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Review

The importance of the macrophage within the human endometrium

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ABSTRACT

The human endometrium is exposed to cyclical fluctuations of ovarian-derived sex steroids resulting in proliferation, differentiation (decidualization), and menstruation. An influx of leukocytes (up to 15% macrophages) occurs during the latter stages of the menstrual cycle, including menses. We believe the endometrial macrophage is likely to play an important role during the menstrual cycle, especially in the context of tissue degradation (menstruation), which requires regulated repair, regeneration, and phagocytic clearance of endometrial tissue debris to re-establish tissue integrity in preparation for fertility. The phenotype and regulation of the macrophage within the endometrium during the menstrual cycle and interactions with other cell types that constitute the endometrium are currently unknown and are important areas of study. Understanding the many roles of the endometrial macrophage is crucial to our body of knowledge concerning functionality of the endometrium as well as to our understanding of disorders of the menstrual cycle, which have major impacts on the health and well-being of women. *J. Leukoc. Biol.* 93: 217–225; 2013.

Introduction

During the normal (nonpregnant) menstrual cycle, the human endometrium is exposed to cyclical fluctuations in ovarian-derived estrogen and progesterone. These sex steroid hormones control repetitive cycles of proliferation, differentiation (decidualization), and shedding of the luminal region of the tissue during menses. The estrogen-dominant proliferative phase is characterized by the regeneration of the functional layer of the endometrium (**Fig. 1**). During the progesterone-dominated secretory phase, the endometrium undergoes a number of changes in preparation for implantation of the embryo, including vascular maturation typified by the formation of spiral arterioles. If implantation occurs, the endometrial stroma completes the process of decidualization [1]. In the absence of pregnancy, progesterone levels decline (as a result of demise of the ovarian corpus luteum), and progesterone withdrawal triggers an inflammatory cascade, changes in ECM, and vascular constriction, culminating in shedding of the upper-functional layer during menses [2, 3].

Within the endometrium, proliferation of cells in the vascular compartment, their differentiation, and the process of vasoconstriction are all tightly regulated so that controlled and self-limited ischemic hemorrhagic tissue degradation and shedding occurs at the time of menstruation. These changes are accompanied by an inflammatory response and the formation of a hypoxic microenvironment that is thought to promote successful healing of the endometrial "wound", ensuring a return to normal architecture in advance of the next cycle of vascular proliferation. Importantly, these repeated cycles of endometrial repair occur without scarring or loss of function [4, 5].

The endometrium hosts a diverse population of immune cells, the numbers of which vary during the normal menstrual cycle. Studies determining the spatial and temporal changes in their location have led to reports that different populations of immune cells play a vital role in regulating tissue injury and repair [6]. For example, macrophages, mast cells, T-lymphocytes, and a phenotypically distinct population of uNK cells are only present in low numbers during the proliferative phase [7, 8]. However, there is a striking influx of leukocytes during the secretory and menstrual phases of the cycle [9, 10]; these original observations contributed to the premise that menstruation is an inflammatory event [2, 6, 11]. Following the discovery that there is an increase in the number of tissue-resident macrophages present during the secretory phase, associated with an increase in macrophage-derived cytokines and proteases, it has been proposed that the endometrial macrophage may be critical in the initiation of menstruation [2], the "clean-up" process [12], and repair and remodeling of the functional layer of the endometrium post-menses [12, 13]. Macrophages are thought to play an important role in the preparation of a receptive endometrium during the "window of implantation"

Abbreviations: HMB=heavy menstrual bleeding, LNG=levonorgestrel, MAF=macrophage-activating factor, MIF=macrophage migration inhibitory factor, MMP=matrix metalloproteinase, MT=membrane type 1, uNK=uterine NK

