10 and TGF-β1, which can reduce the cytotoxic activity of natural killer cells. The reduction observed is not due to increased apoptosis of natural killer cells or decreased proliferation; instead, it is due to reduced expression of activating receptors. Treg cells regulate the function and proliferation of macrophages, MCs, dendritic cells, natural killer cells, endometrial cells, B cells, and T cells. These cells are all involved in menstruation and endometriosis. Treg cells are also one of the main producers of anti-inflammatory cytokines, which can reduce the expression of activating receptors of natural killer cells [76].

4.4 | Endometrioma and MCs

Evidence suggests that the growth of endometrioid cysts is associated with higher levels of MCs in the ovarian medulla and their localization in the cortical area. The structural characteristics of the endometrioma wall influence the differentiation of various MC subpopulations. In endometrioid cysts, immune cells and stromal cells release tryptase and CPA3 (Carboxypeptidase A3) into epithelial cells. The cytoplasmic extensions of MCs expand in the stromal structure and can impact the microenvironment of ovary-specific tissues in pathological conditions. The results of this investigation highlight the possible involvement of MC

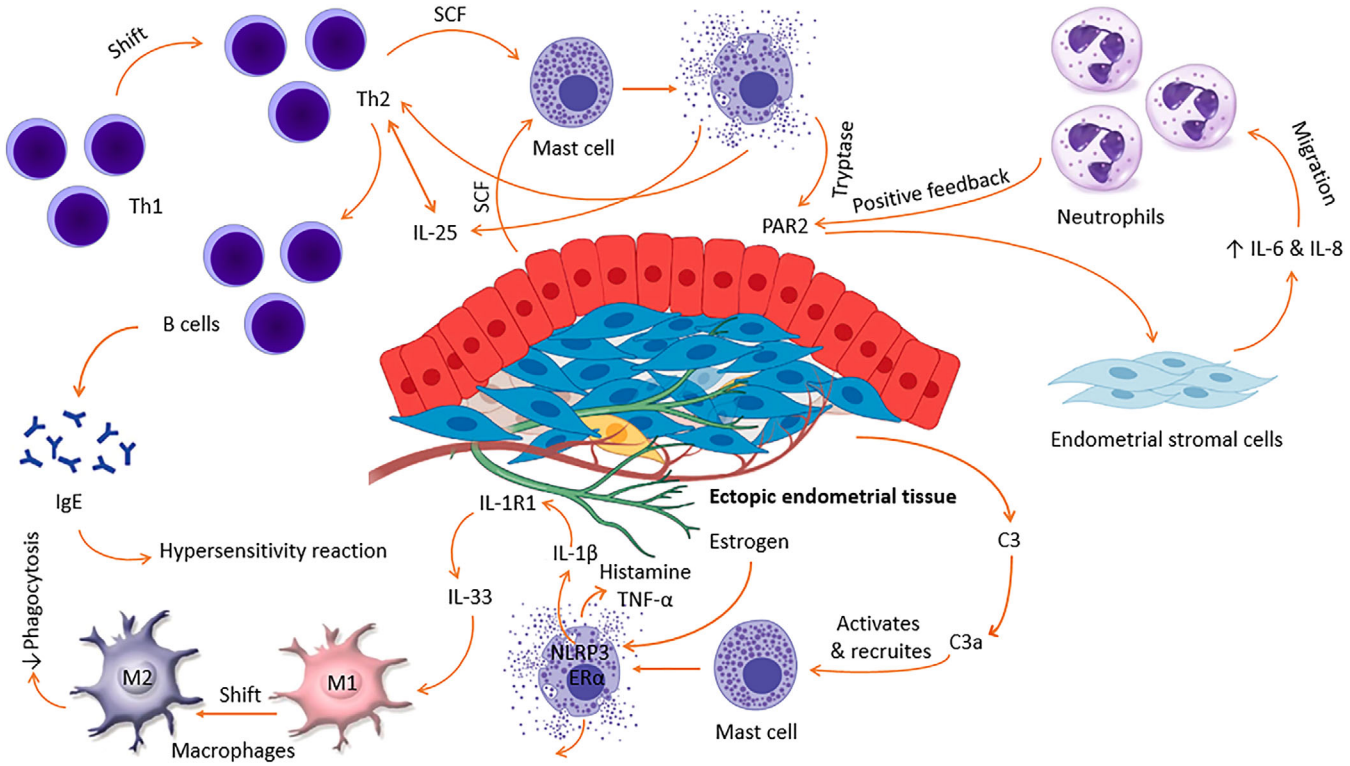

FIGURE 1 | Effect of MCs on other immune system components during endometriosis. Increased SCF induces MCs to release tryptase, activating PAR2 on endometriotic cells. This leads to proliferation and increased secretion of IL-6 and IL-8, attracting neutrophils to the lesion. Neutrophil-derived proteases further enhance cell proliferation through PAR2 activation and disease progression. Pro-inflammatory stimuli cause the endometrial cells to activate C3, which recruits and activates MCs in endometriosis lesions, releasing inflammatory mediators with pathological implications. The T helper 1 (Th1)/T helper 2 (Th2) ratio was altered, leading to an increase in Th2 and elevated MC numbers due to high levels of SCF. Both Th2 cells and MCs express IL-25, which may worsen allergies. Estrogen can stimulate NLRP3 expression in MCs through ER-α and ERE, which is essential for NLRP3 inflammasome activation and IL-1b production. This leads to overexpression of IL1R1 in the endometrial stroma, promoting IL-33 production and M2 subtype polarization of monocytes. The M2 subtype then produces IL-1β, which induces more IL-33 production in lesions through positive feedback. MCs indicates mast cells; PAR2, protease-activated receptor 2; SCF, stem cell factor.

CPA3 and tryptase in the progression of ovarian endometriosis, providing new insights into their potential as targets in personalized medicine. The identification of various proteases within the ovarian tissue microenvironment has introduced a novel mechanism through which MCs may influence regulatory processes [83].

4.5 | AhR and MC

The AhR plays a crucial role in both the immediate and delayed responses of MCs. This activation leads to MC degranulation and cytokine release. However, the impact of AhR on MC homeostasis is not fully understood. Compared to healthy endometrium, the levels of AhR mRNA are higher in endometriotic tissue [80]. Studies have shown that activated AhR in the endometrium can induce early production of IL-10 and promote the polarization of peritoneal M2 macrophages with tolerogenic properties. Indoleamine 2,3-dioxygenase (IDO) is believed to contribute to the development of endometriosis. Endometriotic tissue contains high levels of IDO1 and the AhR ligand kynurenine, which promotes chronic inflammation and cytokine production. Furthermore, AhR-expressing MCs in endometriotic tissue produce IL-17 and IL-10 [76, 84]. Upregulation of IDO1 in endometriotic tissue leads to increased kynurenine levels, possibly through AhR activation of MCs. Studies have shown that AhR antagonists positively affect the healing of endometriotic tissue. Moreover, activation of AhR leads to the release of growth promoters from MCs, which promote the proliferation of endometrial stromal cells [80, 84]. Levo-1-methyl-tryptophan (L-1-MT), an IDO1 enzyme inhibitor, is currently under clinical investigation as a potential anticancer drug, showing promise for endometriosis treatment [84].

4.6 | Pathophysiology of Pain and MCs

Endometrial lesions show an increase in the number of MCs near blood vessels and nerves, particularly in deeply infiltrating endometriosis [56]. The presence of activated and degranulating MCs in painful endometrial lesions suggests that they may contribute to pain and hypersensitivity by affecting nerve endings [55, 68, 75, 85, 86]. The interaction between MCs and nerves is well-documented in conditions like interstitial cystitis, irritable bowel syndrome, psoriasis, contact dermatitis, celiac disease, and endometriosis [70].

