Significance of mast cells in spermatogenesis, implantation, pregnancy, and abortion: Cross talk and molecular mechanisms

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Both subsets of MCs including MCₜᶜ (tryptase-positive, chymase-positive) and MCₜ (tryptase-positive, chymase-negative) are present in the testis and epididymis. Increased number of MCs, higher levels of MC-released tryptase in testis and seminal plasma of males with fertility problems, and promoting sperm motility in individuals with oligozoospermia after using MC blockers provide evidence that MCs may play a role in male infertility/subfertility disturbances. MC-released tryptase and histamine contribute to the fibrosis and may disrupt spermatogenesis. MCs not only influence the process of spermatogenesis but also have effects on the function of other testis-residing cells. MC-derived histamine may influence the steroidogenesis of Leydig cells by acting through H1R and H2R receptors. Additionally, the interaction between MC-released ATP and P2X receptors expressed on the peritubular cells may induce the production of the pro-inflammatory mediators by peritubular cells. Further investigations showed that MCs may be involved in the pathology of female infertility during implantation, pregnancy, and abortion. In the uterus, MCₖ subtype is abundant in myometrium and adjacent basal layer while MCₜᶜ subtype is distributed in all layers. MCs in response to hormones mainly estradiol and progesterone become activated and release a wide range of mediators including histamine, VEGF, proteases, and metalloproteinases (MMPs) that have a role in different stages of pregnancy. An increasing influx of MCs to the cervix during the pregnancy occurs that helps to the physiologic cervical ripening. While MMPs degrade the extracellular matrix (ECM), VEGF modulates neovascularization and histamine influences the embryo implantation. MC-derived histamine may have a positive effect during implantation due to its participation in tissue remodeling. MC proteases including tryptase and chymase activate the precursors of MMP2 and MMP9 to mediate ECM degradation during the physiologic menstrual cycle. There is a line of evidence that MCs have a role in abortion by releasing TNF-α.

KEYWORDS
fertility, implantation, mast cell, pregnancy, spermatogenesis
INTRODUCTION

Infertility in men is a widespread problem which could be the result of disruption of hypothalamic-pituitary-testicular axis, cryptorchidism, varicocele, testicular tumors, microbial infections (including Neisseria spp.), and inflammation. Testicular disorders have roots in abnormal development or proliferation of the cells involved in spermatogenesis. There are three phases in the process of spermatogenesis: spermatogonia proliferation, meiosis of spermatocytes, and spermiogenesis to produce haploid spermatids and finally functional sperms. Interestingly, c-KIT/SCF interaction plays a role in spermatogonial proliferation and development. Orchestration of immune responses in testis is intricate due to the immune-privileged status of the organ and the function of the blood-testis barrier. Moreover, tight junctions between Sertoli cells are capable of protecting germ cell autoantigens within seminiferous tubules from autoimmune scenarios. Testicular immune privilege guarantees the immunologic protection of germ cells during spermatogenesis from an immune attack. Moreover, the localized cells of innate immunity protect the organ from pathogens that threaten the organ from blood circulation and genitourinary tract. Sertoli cells and Leydig cells secrete activin A, TGF-β, PDL-1, growth arrest-specific gene (Gas6), protein S, and testosterone, which possess immunosuppressive properties. Additionally, macrophages and MCs secrete IL-10 and TGF-β to suppress the immune responses. A slight increase in MCs number in the testis and epididymis during infancy followed by decreasing their number during childhood and then increasing during adolescence shows that their number varies in different developmental stages of life. Investigations with immunohistological techniques revealed an increase in the number of testicular MCs in men with fertility disturbances. Interestingly, a shift from MCγ—predominant MC subtype in healthy men—to MCγ in patients with fertility problems was reported. Histologically, human testicular MCs can be divided into interstitial and peritubular MCs. The latter group localizes in the lamina propria or close to seminiferous tubules. In contrast to interstitial MCs (also known as globoïd MC), peritubular MCs (elongated or fascicular MCs) were found near seminiferous tubules or in the lamina propria itself. MCs not only are found in male reproductive organs, but also abound in female reproductive organs including uterus and ovaries. MCs become activated in response to various stimuli in the uterus environment including estrogens, and neurotransmitters after which they release mediators that influence tuned biologic processes such as implantation of the blastocyst into the endometrium and tissue remodeling. MCs produce a variety of inflammatory mediators and are believed to have a role in cervical ripening. The number of MCs in cervical biopsies is significantly higher in women at term compared with pregnant females in the first trimester. Molecular investigations revealed mechanisms by which MCs contribute to the establishment of pregnancy. For example, MCs residing in decidual tissues of parous females express 2DL4 (a killer cell immunoglobulin-like receptor [KIR]) that acts as the receptor for trophoblast expressed human leukocyte antigen-G (HLA-G). It is reported that infertility females have decreased numbers of decidual MCs and lower expression of KIR2DL4. Interestingly, the presence of MCs throughout the endometrium layers and producing pro-inflammatory mediators have been reported to contribute to the recurrent pregnancy losses.