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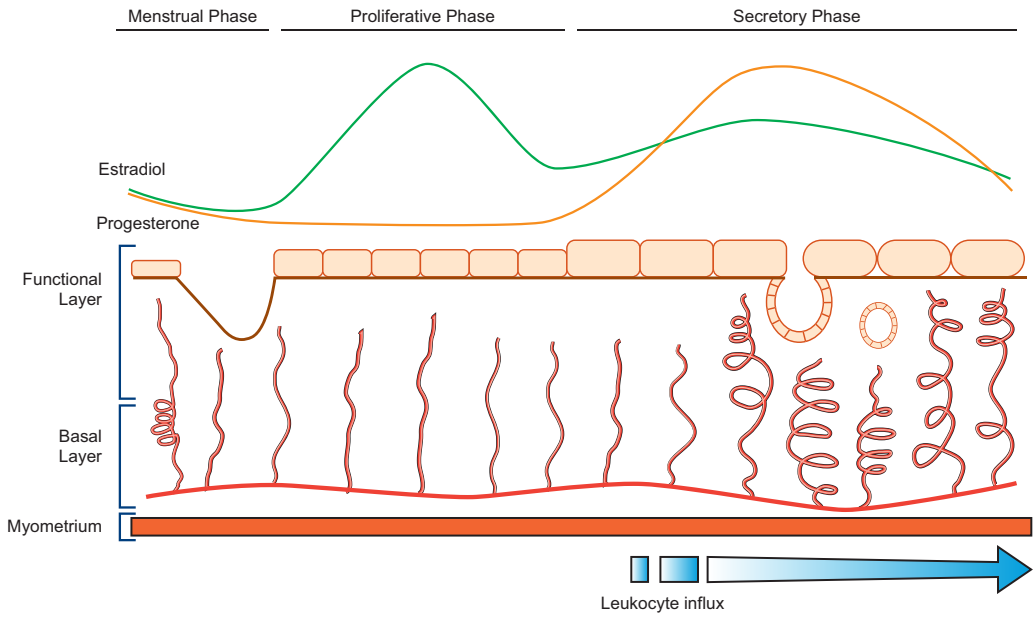

Figure 1. Schematic diagram of the 28-day menstrual cycle showing the estradiol-dominant proliferative phase (vessel regrowth) and the progesterone-dominant secretory phase (maturation of spiral arterioles and glandular transformation). Progesterone withdrawal results in vessel breakdown and loss of the functional layer of the endometrium (menstruation). An influx of leukocytes is observed during the progression of the secretory phase.

[14, 15] and subsequent decidualization of the endometrial stroma—a necessary prerequisite for successful implantation and establishment of early pregnancy. Notably, macrophages constitute up to 20% of the leukocyte population within decidual tissue of early pregnancy [16] and have been found to have roles in lipid metabolism, inflammation, ECM formation, muscle regeneration, and tissue growth [17]. The decidual macrophage has been studied by a number of groups [16–19] and it's functions reviewed recently [20–22]. This review is focused on the macrophage within the endometrium during the menstrual cycle, as evidence to support the above putative roles in regulation is only now emerging, and unanswered questions remain.

THE MACROPHAGE

Development of cells of the mononuclear phagocyte lineage from hematopoietic stem cells is well characterized [23–25]. Following recruitment of monocytes from blood, or the splenic reservoir, cells differentiate into tissue-resident macrophages capable of performing key roles, including phagocytosis, maintenance of tissue homeostasis, regulation of wound healing, and trophic interactions and regulation of other immune cell populations [26–28]. It is well established that the phenotype(s) of macrophages and their impact on tissue function are influenced by their immediate environment, and the following sections discuss the evidence supporting a role for tissue-resident macrophages in regulation of endometrial function.