Leukotriene antagonists have shown promise in reducing pain in endometriosis by decreasing MC infiltration, suggesting a potential treatment for chronic pelvic pain in women. However, the exact mechanism behind MC-mediated pain in endometriosis is still unknown Activating MCs through DAMPs (Damage-associated molecular patterns) and TLR (toll-like receptor) signaling contribute more significantly to endometriosis-related pain than the allergen-induced IgE activation pathway. According to the DAMP-TLR model, molecules released during the menstrual cycle and from lesions associated with endometriosis can stimulate MCs through TLR receptors. This stimulation is believed to contribute to the sensitization of nerve endings through the TRPV1 (transient receptor potential vanilloid subfamily 1) channel [54, 58, 87]. Continuous sensitization may trigger the release of SP and calcitonin gene-related peptide (CGRP) from nerve terminals, which in turn amplifies MC activation and promotes their degranulation. Consequently, MCs may release TNFα and IL-6, which contribute to the development of chronic pelvic pain associated with endometriosis [54]. Studies have identified increased expression of SP, CGRP, and TLR4 within endometriotic lesions [58, 87]. TLRs can initiate IL-1 secretion by MCs, leading to PG synthesis. PGs are essential mediators of pain and are involved in the activation and growth of fibroblasts. These processes contribute to the development of fibrosis and the formation of adhesions, mainly through the deposition of fibrinogen followed by collagen synthesis [58]. Moreover, PGs can boost the production of estrogen catalyzed by aromatase. This interaction subsequently leads to an elevation in PG levels. Estrogen can activate MCs through the estrogen receptor, leading to the release of PGs. Also, previous studies have indicated that estrogen induces visceral hypersensitivity in stressed rats through GPR30 [70]. Therefore, several feed-forward pathways, including estrogen-driven, neurogenic, and DAMP-TLR-mediated pathways, could potentially contribute to chronic pelvic pain in patients with endometriosis [87]. When ectopic endometrial cells are exposed to estrogen, they can elicit the recruitment of RBL2H3 cells, which are a rat basophilic leukemia cell line. These recruited cells release biologically active NGF, thereby promoting the growth of neurites and increasing the sensitivity of dorsal root ganglion cells [68, 71, 82, 88].

Activation of MCs directly releases mediators such as leukotrienes, TNF-α, histamine, tryptase, PGs, serotonin, IL-1β, IL-8, and growth factors like insulin-like growth factor 1 (IGF-1) [13, 58, 82]. This activation can also indirectly contribute to pain progression by attracting leukocytes that release pain-inducing agents [13, 82]. Increased peritoneal inflammation can cause nerve damage, resulting in chronic pelvic pain. Additionally, stimulation of the nervous system activates MCs, which leads to the release of pro-inflammatory mediators and creates a feedback loop called "neurogenic inflammation." Furthermore, activation of peripheral nerve terminals causes central sensitization by transmitting impulses to the spinal cord [89].

The development and persistence of chronic pain are linked to several mechanisms, including heightened sensitivity of pain nerve fibers due to repetitive stimulation. The increased sensitivity leads to pain hypersensitivity and allodynia associated with endometriotic lesions [13]. The interaction between nociceptors and cytokines can initiate nerve sensitization, which may result in the development of chronic pain. Studying the imbalance of immune-inflammatory cells around endometriotic lesions is essential for effectively managing pain in endometriosis. Microglia cells can trigger neuronal activity, resulting in the release of neurotransmitters such as glutamate. They can also activate voltage-gated calcium channels, stimulate microglial neurons within the spinal cord, and contribute to neurosensitization and the development of pain symptoms. Activated MCs also increase the production of fibroblast growth factor-2 (FGF-2), which promotes neurite outgrowth and calcium influx in dorsal root ganglion cells [70]. Targeting the interactions between sensory nerves and MCs may be a practical approach to relieving pain [54].

Green et al. discovered that the Mrgprb2 gene in MCs affects neurogenic inflammation and pain. Their research showed that SP and Mrgprb2 contribute to inflammatory hyperalgesia and immune cell recruitment. Mrgprb2 and MRGPRX2 genes are expressed in specific subsets of MCs. These findings highlight Mrgprb2 as a key player in pain modulation and indicate its promise as a target for therapeutic strategies in treating and preventing inflammatory pain [39, 90]. The relationship between MCs and pain is summarized in Figure 2.

4.7 | Role of MCs in Infertility in Endometriosis

Patients with endometriosis may experience infertility at a rate of 35%–50%, even in the early stages of the condition [91]. The exact mechanism behind endometriosis-associated infertility remains unclear. Several factors may contribute to this phenomenon, particularly the negative impact of cytokine-rich peritoneal fluid on sperm function, which can obstruct the acrosome reaction and impair its motility. Human recombinant tryptase, produced by MCs in pregnant women, has been demonstrated in laboratory experiments to decrease sperm motility in humans, potentially impacting fertilization [59]. MC agents can directly influence the motility of sperm, as their interaction may lead to their degranulation in the peritoneal fluid of individuals suffering from endometriosis [75].

4.8 | The Function of MCs in Angiogenesis

Angiogenic factors are essential for the establishment of blood circulation, and their presence is critical for effective implantation. They facilitate the adhesion and proliferation of endometrial cells [91]. Angiogenesis is characterized by a series of interconnected events, including the blood vessel sprouting, migration of endothelial cells, proliferation, formation of tubes, and survival. Angiogenic factors can be synthesized by a variety of cell types, ranging from embryonic and adult cells to inflammatory and tumor cells. MCs play a role in regulating neovascularization and are increased in conditions related to angiogenesis. Immunohistochemistry staining showed that MCs contain FGF-2 and VEGF, indicating their involvement in angiogenesis. MC enzymes like tryptase and chymase promote vascular permeability [34]. MCs also produce histamine, heparin, VEGF, nitric oxide, and other factors that modulate microvascular function and promote angiogenesis [92]. Additionally, MCs produce pro-angiogenic factors like TNF-α, IL-8, and TGF-β, which are linked to both normal and tumor-related angiogenesis [34, 36].