MAST CELL BIOLOGY: ORIGIN, DEVELOPMENT, AND ACTIVATION

MCs are long-lived granular cells of innate immunity which develop from CD34+/CD117+ pluripotent progenitor cells (MCPs). These progenitors after being released from bone marrow in circulation migrate to the target organs and differentiate to MCs under the influence of growth factors mainly stem cell factor (SCF). Human MCs are classified into two subtypes, namely MCγ which express high levels of tryptase and MCα that express both tryptase and chymase in their cytoplasmic granules. In rodents, MCs are classified in two subtypes: mucosal MCs (MCCs) and connective tissue MCs (CTMCs). MCs become activated upon recognizing IgE bounded allergens and release a wide spectrum of preformed (including chymase, heparin, histamine, and tryptase), newly synthesized mediators mainly lipid mediators such as prostaglandins and leukotrienes and cytokines (eg, TGF-β, TNF-α, and VEGF).

MALE REPRODUCTION SYSTEM RESIDING MAST CELLS

3.1 | Testicular MCs

Generally, the number of MCs increases in the peritubular walls of infertile men which is likely due to induced migration of MC precursors (MCPs) to the organ, followed by maturation within the testis. Both MC subtypes (MCα and MCγ) have been reported in human testis and epididymis. MC-derived tryptase and histamine induce fibrosis and may affect normal spermatogenesis in infertile individuals. Studies on undescended testis after orchiopexy revealed an increased number of MCs. Trichrome staining of testicular sections showed a wide range of fibrotic regions. Considering that MC-derived tryptase and chymase have mitogenic effects on fibroblasts, MCs may contribute to the development of testicular fibrosis and collagen deposition. Thickening of tubular walls disrupts the exchange of fluids between the tubular and the interstitial regions. Moreover, MC-derived matrix metalloproteinases (MMPs), especially MMP-9, contribute to the development of fibrosis. Interestingly, estradiol (E2) triggers MC degranulation which results in releasing of β-hexaminidase and leukotrienes (LTs). α estrogen receptors (αER) expressed on human MCs may respond to high levels of estradiol which are notably higher in cryptoorchid testes. Adam et al studied myofibroelastic, peritubular cells which along with laminin, type IV collagen, and fibronectin containing...
ECM form the walls of seminiferous tubules. They reported that MC-derived tryptase may induce the production of decorin by testicular peritubular cells. Decorin regulates the collagen fibrillogenesis and has the ability to bind to TGF-β and PDGF. Decorin may play a role in men infertility through interfering with signaling of growth factor including epidermal growth factor (EGF). In addition to ECM proteins, testicular peritubular cells produce IL-6, MCP-1, NGF, and GDNF. PAR-2 expressing spermatogonia in seminiferous epithelium could be influenced by tryptase-releasing MCs. Investigations on TCam-2 seminoma cells with high expression levels of PAR-2 showed that tryptase prevents apoptosis and supports their proliferation. Sezer et al reported the elevated expression levels of iNOS in Leydig cells correlate with MC index in Sertoli cell-only syndrome (SCO) and severe damage of the germ cell. MC-derived histamine by acting through H1R and H2R receptors expressed by Leydig cells may induce the steroidogenesis in nanomolar concentrations while hampering the process when added to the MA-10 cell line at micromolar concentrations. The activation of H2R induces the steroidogenesis, while H1R activation inhibits the process. MC-derived chymase generates Ang II, to activate peritubular cells expressing AT1R. Moreover, MCs release ATP in their surrounding environment which can be sensed by purinergic receptors (P2X) expressed on the peritubular cells. Driving the signaling pathways of both AT1R and P2X induces the production of pro-inflammatory factors by peritubular cells. Interestingly, estradiol (E2) produced by these cells boosts the levels of biglycan which in turn activates peritubular cells TLR-2. The activation of TLR-2 supports the production of pro-inflammatory factors. Moreover, MC-released TNFα may promote the expression of TLR-2 by peritubular cells (Figure 2).