Macrophage phenotypes: M1 and M2

It is becoming clear that a simple classification of macrophages into M1 or M2 phenotypes [29–33] does not explain the diversity of macrophages in different tissues. Gordon and Martinez [34] explained that the activation of macrophages is carried out in a number of stages of differentiation to meet the functional demands of the tissue environment (**Fig. 2**). The ability of macrophages to functionally adapt to their tissue microenvironment in response to the availability/mix of a cocktail of macrophage-modulating chemokines enables the development and progression of the immune response and its subsequent resolution to take place [35–37]. Extensive in vitro

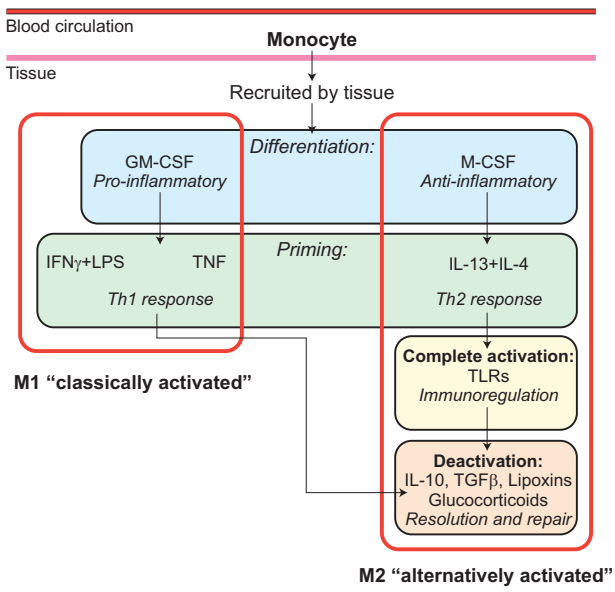

Figure 2. Polarization, activation,and resolution of the macrophage inflammatory response upon recruitment from the circulation into tissue. Monocytes are recruited from the circulating blood into tissues in response to release of chemoattractants. Upon exposure to the tissue microenvironment, the monocyte differentiates into a macrophage enabling it to undertake tissue-dependent functions. (Adapted from Gordon and Martinez [34].)

macrophage phenotyping studies have revealed the complexity of the mononuclear phagocyte system and helped to understand control of their diverse functions. However, the phenotype and function of in vivo-derived macrophages are less understood [38].

It is also becoming clear that populations of tissue-resident macrophages can change the phenotype and hence, functionality of recruited leukocytes into a tissue. For example, in tumors, two phenotypically different macrophage subsets have been reported to play a role in pathogenesis of tumor growth [39]. During the progression of tumorigenesis, macrophages with an M1 phenotype have been identified and are thought to have a role in the establishment of neoplastic transformation [40] via the exacerbation of local M1 inflammation [41]. However, gradual inhibition of NFκB) activity results in the transformation of tumor-associated macrophages into an M2 macrophage [42, 43], which encourages tumor growth, invasion, metastasis, stroma remodeling, and angiogenesis [44, 45].

A single macrophage may also express proinflammatory and anti-inflammatory markers. For example, it has been postulated that decidual macrophages may be unique in that they can secrete proinflammatory and anti-inflammatory cytokines and so, do not conform to the M1/M2 phenotype characterization [17].

THE ENDOMETRIAL MACROPHAGE

Macrophages within the endometrium have been identified as an important source of proinflammatory and anti-inflammatory chemokines. Notably, a number of studies have documented macrophage-specific expression of role-specific markers within endometrium at different stages of the menstrual cycle (**Fig. 3**).