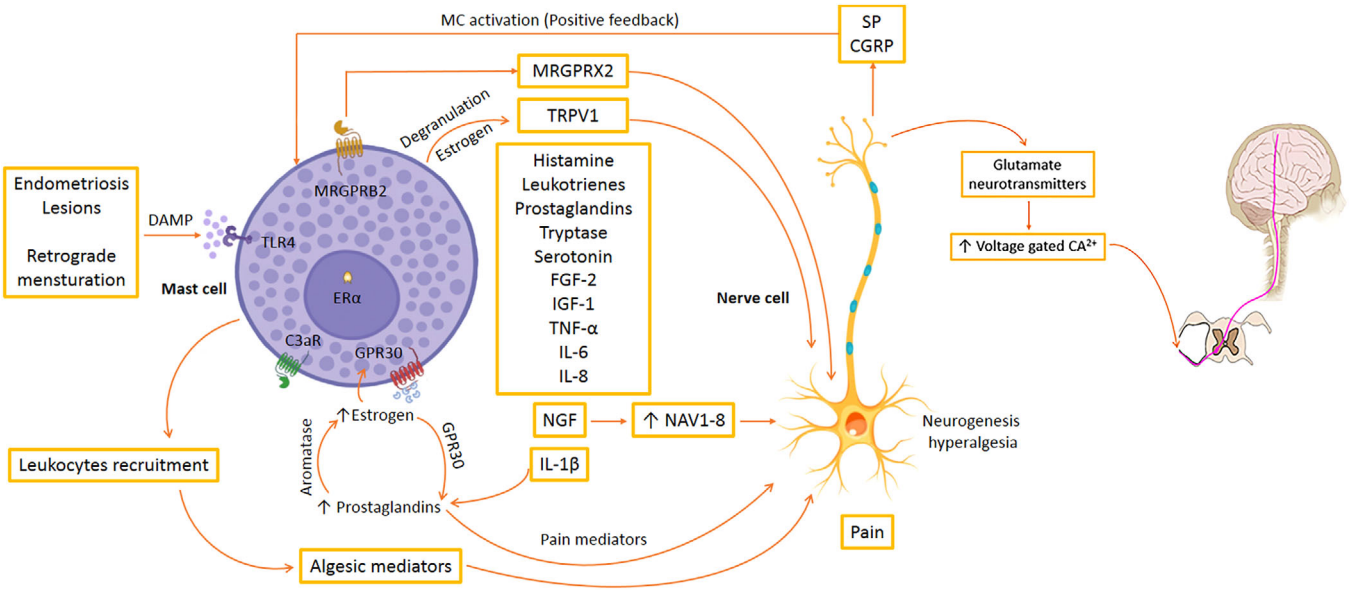

FIGURE 2 | MCs and pain. DAMPs activate MCs through TLR receptors, potentially increasing nerve sensitivity through the TRPV1 channel and leading to the secretion of neuropeptides like SP and CGRP. These neuropeptides can further activate MCs to release TNFα and IL-6, extending pain sensitivity in the nervous system. Endometriotic lesions display increased SP, CGRP, and TLR4 levels. IL-1, released by MCs when TLR is activated, stimulates PG production, which is important for pain control. IL-1 also boosts fibroblast activity, leading to fibrosis and adhesions. PGs can enhance estrogen production, further increasing their expression in endometriosis. Estrogen stimulates MCs through ERα, leading to the release of mediators like PGs. Studies show that estrogen, via GPR30, plays a role in visceral hypersensitivity. This activation of MCs by estrogen triggers the production of NGF, which enhances neurite growth and boosts sensitivity in dorsal root ganglion cells by upregulating Nav1.8 expression. MC activation directly causes neuropathic pain symptoms by releasing substances like histamine, leukotrienes, tryptase, TNF-α, PGs, serotonin, IL-1β, IL-8, and growth factors like IGF-1. It can also indirectly contribute to pain by recruiting leukocytes that release pain-inducing mediators. MCs can activate sensory nerve fibers by releasing mediators, leading to the release of glutamate and neurotransmitters, opening calcium channels, and stimulating spinal cord neurons. This causes central sensitization and pain. Additionally, the expression of Mrgprb2 in MCs can affect neurogenic inflammation and pain. CGRP indicates calcitonin gene-related peptide; DAMPs, damage-associated molecular pattern; IGF-1, insulin-like growth factor 1; MCs, mast cells; NGF, nerve growth factor; PG, prostaglandin; TRPV1, transient receptor potential vanilloid subfamily 1; TLR, toll-like receptor.

Angiogenesis is initiated by the breakdown of the basement membrane by cellular proteases, including MC-derived tryptase [93]. The secretion of heparin and proteases by MSc results in the release of pro-angiogenic factors that bind to heparin. In addition, MCs release histamine, which increases the permeability of microvasculature, thus promoting angiogenesis [36]. The enhanced permeability facilitates the migration of endothelial cells through the extracellular matrix, which promotes cell proliferation. CTMCs are strategically located near small vessels to provide the necessary mediators for normal angiogenesis [93].

VEGF and VEGFR are important in regulating angiogenesis [20]. VEGF is a glycoprotein that plays a significant role as a growth factor, affecting cellular interactions within and between cells. It promotes the formation of new blood vessels by regulating various processes like permeability, matrix formation, and cell proliferation [14, 18, 20, 21]. Different tissues, including eutopic endometrium, ectopic endometriotic tissue, peritoneal fluid, MCs, and macrophages, secrete VEGF in response to low oxygen [14, 28, 31].

Endometriotic lesions in the angiogenic microenvironment release cytokines and create chemotactic gradients. Patients with endometriosis exhibit higher levels of VEGF, TNF-α, IL-1, IL-6, and IL-8. The levels of TNF-α are associated with the severity of the endometriosis. Elevated TNF-α levels in the peritoneal fluid of affected women contribute to cell adhesion and angiogenesis. As a result, TNF-α could serve as a potential biomarker for the diagnosis of endometriosis [94, 95].

Increased levels of cytokines and steroid hormones in endometrial tissue result in elevated concentrations of MMP-9 [32]. This enzyme is essential for ectopic implantation and endometrial tissue invasion, as it impacts the basement membrane and stimulates neovascularization, which is a fundamental aspect of these mechanisms. Additionally, MMP-9 supports the growth of vascular endothelial cells and is essential for the ectopic implantation, adhesion, and proliferation of endometrial cells [18, 28, 91].

The angiogenesis process, which forms new blood vessels, is influenced by molecules like VEGF and TGF-β, as well as macromolecules in the extracellular matrix [8]. TGF-β may promote fibrosis and angiogenesis in abnormal tissues and contribute to the development of endometriosis. In patients with severe endometriosis, TGF-β levels are elevated in peritoneal fluid. However, treatment with gonadotropin-releasing hormone (GnRH) agonists can lower these TGF-β concentrations [28].

Previous research has established a link between MCs in endometriotic lesions and MC-induced angiogenesis, which are associated with serum estrogen levels, TNF-α, NGF, and the chemokine CCL8 [56, 71]. CCL8 promotes angiogenesis through