3.2 Prostatic MCs

Infiltration of MCs into benign prostatic hyperplasia (BPH) tissues has been reported. Further investigations revealed that MC-derived IL-6 may induce the proliferation of BPH-1 cells through activation of STAT3/cyclin D1 signaling. Additionally, MCs play a role in promoting the proliferation of prostate cancer cells and the transition of epithelial mesenchymal.
3.3 | Seminal fluid MCs

Analyzing seminal specimens from infertile asthenozoospermic males and healthy control group after toluidine blue-pyronin staining showed that these patients had a higher MC number when compared to healthy men. Cincik et al reported the negative effects of seminal MCs on sperm concentration, motility, and morphology after studying 400 semen samples and staining MCs by toluidine blue-pyronine. In varicocele, seminal MCs increasing correlates with the grade laterality of the disease but post-varicocelectomy decreases their number in a negative correlation with sperm parameters. Tryptase after being released from MCs in the seminal fluid may reduce sperm parameters mainly motility in a dose- and time-dependent manner through acting on PAR-2 via ERK1/2 pathway.

3.4 | Interaction of MCs and spermatozoa

Membrane expression of PAR-2 on the acrosome and midpiece of human spermatozoa makes a direct interaction between MC and spermatozoa possible through tryptase-PAR-2 binding. To investigate this interaction, Weidinger et al incubated the sperms obtained from healthy men with human recombinant tryptase. They reported the reduction of sperm motility in a time- and dose-dependent pattern. Pre-treatment with either anti-PAR-2 antiserum and anti-trypase antibody or washing could reverse the negative effects of tryptase on sperm motility.

4 | MAST CELLS AND FERTILITY IN FEMALES

4.1 | Ovarian MCs

Histologic distribution of ovarian MCs differs between humans and rodents in which they can be found in all parts of the organ in humans but are limited to the hilum of the ovary in rodents. An increase in the number of MCs has been reported in ovarian endometriomas. High levels of locally produced estrogen (E2) may activate MCs and induce their degranulation. RBL2H3 cells...
were shown to activate upon incubation with E2 and release nerve growth factor (NGF). Endometriotic cells treated with E2 were reported to play a role in the recruitment of RBL2H3 cells by releasing SCF, TGF-β, and monocyte chemotactic protein-1 (MCP-1).\(^{45}\) In animal models including cats, rats, and cows, it is evident that the number of ovarian MCs varies in different phases of estrous cycle.\(^ {46}\)