For example, during the proliferative phase, macrophages express adhesion and activation markers (CD71, CD69, CD54) [46], suggesting a potential role in regeneration and proliferation of the functional layer of the endometrium. The influx of macrophages in the latter one-half of the menstrual cycle is postulated to underpin a large number of specific roles in regulation of fertility. For example, an increase in macrophages and macrophage products, such as MIP-1β, MIF [15], and CSF-1 [47], have been suggested to be fundamental in creating the proinflammatory environment [48] that plays an essential role in preparing the endometrium for implantation during the so-called window of implantation. The importance of LIF production during the window of implantation has been well established [49, 50]. LIF is thought to be a potent chemoattractant for macrophages [51], as a LIF-knockout mouse model has shown a reduction of macrophage number of $<$50%, which resulted in unsuccessful embryo implantation. Infiltration [52], differentiation, and proliferation [53–57] of other immune cells into the uterine cavity may be regulated in part by endometrial macrophages [58], as along with other cells, such as epithelial cells, they express a large number of chemoattractants during the secretory phase. Progesterone withdrawal, as well as release of paracrine factors from a variety of cells within the endometrium, has been reported to regulate availability and activity of MMPs. MMPs are proteolytic proteinases that break peptide bonds of nonterminal amino acids and so, are considered to be pivotal in the breakdown of the endometrium at menstruation [8]. Macrophages have been found to express various phenotype-dependent MMPs [59], as well as producing a number of molecules that regulate MMPs [8, 60, 61], which would be consistent with a role in the initiation of menstruation (discussed later). Furthermore, macrophages have also been associated with glandular cell loss [12] and regulation of angiogenesis [50] during the menstrual phase. A tissue xenograft model of menstruation, developed by Cheng et al. [62], has also shown that immune-related genes, including those known to be expressed by macrophages, are tightly regulated in response to progesterone withdrawal.

During the late secretory phase, immune cells, including macrophages [63] and uNK cells [64], express receptors capable of binding human chorionic gonadotropin from the early conceptus, which may contribute to an increase in cell number. The endometrial macrophage has also been shown to express estrogen receptor-β and estrogen-related receptor-β, indicating the potential for estrogen-dependent regulation of cell function [65]. However, the endometrial macrophage does not express the progesterone receptor [66], which im-

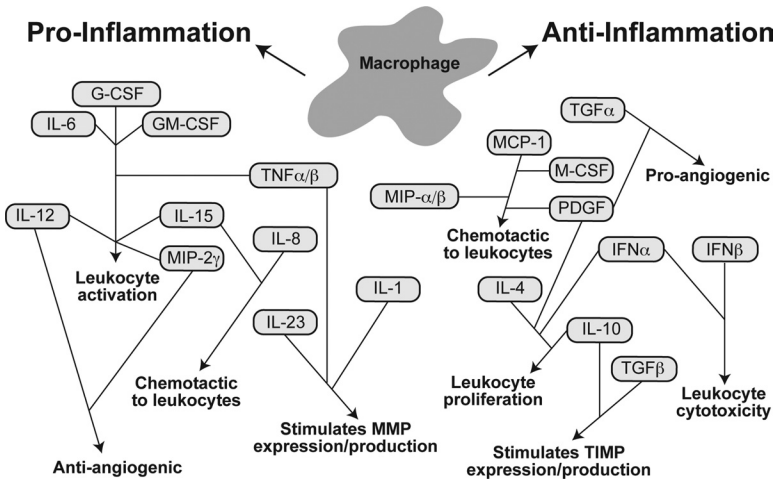

Figure 3. Macrophages release proinflammatory and anti-inflammatory mediators throughout the menstrual cycle. A schematic diagram showing postulated roles of the chemokines released by tissue-resident macrophages identified in endometrium according to their "Pro-Inflammation" and "Anti-Inflammation" functions.

TABLE 1. Chemoattractants with a Potential Role in Monocyte Recruitment into the Human Uterus with Details of Temporal and Spatial Location across the Menstrual Cycle