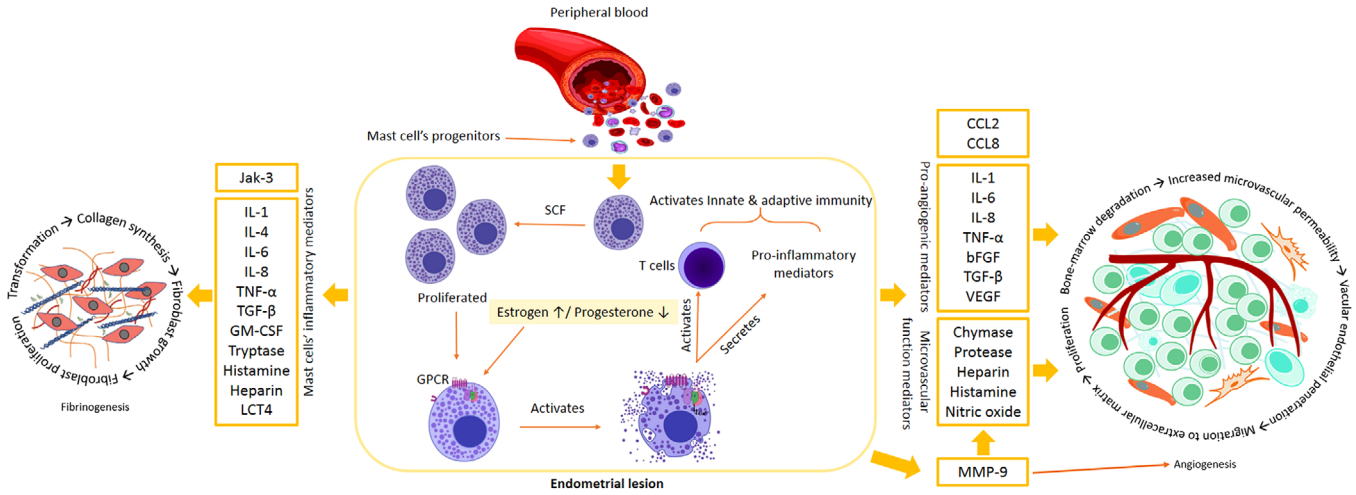

FIGURE 3 | Role of MCs in angiogenesis and fibrosis. MCs are activated by estrogen in endometrial-like tissue, leading to increased SCF levels. GPER, an estrogen receptor, triggers rapid MC responses. MCs release mediators contributing to inflammation, pelvic pain, angiogenesis, and fibrosis, driving disease progression. MC release of mediators influences the immune response, enhancing T-cell activation. Angiogenesis begins with the basement membrane breakdown by cellular proteases, including MC-derived tryptase. MC-derived cytokines such as histamine, heparin, VEGF, nitric oxide, and cytokines affect microvascular function and some of them like TNF-α, TGF-ß, and IL-8 are linked to angiogenesis in both normal and tumor-related processes. Endothelial cells can invade, move, and multiply in the extracellular matrix. Cytokines and steroid hormones in endometrial tissue increase MMP-9 levels, which breaks down the basement membrane to promote new blood vessel formation and vascular endothelial cell growth. CCL8 promotes angiogenesis through interaction with CCR1 and is upregulated in MCs co-cultured with endometrial cells. Higher levels of CCL8 are found in ectopic endometrium and the serum of individuals with endometriosis, where the CCL8-CCR1 pathway enhances the movement and growth of endometrial, epithelial, and stromal cells in affected areas. MCS produce substances that can influence connective tissue and contribute to fibrosis. They release mediators like proteases, histamine, IL-1, IL-4, IL-6, IL-8, TNF-α, TGF-β, and GM-CSF, creating an inflammatory environment that promotes fibroblast growth and collagen synthesis. LTC4 can induce fibroblast proliferation, and MCs may also produce extracellular matrix glycoproteins. JAK3, highly expressed in MCS, plays a role in inflammatory responses that could lead to fibrosis and adhesion formation. LTC4 indicates leukotriene C4; MCs, mast cells.

its receptor CCR1 and is upregulated in MCs cultured with endometrial cells [75]. Additionally, CCL8 expression increases in ectopic endometrium and in the sera of patients with endometriosis [54, 56]. CCR1 is highly expressed in the ectopic endometrium of ovarian endometriomas [75]. The CCL8-CCR1 axis is a key mechanism facilitating cell migration and proliferation in lesions, making it a promising target for endometriosis treatment [54].

Yingxue Li et al. studied the biological activity of tRF-Leu-AAG-001, a tRNA-derived small RNA, in MCs and its release from exosomes in ectopic tissues. Their findings indicated that tRF-Leu-AAG-001 present in MCs contributes to promoting inflammation and angiogenesis in endometriosis [7].

4.9 | MCs and Fibrosis

MCs are primarily found in endometrial cyst tissues. They have a limited presence in the endometrial stroma but are more concentrated around blood vessels and areas of fibrosis. The localization of MCs is strongly associated with adhesion and fibrosis, indicating their likely role in the development of fibrotic conditions [35, 57, 65, 86, 96]. The development of fibrosis in various diseases has been linked to chronic allergic conditions that repeatedly activate MCs. [43, 97]. The substances produced by MCs can alter the connective tissue microenvironment and play a crucial role in fibrogenesis. They trigger localized inflammatory responses by releasing mediators such as proteases, histamine, and cytokines, including IL-1, IL-6, IL-8, TNF-α, TGF-β, and GM-CSF [96]. In endometriosis, elevated levels of cytokines such as IL-1α, IL-6, IL-8, IL-18, and TNFα lead to a strong inflammatory response around the ectopic endometrium, which affects epithelial changes in the body [12, 98]. For instance, tryptase contributes to the increased production of type 1 collagen in endometriosis [98]. Additionally, histamine and heparin promote fibroblast growth and collagen production, potentially influencing scar formation. Tryptase derived from human MCs stimulates fibroblast proliferation [43, 97], while LTC4 (leukotriene C4) promotes proliferation in human skin fibroblasts. Several cytokines produced by MCs, including IL-4, TNF-α, and TGF-β1, are known for their fibrogenic activity. MCs may directly contribute to fibrosis by producing extracellular matrix glycoproteins. Many studies indicate a possible link between MCs and the development, activation, and proliferation of fibrosis [43].

JAK3 is highly expressed in MCs and plays a vital role in the secretion of inflammatory mediators from these cells. This secretion results in increased fibrosis and the development of adhesions [78]. Levels of activated MCs are higher in endometriosis areas positive for corticotropin-releasing hormone and urocortin. These hormones activate MCs, contributing to fibrosis and inflammation in endometriosis [78, 98]. A comparison of gene expression between endometriotic cells and ovarian tissue using oligonucleotide microarrays revealed a higher abundance of activated MCs in endometriotic cells. Additionally, electron

TABLE 2 | The list of research targeting MCs in endometriosis disorder.

Reference	The treatment	Effect	Experimental model
NurInsaniyah et al. [9]	Ethanol extract of basil leaves (*Ocimum basilicum* Lamiaceae)	Decreased MC counts, suppressed arachidonic acid, impacted TLR-NF-KB pathway, and suppressed COX-2 function and PGE2 synthesis	Mouse model of endometriosis
Arangia et al. [26]	Fisetin (a Natural Polyphenol)	The size of endometriotic lesions was diminished, along with changes in tissue structure, infiltration of neutrophils, release of cytokines, quantity of MCs, levels of chymase and tryptase expression, downregulation of α-sma and TGF-β, decreased indicators of oxidative stress and nitrotyrosine, Poly ADP ribose expression, and heightened occurrence of apoptosis	Autotransplantation rat model
Xu et al. [70]	FGFR1 inhibitor NSC12	Mechanical pain tolerance was raised, and the initiation of the heat source was prolonged	Autotransplantation rat model
Guo et al. [53]	NLRP3 inhibitor CY-09	The progression of the lesions is restricted, and there is a development of fibrous tissue	Mouse model of endometriosis
Tiantian Li et al. [27]	BX471 (a potent CCR1 antagonist)	Inhibited the in vivo development and angiogenesis of endometriosis	Mouse model of endometriosis
D'Cruz et al. [78]	Janus Kinase 3 Inhibitor, JANEX-1	strong anti-inflammatory properties, making it a promising candidate for inhibiting T-cell and MC activity, along with reducing inflammation	Mouse and human models of peritonitis, colitis, cellulitis, sunburn, and airway inflammation
Hong Zhu et al. [99]	Ketotifen	Inhibited the progression of hyperalgesia by potentially influencing MC function within cysts, consequently diminishing peripheral sensitization caused by painful stimuli originating from endometriotic lesions	Rat model of endometriosis
Iuvone et al. [100]	Ultramicronized PEA	Viscerovisceral hyperalgesia may be decreased through the modulation of MC expression/activity within cysts, leading to a reduction in central sensitization caused by painful signals originating from endometriotic lesions	Rat model of endometriosis
Cacciottola et al. [13]	Leukotriene receptor antagonists	The proliferation rates of stromal cells have been observed to decrease, accompanied by a decrease in the infiltration and activation of MCs	Rat model of endometriosis
Di Paola et al. [22]	Co-micronized PEA/polydatin	led to a reduced cyst diameter, an enhanced fibrosis score, and a lower MC count	Rat model of endometriosis
Engemise et al. [101]	Levonorgestrel-releasing intrauterine system, Mirena	Decreased numbers of MCs were observed in both ectopic and eutopic endometrial tissues, leading to the modulation of pain perception	Women with minimal to moderate endometriosis
Zhu,Li-bo et al. [102]	Sodium cromoglycate	The stabilization of MCs has the potential to alleviate the clinical manifestations of endometriosis by diminishing the levels of TNF-α and tryptase, thereby preventing degranulation	Autotransplantation rat model
Genovese et al. [89]	Cannabidiol (CBD)	The lesions' diameter, volume, and area were decreased, leading to notable analgesic effects through the reduction of MC recruitment in the spinal cord and the release of neuro-sensitizing and pro-inflammatory mediators	Autotransplantation rat model

(Continues)

TABLE 2 | (Continued)