### 4.2 Uterus-residing MCs

MCs are found in the endometrium as round or ovoid granular cells more often, whereas elongated shapes of them abound in the basal layer and endometrium/myometrium junction.\(^ {18}\) Leo et al investigated the subtypes of MCs during stages of the menstrual cycle. They reported that MC\(_7\) subtype is abundant in myometrium and adjacent basal layer. Moreover, chymase + MCs were distributed in the basal compartment of the endometrium and the myometrium. MC\(_{TC}\) subtype was found in all layers.\(^ {47}\) MC accumulation in endometriotic lesions is evident, and MC-derived proteases play a role in fibrogenesis and accumulation of type I collagen in endometrosis during all stages of cycle.\(^ {48}\) MCs express annexin A1 (ANXA1), an intracellular, membrane, and secretory phospholipid-binding protein with anti-inflammatory properties.\(^ {49,50}\) Epithelial and stromal cells of the human endometrium respond to ANXA1 by expressing formyl peptide receptors (FPR) including FPR2/ALX. Interestingly, FPR1 and ANXA1 were found to be overexpressed in the same regions of the undifferentiated glands from the ectopic endometrium; however, the exact mechanism of action of ANXA1/FPR1 in initiation and development of endometriosis needs further investigation.\(^ {50}\)

Release of tryptase from endometrial residing MCs induces MMP production of stromal cells. These enzymes are capable of degrading ECM components during menstruation.\(^ {51}\) Perivascular localization of MCs and around the interstitium of endometrial cysts would support MC-mediated fibrosis.\(^ {51}\)

### 4.3 Placental and decidual MCs

Investigations of placental samples obtained after abortion or inflammation revealed that the number of placental MCs especially chymase+ subtype rises in such pathologic disorders.\(^ {52}\) Chymase-mediated angiotensin II activation may play a role in fetal malformation.\(^ {52}\) Interaction of immune cells including NKCIs, macrophages, Tregs, regulatory Bregs, and T cells in the decidua contributes to the formation of the suppressive environment to tolerate fetus as a semi-allograft.\(^ {53}\) Matsuno et al using antihuman tryptase mAb investigated the localization of tryptase+ cells and reported that these cells abound on the maternal side. They compared the primary decidual MCs from the early stages of pregnancy with decidua-derived MCs in terms of protease content and reported them as tryptase + chymase+ MC\(_{TC}\) type.\(^ {53}\) One interesting interplay between Tregs and MCs in graft tolerance has been well investigated in which Treg-released IL-9 attracts MCs to graft site and OX40/OX40L interaction stabilizes MCs. The latter cells released TGF-β and IL-10 contribute to the formation of an immunosuppressive microenvironment to protect tolerance.\(^ {54}\) Because the fetus behaves as a semi-allograft, MCs residing in uterus, placenta, and decidua may play a role in the induction and maintaining tolerance.\(^ {54}\)