Location	Proliferative phase	Secretory phase	Menstrual
Glandular epithelium	MIP-1[α] [72], MIP-1β [73], CCL14 [74], CCL16 [75], MCP-1 [76], MCP-3 [58], MIP-2γ [77]	MIP-1α, CCL21, MCP-1, MCP-3	CCL14, IL-8 [80], MCP-1, MCP-3, MIP-1α
	Low levels of CCL21 [78], MCP-2 [79], MDC [58]	Up-regulation of MDC, MIP-2γ, CCL14, IL-8 Down-regulation of MIP-1β Low levels of MCP-2	Low levels of MCP-2
Stromal cells	Fractalkine [81], MCP-1, RANTES [82]	LIF, MCP-1, RANTES	IL-8, RANTES, MCP-1
	Low levels of MCP-2 and LIF [83, 84]	Up-regulation of IL-8 Low levels of MCP-2	Low levels of MCP-2
Vascular endothelium	CCL14, CCL16, MIP-1α	CCL21, MIP-1α	CCL21, IL-8, CCL14, CCL16, MDC, MIP-1α, MIP-1β
		Up-regulation of CCL14, CCL16, MDC, IL-8	Low levels of MCP-2
	Low levels of MCP-2	Low levels of MCP-2	
Leukocytes	CCL16, Fractalkine in uNKs	Fractalkine in uNKs and macrophages	CCL21, MDC, MIP-1β
			Small dip in fractalkine premenstrually
Luminal epithelium		LIF	LIF
Perivascular cells	MCP-1	MCP-1	MCP-1
Vesicles		MCP-3	

MDC, Macrophage-derived chemokine.

plies that the impact of progesterone and its withdrawal on macrophage activity are likely to be mediated indirectly by factors released by other cell types.

REGULATION OF THE ENDOMETRIAL MACROPHAGE THROUGHOUT THE MENSTRUAL CYCLE

The location and "traffic" of macrophages within the endometrium are tightly regulated, temporally and spatially during the menstrual cycle. Macrophage numbers make up 1–2% of all cells within the endometrium during the estrogen-dominant, proliferative phase, and this increases to 3–5% during the progesterone-dominant secretory phase, with the macrophage population reaching its peak at 6–15% during the menstrual phase (following progesterone withdrawal) [6]. Macrophages are reported to be evenly distributed throughout the endometrial stroma but with aggregations observed close to the lumen of superficial secretory glands [67]. The increase in macrophage cell numbers over the menstrual cycle is considered to occur by (i) chemotaxis of monocytes from peripheral blood into the endometrium or (ii) local proliferation in situ within the endometrium [68, 69]. Whether macrophages are retained within the uterine cavity or replaced during the cycle is yet to be established and is an important area for further study.

Evidence for chemoattraction of macrophages to the endometrium

Chemokines are capable of stimulating specific migration of cells via GPCRs on leukocytes. The chemokine receptors expressed on leukocytes direct the migration of specific leukocyte subsets to the endometrium [70, 71].

A number of chemoattractants are present within the endometrium throughout the menstrual cycle (**Table 1**). The expression patterns of many of these chemokines parallel the temporal change in numbers of tissue-resident endometrial macrophages and are implicated in regulation of the observed influx (traffic) of macrophages. For example, the premenstrual withdrawal of progesterone from the uterine cavity (at the time of regression of the corpus luteum and falling circulating progesterone concentrations) results in a hypoxic environment, an influx of immune cells, and up-regulation of progesterone-regulated chemokines and receptors, including IL-8 [85–87], MCP-1 [76, 88], fractalkine [58, 81], and CX3CR1 [89].

Down-regulation of macrophage numbers within the endometrium has also been studied. MIF [90] has been shown to inhibit random migration of macrophages into the uterine cavity, as well as having a postulated, proinflammatory role. MIF has been localized to the glandular epithelium and the stromal cells of the cycling endometrium [91]. Further studies are required to establish the relative impacts of pro- and anti-migratory factors in endometrial biology.