Reference	The treatment	Effect	Experimental model
Tapdigova et al. [103]	Antilipidemic ezetimibe	The anti-inflammatory and anti-angiogenic characteristics of MCs were diminished, leading to a reduction in the quantity of MCs present across the uterine layers	Rat model of endometriosis
Qin Yu et al. [104]	Salbutamol	Immune inflammatory cells and factors, angiogenesis, and fibrosis were diminished, while apoptosis of endometriotic lesions was heightened, and neurogenesis was reduced	Mouse model of endometriosis
Yang et al. [71]	Yikun Yitong ping-containing serum	Suppressed the activity of ER-α, ER- β, NGF, and P75 in RBL2H3 cells, potentially reducing endometriosis-associated dysmenorrhea through the inhibition of ER expression in MCs	Rat basophilic leukemia cell line (RBL2H3).
Cordaro et al. [105]	Hidrox, an aqueous extract of olive pulp containing 40%−50% of hydroxytyrosol,	Decreased the size and magnitude of endometriotic lesions and reduced the recruitment of MCs, myeloperoxidase activity, and lipid peroxidation. Furthermore, it enhanced superoxide dismutase activity and glutathione levels in the endometrial tissue, resulting in lower levels of IL-1β, IL-2, IL-6, TNF-α, and VEGF, as well as decreased peripheral and visceral sensitivity	Autotransplantation rat model
Ankovich et al. [106]	Low FODMAP diet	Elevated luminal histamine due to MC degranulation is linked to an intensified immune reaction, potentially leading to symptom alleviation in individuals suffering from endometriosis and irritable bowel syndrome	A woman with endometriosis
Novella-Maestre et al. [92]	Cabergoline(cb2)	Reduces macrophage and MC numbers and blocks pathways that cause inflammation	Mouse model of endometriosis
Mercedes Binda et al. [51]	Zafirlukast (leukotriene receptor antagonist)	It led to a reduction in stromal proliferation and the suppression of MCs infiltration and activation, as well as the apoptosis of proliferative fibroblasts	Autotransplantation rat model

Abbreviations: MCs, mast cells; NLRP3, NOD-like receptor family pyrin domain containing 3; PEA, palmitoylethanolamide; TLR, toll-like receptor.

microscopy showed that numerous substances were released from MCs into proliferating collagen fibers and fibroblasts, confirming their role in fibrosis and remodeling during the inflammatory process in endometriosis [65]. Figure 3 summarizes the possible connections between MCs, Fibrosis, and angiogenesis.

4.10 | MC-Targeted Treatments for Endometriosis

The presence of MCs in endometriotic tissue indicates that targeting these cells could be a potential therapeutic approach for improving endometriosis treatment and reducing its symptoms [11]. Several studies have investigated treating endometriosis by focusing on MCs, and the details of these studies are outlined in Table 2.

5 | Conclusion

In conclusion, this review article highlights the significant impact of MCs on various aspects of endometriosis pathogenesis. MCs play a crucial role in angiogenesis, pain perception, fibrosis development, and infertility associated with endometriosis. Understanding the complex interactions between MCs and these processes is essential for developing targeted therapeutic strategies for the management of endometriosis. Developing specific treatments that regulate MC activity could open up new avenues for managing endometriosis. It is imperative to convert the outcomes of this fundamental research into clinical practice and adopt a collaborative, interdisciplinary method that engages researchers, clinicians, and other healthcare professionals. Long-term studies focusing on the effects of MC modulation in endometriosis patients are essential to evaluate the effectiveness and safety of this therapeutic strategy, as well as its impact on disease progression and symptom relief.

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The authors have nothing to report.

Ethics Statement

As this is a review article, no ethical approval was required.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Research data are not shared.

References

1. G. C. Tan, Y. P. Wong, and T. Y. Khong. "Menstrual Cycle of Endometrium," in *Gynecologic and Obstetric Pathology*, eds. W. Zheng, O. Fadare, and C. M. Quick (Singapore: Springer Nature Singapore, 2024), 1–30.

2. D. A. Gibson, I. Simitsidellis, F. Collins, and P. T. K. Saunders, "Androgens, Oestrogens and Endometrium: A Fine Balance Between Perfection and Pathology," *Journal of Endocrinology* 246, no. 3 (2020), R75–R93.

3. B. A. Lessey and S. L. Young. "Structure, Function, and Evaluation of the Female Reproductive Tract," in *Yen and Jaffe's Reproductive Endocrinology*, eds. J. F. Strauss and R. L. Barbieri, 8th ed. (Philadelphia: Elsevier, 2019), 206–247.e13.

4. C. R. Wira, M. Rodríguez-García, Z. Shen, and M. V. Patel. "Chapter 10 - Endocrine Control of Mucosal Immunity in the Human Female Reproductive Tract: Bridging Implantation With Pathogen Protection," in *Reproductive Immunology*, ed. G. Mor (Academic Press, 2021), 171–206.

5. J. Vallvé-Juanico, S. Houshdaran, and L. C. Giudice. "The Endometrial Immune Environment of Women With Endometriosis," *Human Reproduction Update* 25, no. 5 (Oxford University Press, 2019): 565–592.

6. A. McCallion, Y. Nasirzadeh, H. Lingegowda et al., "Estrogen Mediates Inflammatory Role of Mast Cells in Endometriosis Pathophysiology," *Frontiers in Immunology* 13 (2022): 961599.

7. Y. Li, S. Cui, Z. Xu et al., "Exosomal tRF-Leu-AAG-001 Derived From Mast Cell as a Potential Non-Invasive Diagnostic Biomarker for Endometriosis," *BMC Womens Health* 22, no. 1 (2022): 253.

8. G. A. Aydin, H. Ayvaci, N. Koc, N. Tarhan, and O. Demirci, "The Relationship Between Decorin and VEGF in Endometriosis," *Journal of the College of Physicians and Surgeons–Pakistan* 31, no. 11 (2021): 1285–1290.

9. K. N. Insaniyah, A. Sa'adi, and W. Widjiati, "Impact of EThanol Extract of Basil Leaves (Ocimum basilicum L.) on Mast Cell Reduction and Prostaglandin E2 Levels in Female Mice as a Model for Endometriosis Development," *Journal of Medicinal and Chemical Sciences* 6, no. 12 (2023): 2941–2951.

10. A. M. I. Ofiteru, S. Berceanu, S. Paitici et al., "Endometriosis of the Abdominal Wall—Clinical, Histopathological and Immunohistochemical Aspects," *Revista De Chimie* 70, no. 8 (2019): 2860–2865.

11. D. Szukiewicz, "Insight Into the Potential Mechanisms of Endocrine Disruption by Dietary Phytoestrogens in the Context of the Etiopathogenesis of Endometriosis," *International Journal of Molecular Sciences* 24, no. 15 (2023): 12195.

12. A. M. Istrate-Ofițeru, E. I. Berbecaru, G. L. Zorilă et al., "Specific Local Predictors That Reflect the Tropism of Endometriosis-A Multiple Immunohistochemistry Technique," *International Journal of Molecular Sciences* 23, no. 10 (2022): 5614.

13. L. Cacciottola, J. Donnez, and M. M. Dolmans, "Can Endometriosis-Related Oxidative Stress Pave the Way for New Treatment Targets?," *International Journal of Molecular Sciences* 22, no. 13 (2021): 7138.

14. S. G. Powell, P. Sharma, S. Masterson et al., "Vascularisation in Deep Endometriosis: A Systematic Review With Narrative Outcomes," *Cells* 12, no. 9 (2023): 1318.

15. I. Jakson, A. L. Hirschberg, and S. B. Gidlöf, "Endometriosis and Menopause—Management Strategies Based on Clinical Scenarios," *Acta Obstetricia Et Gynecologica Scandinavica* 102, no. 10 (2023): 1323–1328.

16. L. B. Afrin, "Mast Cell Activation Disease and the Modern Epidemic of Chronic Inflammatory Disease," *Translational Research* 174 (2016): 33–59.

17. V. Pergialiotis, M. Fanaki, I. Bellos, K. Stefanidis, D. Loutradis, and G. Daskalakis, "The Impact of Vascular Endothelial Growth Factor Single Nucleotide Polymorphisms in the Development and Severity of Endometriosis: A Systematic Review of the Literature," *Journal of Gynecology Obstetrics and Human Reproduction* 49, no. 10 (2020): 101732.