### 5 MAST CELLS IN IMPLANTATION, PREGNANCY, AND DELIVERY

MC-derived histamine is believed to have a positive effect during implantation due to its participation in tissue remodeling.\(^ {55}\) Investigation of the kinetic of implantation in MC-deficient C57BL/6J-Kit\(^ {W-sh}\) (W-sh) revealed impaired implantation when compared with the control group with normal function MCs which could be compensated by local transfer of wild-type (WT) bone marrow-derived MCs (BMMCs).\(^ {56}\) Additionally, MCs support trophoblast survival, placentation, and growth of fetus by secreting galectin-1 (a glycan-binding protein).\(^ {56}\) Rodent studies using disodium cromoglycate to prevent MC degranulation revealed a role for MC-derived VEGF which acts as a necessary pro-angiogenic factor to regulate implantation. Releasing VEGF upon MC degranulation was reported to support endothelial cell proliferation and angiogenesis in the uterus of the pregnant rats.\(^ {57,58}\) MC-derived leptin and tryptase like VEGF have angiogenic activity, and the extent of angiogenesis in leiomyomas has been reported to correlate with the expression of these cytokines in MCs granules.\(^ {59}\) Interestingly, a significant rise in pre-term deliveries in women suffering from asthma provides a line of evidence that MCs may play a role in delivery.\(^ {60}\) Moreover, boosted levels of histamine induce pregnant myometrial contractions in vitro. This finding may be associated with higher rates of pre-term labor in vivo. One clinical finding in females with systemic mastocytosis is pre-term delivery which may be due to the aberrant accumulation of MCs and their activation in target tissues.\(^ {61}\) Agrawal et al provided a line of evidence of MC involvement in implantation by showing that inhibition of MC expressed H2 receptors by ranitidine and famotidine as H2 blockers and also inhibition of cyclo-oxygenase (COX) by Cox-inhibitor meloxicam may be promising in prevention of implantation in rats.\(^ {62}\) The role of the immune-neuro-endocrine network in pregnancy has been reported in several investigations of which is Yuan et al report that showed an interplay between uterus nerves and MCs. They reported uterus MC number significantly increases after the amputation of the autonomic nerves of the uterus. Moreover, this effect resulted in decreasing histamine storage of uterus MCs and increasing histamine release. Excessive levels of histamine enhance Th1 response while suppressing Th2 response before implantation which may lead to immunologic failure of implantation.\(^ {63}\) MC-derived MMPs may also play a role in implantation by mediating the tissue remodeling needed for the process.\(^ {64,65}\) MMPs are involved in the histologic remodeling of the endometrium during the menstrual cycle. Their expression during the cycle varies...
in which they show a higher expression during the menstrual and tissue proliferative phase while a decreased expression levels during the secretory phase. Chymase secreted by uterus-residing MCs supports the pregnancy by mediating the remodeling of spiral arteries to maintain steady blood supplies for fetus (Figure 3).

6 | MAST CELLS AND PREGNANCY LOSSES

Accumulation of MCs throughout all layers of the endometrium has been reported in women with a history of pregnancy loss. MC activation in these women resulted in higher levels of SCF, tryptase, heparin sulfate, and MMP-2. To elucidate the role of MCs in abortion, Woidack et al decided to perform the adoptive transfer of Tregs to support the MC-mediated angiogenesis in abortion-prone mice which have lower MC numbers in their uterus tissue. After performing the adoptive transfer of Tregs, they concluded that Tregs may induce the angiogenic effects of MCs to prevent the abortion and to rescue placental and spiral artery defects. Marx et al reported a dramatic rise in the number of MCs obtained from decidua specimens obtained from women experiencing primary and secondary abortions (448.7 and 469.2 MC/mm2 decidua, respectively) comparing to MC number obtained from women with normal delivery (36.7 MC/mm2 decidua). Their results were consistent with previous investigations on mice models, and they concluded that MC-derived TNF-α may have a role in abortion. Moreover, MCs may participate in abortion via another molecular mechanism. Anatomical association of MCs and nerves in different tissues is well established. It is reported that substance P (SP)-positive nerve fibers increase dramatically in the decidua of women with abortion and MCs react to SP; therefore, MCs may become activated in humans by SP and release abortogenic cytokines mainly TNF-α. Further investigations revealed that stress may trigger the release of SP from nerves that potentially can activate MCs. Inhibition of SP receptors by SP NK1-receptor antagonist (SP-RA) could decrease the rate of abortion under stress DBA/2J-mated CBA/J female mice.

7 | CLINICAL IMPLICATION OF MC INVOLVEMENT IN FERTILITY AND PREGNANCY

Considering the reviewed role of MCs in human infertility, they can potentially be a key cell type to target. Among the targeting approaches is the application of MC blockers. Intraperitoneally, injection of ketotifen fumarate in rats with experimental autoimmune orchitis and testicular cord torsion was reported to have beneficial effects in the prevention of MC infiltration and reducing inflammation. Prevention of MC activation and applying stabilizing agents have been also investigated in human models. Hibi et al reported the benefits of tranilast administration in the treatment of
TABLE 1 Unmet questions regarding the role of MCs in fertility in males and females