Evidence for in situ proliferation of endometrial macrophages

It has also been proposed that the increase in macrophage population density during the secretory phase of the menstrual cycle may be a result of in situ proliferation. A model using human endometrial xenografts, maintained in immune-compromised mice, was supplemented with hormones simulating those of the normal menstrual cycle. On Day 28 of the stimulated cycle, in situ proliferation of the human leukocytes, including macrophages, were at their highest numbers [68]. Three days after progesterone withdrawal (Day 31), leukocyte numbers within the xenograft reached a maximum, with most of the cells identified as infiltrating mouse leukocytes coinciding with a peak in MMP-9 production by the tissue. Leukocytes generated via in situ proliferation might therefore be responsible for cytokine secretion and promotion of decidualization [68, 92]. Although it is also possible that leukocyte precursors or progenitor cells were present within the transplanted endometrial tissue matrix, and these matured within the xenograft, contributing to the observed increase in human macrophages. In contrast, infiltrating leukocytes brought into the uterine cavity in response to progesterone withdrawal may be involved in tissue breakdown and repair [2, 68].

In situ proliferation of leukocytes has been reported to occur in the presence of IL-4 during a TH2 inflammatory response [69]. Furthermore, in situ proliferation may be an alternative component of an inflammatory response that allows macrophages to accumulate in sufficient numbers to perform critical functions, such as wound repair in the absence of potentially damaging inflammatory cell recruitment during sustained classical inflammation [69]. It has been postulated that IL-4 may suppress MAF and MAFB transcription factors that would ordinarily reduce macrophage proliferation [93].

A ROLE FOR MACROPHAGES IN TISSUE AND VESSEL BREAKDOWN AT MENSTRUATION

MMPs are expressed in endometrial stromal cells, epithelial cells, and subsets of leukocytes at menstruation, including macrophages [8]. Up-regulation of MMPs in areas of lysis is stimulated by a number of cytokines, such as IL-1α, left–right determination factor 2 (LEFTY-2), and TNF-α, which recruit MMP-rich immune cells into the uterine cavity [94]. Expression of MMPs is reported to be negatively regulated by progesterone and TIMPs via TGF-β [61, 95].

Macrophage release of latent forms of MMP-9 (gelatinase B), MMP-12 (metalloelastase), MMP-14 (MT-MMP-1), and plasminogen activator (followed by subsequent cleavage) is implicated in the breakdown of the functional layer of the endometrium (**Table 2**) [6, 94, 96]. MMP-9 is detected in stromal cells, epithelial cells, and infiltrating leukocytes throughout the cycle and up-regulated during the menstrual phase [96]. Expression of MMP-3 is strikingly up-regulated at menses and activates pro-MMP-9 to form active MMP-9, which is capable of breaking down small fragments of collagen within the functional layer of the endometrium [97]. MMP-12 is also present throughout the cycle in low levels but massively increased during the menstrual phase [97].

TABLE 2. Summary of MMP Production in Endometrium and Proposed Roles

MMP	Role
MMP-9 (gelatinase B)	Up-regulated at menstruation
MMP-12 (metalloelastase)	Up-regulated at menstruation
MMP-14 (MT-MMP-1)	Slightly up-regulated at menstruation
Plasminogen activator	Premenstrual

MMP-14 is expressed throughout the cycle and only increases slightly during the menstrual phase. ProMMP-2 can be converted into MMP2 by MMP-14, allowing MMP2 to act in concert with MMP-9 and other MMPs at the time of menstruation [97].

The urokinase form of the plasminogen activator is reported to be up-regulated premenstrually [98] and has been shown to be released from mast cells and macrophages [99]. At this stage of the menstrual cycle, it converts plasminogen into its active form, plasmin, which cleaves pro-MMP1 to form MMP-1 [97]. MMP-1 therefore represents an essential enzyme in the events leading to menstruation [100].