18. D. Zhao, Q. Bao, L. Chen, and L. Zheng, "Effects of SU5416 on Angiogenesis and the ERK-VEGF/MMP-9 Pathway in Rat Endometriosis," *Investigación Clínica* 64, no. 4 (2023): 482–494.

19. S. Kamrani, E. Amirchaghmaghi, F. Ghaffari, M. Shahhoseini, and K. Ghaedi, "Altered Gene Expression of VEGF, IGFs and H19 lncRNA and Epigenetic Profile of H19-DMR Region in Endometrial Tissues of Women With Endometriosis," *Reproductive Health* 19, no. 1 (2022): 100.

20. D. Q. A'Yuni, A. Sa'adi, and W. Widjiati, "EThanol Extract of Basil (Ocimum Basilicum L.) Leaves Inhibits Endometriosis Growth in a Mouse Model by Modulating Vascular Endothelial Growth Factor (VEGF) Expression," *Journal of Medicine and Life* 16, no. 8 (2023): 1224–1230.

21. O. A. Babah, O. O. Ojewunmi, A. A. Osuntoki, M. A. Simon, and B. B. Afolabi, "Genetic Polymorphisms of Vascular Endothelial Growth Factor (VEGF) Associated With Endometriosis in Nigerian Women," *Human Genomics* 15, no. 1 (2021): 64.

22. R. Di Paola, R. Fusco, E. Gugliandolo et al., "Co-Micronized PalmitoyleThanolamide/Polydatin Treatment Causes Endometriotic Lesion Regression in a Rodent Model of Surgically Induced Endometriosis," *Frontiers in Pharmacology* 7 (2016): 382.

23. L. Gan, J. Sun, and J. Sun, "Bioinformatical Analysis Identifies PDLIM3 as a Potential Biomarker Associated With Immune Infiltration in Patients With Endometriosis," *PeerJ* 10 (2022): e13218.

24. T. C. Theoharides and J. M. Stewart, "Genitourinary Mast Cells and Survival," *Translational Andrology and Urology* 4, no. 5 (2015): 579–586.

25. M. Cuevas, I. Flores, K. J. Thompson, D. L. Ramos-Ortolaza, A. Torres-Reveron, and C. B. Appleyard, "Stress Exacerbates Endometriosis Manifestations and Inflammatory Parameters in an Animal Model," *Reproductive Sciences* 19, no. 8 (2012): 851–862.

26. A. Arangia, Y. Marino, R. Fusco et al., "Fisetin, a Natural Polyphenol, Ameliorates Endometriosis Modulating Mast Cells Derived NLRP-3 Inflammasome Pathway and Oxidative Stress," *International Journal of Molecular Sciences* 24, no. 6 (2023): 5076.

27. T. Li, J. Wang, X. Guo et al., "Possible Involvement of Crosstalk Between Endometrial Cells and Mast Cells in the Development of Endometriosis via CCL8/CCR1," *Biomedicine & Pharmacotherapy* 129 (2020): 110476.

28. T. Arablou, N. Aryaeian, S. Khodaverdi et al., "The Effects of Resveratrol on the Expression of VEGF, TGF-β, and MMP-9 in Endometrial Stromal Cells of Women With Endometriosis," *Scientific Reports* 11, no. 1 (2021): 6054.

29. C. Agostinis, S. Zorzet, A. Balduit et al., "The Inflammatory Feed-Forward Loop Triggered by the Complement Component C3 as a Potential Target in Endometriosis," *Frontiers in Immunology* 12 (2021): 693118.

30. Y. Yu, H. M. Chang, and J. E. Schjenken, "Editorial: Reproduction and the Inflammatory Response," *Frontiers in Endocrinology (Lausanne)* 12 (2021): 835854.

31. R. Fusco, R. D'Amico, M. Cordaro et al., "Absence of Formyl Peptide Receptor 1 Causes Endometriotic Lesion Regression in a Mouse Model of Surgically-Induced Endometriosis," *Oncotarget* 9, no. 59 (2018): 31355–31366.

32. W. Windarti, A. Sa'adi, and W. Widjiati, "Correlation Between Vitamin D Administration and Reduced Expression of VEGF and MMP-9 in Abnormal Endometrial Stroma (Experimental in Mice Models With Endometriosis)," *Journal of Medicinal and Chemical Sciences* 6, no. 12 (2023): 2952–2963.

33. H. Sauqi, B. Santoso, W. Widjiati, and H. Hendarto, "Red Fruit (Pandanus conoideus) Inhibits the Development of Endometriosis Lesions Through Downregulation of NF-kB and VEGF Expression," *Rawal Medical Journal* 45, no. 4 (2020): 985–989.

34. E. Crivellato, C. A. Beltrami, F. Mallardi, and D. Ribatti, "The Mast Cell: An Active Participant or an Innocent Bystander?," *Histology and Histopathology* 19, no. 1 (2004): 259–270.

35. K. Amin, "The Role of Mast Cells in Allergic Inflammation," *Respiratory Medicine* 106, no. 1 (2012): 9–14.

36. M. Krystel-Whittemore, K. N. Dileepan, and J. G. Wood, "Mast Cell: A Multi-Functional Master Cell," *Frontiers in Immunology* 6 (2015): 620.

37. S. Tikoo, N. Barki, R. Jain et al., "Imaging of Mast Cells," *Immunological Reviews* 282, no. 1 (2018): 58–72.

38. J. Baran, A. Sobiepanek, A. Mazurkiewicz-Pisarek et al., "Mast Cells as a Target-A Comprehensive Review of Recent Therapeutic Approaches," *Cells* 12, no. 8 (2023): 1187.

39. S. J. Galli, N. Gaudenzio, and M. Tsai, "Mast Cells in Inflammation and Disease: Recent Progress and Ongoing Concerns," *Annual Review of Immunology* 38 (2020): 49–77.

40. J. Vallvé-Juanico, S. Houshdaran, and L. C. Giudice, "The Endometrial Immune Environment of Women With Endometriosis," *Human Reproduction Update* 25, no. 5 (2019): 564–591.

41. J. S. Dahlin, M. Maurer, D. D. Metcalfe, G. Pejler, R. Sagi-Eisenberg, and G. Nilsson, "The Ingenious Mast Cell: Contemporary Insights Into Mast Cell Behavior and Function," *Allergy* 77, no. 1 (2022): 83–99.

42. S. Bais, R. Kumari, Y. Prashar, and N. S. Gill, "Review of Various Molecular Targets on Mast Cells and its Relation to Obesity: A Future Perspective," *Diabetes & Metabolic Syndrome* 11, no. Suppl 2 (2017): S1001–S1007.

43. D. D. Metcalfe, D. Baram, and Y. A. Mekori, "Mast Cells," *Physiological Reviews* 77, no. 4 (1997): 1033–1079.

44. D. Elieh Ali Komi, S. Wöhrl, and L. Bielory, "Mast Cell Biology at Molecular Level: A Comprehensive Review," *Clinical Reviews in Allergy & Immunology* 58, no. 3 (2020): 342–365.

45. A. M. Gilfillan, S. J. Austin, and D. D. Metcalfe, "Mast Cell Biology: Introduction and Overview," *Advances in Experimental Medicine and Biology* 716 (2011): 2–12.

46. T. C. Moon, A. D. Befus, and M. Kulka, "Mast Cell Mediators: Their Differential Release and the Secretory Pathways Involved," *Frontiers in Immunology* 5 (2014): 569.

47. G. J. Molderings and L. B. Afrin, "A Survey of the Currently Known Mast Cell Mediators With Potential Relevance for Therapy of Mast Cell-Induced Symptoms," *Naunyn-Schmiedeberg's Archives of Pharmacology* 396, no. 11 (2023): 2881–2891.