| Aspects of MC involvement in male fertility which require further investigations | Ref. |
|---|---|
| It is not clear whether the increase in the number of the MCs within testis is due to induced migration of MCPs or MC infiltration | 23 |
| The role of MC mediators in seminal fluid needs to be studied. Tryptase is the main mediator investigated | 41,42 |
| The effects of MC mediators on a variety of sperm parameters including morphology and motility need further investigations | 11 |
| Our understanding of the histopathologic effects of mastectomy on male fertility and testis is quite poor | 85 |
| SCF/c-KIT interaction plays a pivotal role in spermatogenesis, and sperm precursors express c-KIT. The molecular mechanism by which SCF/c-KIT interaction contributes to the development of testis germ cells, and the possible sources of SCF needs further study | 86 |
| Testicular MCs express melatonin receptors, and melatonin has anti-proliferative and anti-inflammatory effects on MCs. The possibility of controlling testicular MCs by targeting melatonin receptors in vivo and in vitro needs to be studied | 87 |
| One interesting theme for investigating the role of MCs in maintaining the function of the testis is their capability of expressing a wide variety of TLRs and MHC class II molecules, therefore the ability to participate in the host-pathogen defense | 10 |
| The major feature of orchitis is the infiltration of leukocytes into the testis which results in damaging its anatomical structures especially the seminiferous epithelium. In many settings, MC mediators orchestrate the infiltration of inflammatory cells into tissues. The role of MC mediators in the recruitment of inflammatory cells into testis remains unclear | 10 |
| β-endorphin released during stress stimulates MC degranulation. The possibility of MC involvement in the impact of stress on infertility is poorly understood | 88 |
| Testis benefits from an immunosuppressive microenvironment to protect the spermatogenesis. The immunosuppressive role of MCs in terms of mediators and cross talk with immunoregulatory cells is unclear | 10 |
| The presence of other potential testis-residing cells rather than MCs with the ability of histamine production needs more investigations | 32 |
| The interaction between oxidative stress and prostate-residing MCs in prostatitis and tissue damage is unclear | 89 |
| Recruitment of MCs through CXCL12/CXCR4 and other chemokine-based pathways into prostate tissue needs further investigation | 90 |
| The selective expansion and shifting MC T to MC TC in men with infertility disorders and the possible effect of testis microenvironment on driving the shift could be considered for investigation | 12 |
| Selective targeting of tryptase as the main MC-released mediator involved in the thickening of testis tubular walls instead of blocking MC degranulation may be promising | 27 |

| Aspects of MC involvement in female fertility which require further investigations | Ref. |
|---|---|
| The role of MCs in implantation and placental angiogenesis in women with recurrent pregnancy loss needs to be elucidated | 48 |
| MC releases mediators with immunosuppressive property; however, the immunosuppressive role of MCs in decidua and placenta has not been elucidated | 53 |
| Hormonal changes throughout the menstrual cycle may affect the biologic function of MCs. In this regard, for example, estradiol is capable of inducing MC degranulation | 55 |
| Considering that MCs play a role in transplantation biology, and that from the immunologic point of view fetus is a semi-allograft, the role of MC mediators and cross talk with other immune cells residing in the uterus, decidua, and placenta in establishing a state of tolerance during pregnancy need to be studied | 54 |
| Trafficking of MCPs from circulation to target tissues is controlled by a molecular mechanism including integrin-based interactions. The exact molecular mechanism of trafficking of MCPs in genital organs of females and also involved adhesion molecules, integrin, and ligands could be considered for further investigation. Targeting the trafficking of MCPs into genital organs may be a promising approach to clarify the effects of MC presence during pregnancy | 91 |
| Monitoring the pregnancy in women with mastectomy may elucidate further aspects of MC involvement in female fertility/infertility | 61 |

oligoasthenozoospermia and severe idiopathic oligozoospermia which improved semen parameters including total sperm count.74,75 Yamamoto et al after administration of tranilast in a placebo-controlled study reported a pregnancy rate of 28.6% in the test group compared with 0% in the control group.76 The beneficial effects of ketotifen, another MC blocker on men fertility, were reported by Saharkhiz et al. This group of researchers included 40 infertile couples with asthenospermic infertility, and men included in the test group received oral ketotifen. A comparison of sperm parameters prior and after taking ketotifen showed an improvement in the test group. Sperm motility improved ranging from 16.7% to 21.4%. The rate of pregnancy was reported 12.5% in infertile couples.77 The benefits of Ketotifen have also been reported in increasing the rate of pregnancy in post-varicocelectomy.78 Additionally, improvement of sperm morphology in male patients with leukocytospermia was reported after using ketotifen. Decreasing the number of leukocytes and significant production of sperms with normal morphology were observed in 4 and 8 weeks post-treatment, respectively.79 Zaazaa et al in their investigation of the ketotifen effects on sperm DNA fragmentation reported promising results. They concluded that surgery in infertile men with varicocele followed with ketotifen could improve the sperm DNA fragmentation index comparing with those patients who either used ketotifen alone or underwent surgery without ketotifen.80
8 | DISCUSSION AND CONCLUSION

Beyond their classic role as master cells of allergy scenarios, MCs participate in the pathophysiology of non-allergic diseases too. They abound in genital organs of male and female and interact with immune and non-immune cells through which they modulate immune responses with both negative and positive effects on spermatogenesis and pregnancy. Upon activation, MCs release mediators with pro-inflammatory or immunosuppressive properties which we reviewed their biofunction through the manuscript. Histamine receptors mediate a part of cross talk between MCs and other immune/non-immune cells. Investigation of H1-H4 receptors in human testis is needed to have a better understanding of such cross talk. Abiuso et al reported the expression of the H4 receptor on MA-10 Leydig tumor cells and that H4 receptor activation inhibits the proliferation of MA-10 cells.81 The biologic role of MCs in cryptorchid testes needs to be studied. It is reported that high levels of intratesticular estrogen in cryptorchid testes promote MC migration and proliferation.25 The role of MC mediators may differ according to the physiology of reproductive systems. For instance, after emerging Cox-deficient mice (mice not able to produce PGs) it was observed that male fertility, unlike the female mice, was not affected. However, there are pieces of evidence that compensatory pathways such as hormone-dependent induction of Cox expression in Leydig and Sertoli cells may explain the maintenance of fertility in male Cox-deficient mice.82 Cross talk of uterus-residing MCs with other immune cells needs to be investigated to clarify their exact role in maintaining a normal pregnancy. In this regard, Meyer et al reported a counterbalancing interplay between MCs and NKS of the uterus during pregnancy in which MC-deficient C57BL/6J-KiIw(sh)/W-sh (W-sh) mice had a dramatic rise in the number of NKC and interestingly NKC-deficient mice C57BL/6NTac-il15tm1Imm5 (IL-15−/−) had elevated uterus-residing MCs. They concluded that MCs and NKC counterbalance their effects to support a normal spiral artery remodeling and placenta.83 Table 1 summarizes various aspects of MC involvement in male and female reproduction from an immunologic point of view. Investigations aimed to clarify the role of MCs in fertility, and different phases of pregnancy have some challenges ahead which should be considered; for example, obtaining tissue samples during pregnancy is an invasive approach. Differences in MC anatomical distribution, localization within female reproductive organs (such as mice and humans), and density (eg, MRL/MpJ strains have a significantly higher number of MCs at post-natal day 084) may raise inconsistency in results.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Daniel Elieh Ali Komi, Farzaneh Shafaghat, and Gerhard Haidl have been directly involved in the preparation of the manuscript. Daniel Elieh Ali Komi has designed and created the figures. Gerhard Haidl has reviewed, revised, and added inputs.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animal models.

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