48. A. Niarakis and M. Daëron. "Activating and Inhibitory Receptors on Mast Cells," in *Encyclopedia of Medical Immunology: Allergic Diseases*, eds. I. R. Mackay, N. R. Rose, D. K. Ledford, and R. F. Lockey (New York, NY: Springer New York, 2014), 1–10.

49. H. Migalovich-Sheikhet, S. Friedman, D. Mankuta, and F. Levi-Schaffer, "Novel Identified Receptors on Mast Cells," *Frontiers in Immunology* 3 (2012): 238.

50. J. Agier, J. Pastwińska, and E. Brzezińska-Błaszczyk, "An Overview of Mast Cell Pattern Recognition Receptors," *Inflammation Research* 67, no. 9 (2018): 737–746.

51. M. M. Binda, J. Donnez, and M. M. Dolmans, "Targeting Mast Cells: A New Way to Treat Endometriosis," *Expert Opinion on Therapeutic Targets* 21, no. 1 (2017): 67–75.

52. C. Agostinis, A. Mangogna, F. Bossi, G. Ricci, U. Kishore, and R. Bulla, "Uterine Immunity and Microbiota: A Shifting Paradigm," *Frontiers in Immunology* 10 (2019): 2387.

53. X. Guo, X. Xu, T. Li et al., "NLRP3 Inflammasome Activation of Mast Cells by Estrogen via the Nuclear-Initiated Signaling Pathway Contributes to the Development of Endometriosis," *Frontiers in Immunology* 12 (2021): 749979.

54. S. K. Godin, J. Wagner, P. Huang, and D. Bree, "The Role of Peripheral Nerve Signaling in Endometriosis," *FASEB BioAdvances* 3, no. 10 (2021): 802–813.

55. D. A. Hart, "Curbing Inflammation in Multiple Sclerosis and Endometriosis: Should Mast Cells Be Targeted?," *International Journal of Inflammation* 2015 (2015): 452095.

56. N. Lampiasi, "Interactions Between Macrophages and Mast Cells in the Female Reproductive System," *International Journal of Molecular Sciences* 23, no. 10 (2022): 5414.

57. H. Fujiwara, R. Konno, S. Netsu et al., "Localization of Mast Cells in Endometrial Cysts," *American Journal of Reproductive Immunology* 51, no. 5 (2004): 341–344.

58. D. Kirchhoff, S. Kaulfuss, U. Fuhrmann, M. Maurer, and T. M. Zollner, "Mast Cells in Endometriosis: Guilty or Innocent Bystanders?," *Expert Opinion on Therapeutic Targets* 16, no. 3 (2012): 237–241.

59. V. Borelli, M. Martinelli, S. Luppi et al., "Mast Cells in Peritoneal Fluid From Women With Endometriosis and Their Possible Role in Modulating Sperm Function," *Frontiers in Physiology* 10 (2019): 1543.

60. S. Bacci, J. M. Brown, and D. Ribatti, "Editorial: Mast Cells in Health, Disease and Forensic Practice: A Mystery Not yet Revealed," *Frontiers of Medicine (Lausanne)* 10 (2023): 1288565.

61. I. E. Oală, M. I. Mitranovici, D. M. Chiorean et al., "Endometriosis and the Role of Pro-Inflammatory and Anti-Inflammatory Cytokines in Pathophysiology: A Narrative Review of the Literature," *Diagnostics (Basel)* 14, no. 3 (2024): 312.

62. M. Sugamata, T. Ihara, and I. Uchiide, "Increase of Activated Mast Cells in Human Endometriosis," *American Journal of Reproductive Immunology* 53, no. 3 (2005): 120–125.

63. G. Zou, J. Wang, X. Xu et al., "Cell Subtypes and Immune Dysfunction in Peritoneal Fluid of Endometriosis Revealed by Single-Cell RNA-Sequencing," *Cell & Bioscience* 11, no. 1 (2021): 98.

64. S. Matsuzaki, M. Canis, C. Darcha, T. Fukaya, A. Yajima, and M. A. Bruhat, "Increased Mast Cell Density in Peritoneal Endometriosis Compared With Eutopic Endometrium With Endometriosis," *American Journal of Reproductive Immunology* 40, no. 4 (1998): 291–294.

65. R. Konno, H. Yamada-Okabe, H. Fujiwara et al., "Role of Immunoreactions and Mast Cells in Pathogenesis of Human Endometriosis–Morphologic Study and Gene Expression Analysis," *Human Cell* 16, no. 3 (2003): 141–149.

66. S. Tsuji, K. Tsuji, H. Otsuka, and T. Murakami, "Increased Mast Cells in Endocervical Smears of Women With Dysmenorrhea," *CytoJournal* 15 (2018): 27.

67. R. Paula Jr, A. H. Oliani, D. C. Vaz-Oliani, S. C. D'Ávila, S. M. Oliani, and C. D. Gil, "The Intricate Role of Mast Cell Proteases and the Annexin A1-FPR1 System in Abdominal Wall Endometriosis," *Journal of Molecular Histology* 46, no. 1 (2015): 33–43.

68. G. F. Meresman, M. Götte, and M. W. Laschke, "Plants as Source of New Therapies for Endometriosis: A Review of Preclinical and Clinical Studies," *Human Reproduction Update* 27, no. 2 (2021): 367–392.

69. K. Q. Lin, L. B. Zhu, X. M. Zhang, and J. Lin, "Role of Mast Cells in Estrogen-Mediated Experimental Endometriosis in Rats," *Zhejiang Da Xue Xue Bao Yi Xue Ban = Journal of Zhejiang University Medical Sciences* 44, no. 3 (2015): 269–277.

70. X. Xu, J. Wang, X. Guo et al., "GPR30-Mediated Non-Classic Estrogen Pathway in Mast Cells Participates in Endometriosis Pain via the Production of FGF2," *Frontiers in Immunology* 14 (2023): 1106771.

71. F. Yang, Y. Yu, and H. Liu, "Mechanism of Action of Yikun Yitong Ping-Containing Serum on Mast Cells and Its Possible Involvement in Endometriosis-Related Dysmenorrhea," *Natural Product Communications* 19, no. 2 (2024): 1934578×241229929.

72. Q. Zhong, F. Yang, X. Chen, J. Li, C. Zhong, and S. Chen, "Patterns of Immune Infiltration in Endometriosis and Their Relationship to R-AFS Stages," *Frontiers in Genetics* 12 (2021): 631715.

73. C. Xie, C. Lu, Y. Liu, and Z. Liu, "Diagnostic Gene Biomarkers for Predicting Immune Infiltration in Endometriosis," *BMC Womens Health* 22, no. 1 (2022): 184.

74. Y. Osuga, "Current Concepts of the Pathogenesis of Endometriosis," *Reproductive Medicine and Biology* 9, no. 1 (2010): 1–7.

75. D. Szukiewicz, P. Wojdasiewicz, M. Watroba, and G. Szewczyk, "Mast Cell Activation Syndrome in COVID-19 and Female Reproductive Function: Theoretical Background vs. Accumulating Clinical Evidence," *Journal of Immunology Research* 2022 (2022): 9534163.

76. W. J. Zhou, H. L. Yang, J. Shao et al., "Anti-Inflammatory Cytokines in Endometriosis," *Cellular and Molecular Life Sciences* 76, no. 11 (2019): 2111–2132.

77. H. F. Bungum, U. Nygaard, C. Vestergaard, P. M. Martensen, and U. B. Knudsen, "Increased IL-25 Levels in the Peritoneal Fluid of Patients With Endometriosis," *Journal of Reproductive Immunology* 114 (2016): 6–9.

78. O. J. D'Cruz and F. M. Uckun, "Targeting Mast Cells in Endometriosis With Janus Kinase 3 Inhibitor, JANEX-1," *American Journal of Reproductive Immunology* 58, no. 2 (2007): 75–97.

79. I. B. L. de Barros, H. Malvezzi, B. Y. Gueuvoghlanian-Silva, C. A. Piccinato, L. V. Rizzo, and S. Podgaec, ""What Do We Know About Regulatory T Cells and Endometriosis? A Systematic Review"," *Journal of Reproductive Immunology* 120 (2017): 48–55.

80. L. Mariuzzi, R. Domenis, M. Orsaria et al., "Functional Expression of Aryl Hydrocarbon Receptor on Mast Cells Populating human Endometriotic Tissues," *Laboratory Investigation* 96, no. 9 (2016): 959–971.

81. M. Krystel-Whittemore, K. N. Dileepan, and J. G. Wood, "Mast Cell: A Multi-Functional Master Cell," *Frontiers in Immunology* 6 (2016): 620.

82. Y. Wei, Y. Liang, H. Lin, Y. Dai, and S. Yao, "Autonomic Nervous System and Inflammation Interaction in Endometriosis-Associated Pain," *Journal of Neuroinflammation* 17, no. 1 (2020): 80.

83. D. Atiakshin, O. Patsap, A. Kostin, L. Mikhalyova, I. Buchwalow, and M. Tiemann, "Mast Cell Tryptase and Carboxypeptidase A3 in the Formation of Ovarian Endometrioid Cysts," *International Journal of Molecular Sciences* 24, no. 7 (2023): 6498.

84. H.-L. Yang, M.-Q. Li, and Y.-Q. Zhu, "Indoleamine 2,3-Dioxygenase in Endometriosis," *Reproductive and Developmental Medicine* 03, no. 02 (2019): 110–116.

85. V. Anaf, C. Chapron, I. El Nakadi, V. De Moor, T. Simonart, and J. C. Noël, "Pain, Mast Cells, and Nerves in Peritoneal, Ovarian, and Deep Infiltrating Endometriosis," *Fertility and Sterility* 86, no. 5 (2006): 1336–1343.

86. C. Agostinis, A. Balduit, A. Mangogna et al., "Immunological Basis of the Endometriosis: The Complement System as a Potential Therapeutic Target," *Frontiers in Immunology* 11 (2020): 599117.

87. A. Aich, L. B. Afrin, and K. Gupta, "Mast Cell-Mediated Mechanisms of Nociception," *International Journal of Molecular Sciences* 16, no. 12 (2015): 29069–29092.

88. T. H. Zhu, S. J. Ding, T. T. Li, L. B. Zhu, X. F. Huang, and X. M. Zhang, "Estrogen Is an Important Mediator of Mast Cell Activation in Ovarian Endometriomas," *Reproduction (Cambridge, England)* 155, no. 1 (2018): 73–83.

89. T. Genovese, M. Cordaro, R. Siracusa et al., "Molecular and Biochemical Mechanism of Cannabidiol in the Management of the Inflammatory and Oxidative Processes Associated With Endometriosis," *International Journal of Molecular Sciences* 23, no. 10 (2022): 5427.

90. D. P. Green, N. Limjunyawong, N. Gour, P. Pundir, and X. Dong, "A Mast-Cell-Specific Receptor Mediates Neurogenic Inflammation and Pain," *Neuron* 101, no. 3 (2019): 412–420.e3.

91. J. Cheng, C. Li, Y. Ying et al., "Metformin Alleviates Endometriosis and Potentiates Endometrial Receptivity via Decreasing VEGF and MMP9 and Increasing Leukemia Inhibitor Factor and HOXA10," *Frontiers in Pharmacology* 13 (2022): 750208.

92. E. Novella-Maestre, S. Herraiz, J. M. Vila-Vives, C. Carda, A. Ruiz-Sauri, and A. Pellicer, "Effect of Antiangiogenic Treatment on Peritoneal Endometriosis-Associated Nerve Fibers," *Fertility and Sterility* 98, no. 5 (2012): 1209–1217.

93. D. E. A. Komi, K. Khomtchouk, and P. L. Santa Maria, "A Review of the Contribution of Mast Cells in Wound Healing: Involved Molecular and Cellular Mechanisms," *Clinical Reviews in Allergy & Immunology* 58, no. 3 (2020): 298–312.

94. M. Khodarahmian, F. Amidi, A. Moini et al., "A Randomized Exploratory Trial to Assess the Effects of Resveratrol on VEGF and TNF-α 2 Expression in Endometriosis Women," *Journal of Reproductive Immunology* 143 (2021): 103248.

95. I. Mulyantoro, N. P. Noerpramana, Y. Heru Febrianto et al., "Effect of Adipose-Derived Mesenchymal Stem Cell on the Expressions of Bax/Bcl-2, Ki67, VEGF, TNF-α, and Endometrial Implants in Metformin-Administered Endometriosis Mice (A Mouse Model in Endometriosis Study)," *Turkish Journal of Immunology* 9, no. 1 (2021): 36–49.

96. A. M. Istrate-Ofiţeru, C. A. Mogoantă, G. L. Zorilă et al., "Clinical Characteristics and Local Histopathological Modulators of Endometriosis and Its Progression," *International Journal of Molecular Sciences* 25, no. 3 (2024): 1789.

97. M. Cuevas, M. L. Cruz, A. E. Ramirez et al., "Stress During Development of Experimental Endometriosis Influences Nerve Growth and Disease Progression," *Reproductive Sciences* 25, no. 3 (2018): 347–357.

98. D. Kempuraj, N. Papadopoulou, E. J. Stanford et al., "Increased Numbers of Activated Mast Cells in Endometriosis Lesions Positive for Corticotropin-Releasing Hormone and Urocortin," *American Journal of Reproductive Immunology* 52, no. 4 (2004): 267–275.

99. T. H. Zhu, G. Zou, S. J. Ding et al., "Mast Cell Stabilizer Ketotifen Reduces Hyperalgesia in a Rodent Model of Surgically Induced Endometriosis," *Journal of Pain Research* 12 (2019): 1359–1369.

100. T. Iuvone, G. Affaitati, D. De Filippis et al., "Ultramicronized PalmitoyleThanolamide Reduces Viscerovisceral Hyperalgesia in a Rat Model of Endometriosis Plus Ureteral Calculosis: Role of Mast Cells," *Pain* 157, no. 1 (2016): 80–91.

101. S. L. Engemise, J. M. Willets, J. O. Emembolu, and J. C. Konje, "The Effect of the Levonorgestrel-Releasing Intrauterine System, Mirena on Mast Cell Numbers in Women With Endometriosis Undergoing Symptomatic Treatment," *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 159, no. 2 (2011): 439–442.

102. L. B. Zhu, K. Q. Lin, X. M. Zhang, and J. Lin, "Sodium Cromoglycate Attenuates Experimental Endometriosis in Rats by Regulating Mast Cells," *Zhejiang Da Xue Xue Bao Yi Xue Ban = Journal of Zhejiang University Medical Sciences* 44, no. 3 (2015): 278–284.

103. R. Tapdıgova, G. Bayrak, B. C. Yılmaz, and H. Aytan, "Antilipidemic Ezetimibe Induces Regression of Endometriotic Explants in a Rat Model of Endometriosis With Its Anti-Inflammatory and Anti-Angiogenic Effects," *Naunyn-Schmiedebergs Archives of Pharmacology* 395, no. 6 (2022): 673–680.

104. Q. Yu, L. Chen, J. Wang et al., "Investigation of the Therapeutic Effect of Salbutamol on Endometriosis in a Mouse Model," *Reproductive Sciences* 31, no. 2 (2024): 430–440.

105. M. Cordaro, A. Trovato Salinaro, R. Siracusa et al., "Hidrox and Endometriosis: Biochemical Evaluation of Oxidative Stress and Pain," *Antioxidants (Basel)* 10, no. 5 (2021): 720.

106. E. Jankovich and A. Watkins, "The Low FODMAP Diet Reduced Symptoms in a Patient With Endometriosis and IBS," *South African Journal of Clinical Nutrition* 30, no. 4 (2017): 32–36.