A hypoxic environment within the endometrium stimulates production and release of VEGF by macrophages and other endometrial cells [50, 101]. Such conditions could also result in the transformation of macrophages into a proangiogenic cell as a result of low oxygen tensions [102] or to wound-like concentrations of lactate [103, 104], pyruvate [104], or hydrogen ions [103, 104]. They may also be activated by cytokines, such as IFN-γ, GM-CSF, platelet activating factor, or MCP [105]. These "activating" cytokines are released by a number of cells that include activated endothelial cells. MMP activation has also been found to alter angiogenic activity by the release of cytokines and angiogenic inhibitors [106]. A hypoxic environment may be critical for establishment of a monocyte gradient in inflammatory sites, where the local microenvironment influences monocyte transendothelial migration and recruitment by up-regulating expression of endothelial cell adhesion molecules and various chemoattractants, i.e., VEGF, endothelin, endothelial-monocyte activating polypeptide-2, angiopoeitin 2, and CXCL12, as studied in tumor lesions [39, 107].

CLINICAL CONTEXT OF A TISSUE-RESIDENT ENDOMETRIAL MACROPHAGE

Examples of clinical situations where macrophage phenotype and function may play a significant role in physiology and pathology include benign gynecological complaints, such as endometriosis and abnormal uterine bleeding (unscheduled bleeding with exogenous hormone administration and HMB) and endometrial malignancy. If macrophage activation/function is demonstrated to play a pivotal role(s) and to be perturbed in these clinical conditions, then manipulation of macrophage activation/function may provide a novel target for therapeutic opportunities for management of these debilitating clinical complaints.

ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding may be a result of a number of different causes. When ovulatory and structural disorders have been excluded, it is likely that the problem resides within the endometrium [108, 109].

HMB, in some cases, is a likely consequence of dysregulation of local endometrial hemostatic mechanisms [110]. It is well documented that the endometrial macrophage, as discussed above, is a key regulator of a number of factors involved in the initiation of menstruation [9, 111] and is found in focal sites of endometrial remodeling [6], supporting claims that it is likely to play a key, functional role in successful repair of the endometrium [112]. The importance of leukocytes during menstruation has been documented in a study by Kaitu'u-Lino et al. [113], where neutrophil depletion hindered endometrial repair in a mouse model of menstruation. It is unknown what effect macrophage depletion would have on menstrual function. Unscheduled bleeding is thought to be the most common reason for discontinuation of contraceptives [114–116]. Clark et al. [117] clearly showed an increase in macrophages and their cytokines in the endometrium of women using a LNG contraceptive or those with intrauterine delivery of LNG who complained of unscheduled bleeding. Further studies using progestin-only contraceptives have also shown an increase in endometrial MMPs [118–120] as a result of a "suppressed secretory phase" [121]. These observations highlight the potential importance of dysregulation of macrophage numbers in the context of endometrial function/bleeding patterns. However, as a role for macrophages in regulation of menstrual function is yet to be defined, the actual impact of dysregulation of macrophage function and number on endometrial bleeding remains to be determined.

ENDOMETRIOSIS

Endometriosis is a chronic condition where endometriotic-like tissue is deposited in areas outside of the uterus (in the pelvis) causing pelvic pain, pain during intercourse, and infertility [122]. Macrophages are thought to play a role in the pathogenesis of endometriosis with evidence for augmentation of macrophage function (i.e., clearance) in endometrial tissue found outside of the uterine cavity [123], which may be estrogen [124] or oxidative damage-dependent [125–127]. Abnormal immune responses involve a lack of scavenger function [128, 129], an increase in PG [130, 131] and IL production [128, 132, 133], as well as the creation of a positive feedback loop in NFκB [134, 135] and RANTES [136] production. Bacci et al. [137] have recently shown a proinflammatory role for macrophages that exacerbates growth and vascularization of endometriotic lesions in a mouse model. The pathology leading to altered macrophage function in endometriosis is yet to be defined.

ENDOMETRIAL CANCER

Endometrial cancer is the most frequent gynecological cancer and the fourth most common cancer in women in the developed world [138].

A number of remodeling proteinases have been identified as factors involved in remodeling of the endometrial stroma during tumor invasion [139–143]. Correlative studies suggest that progression of carcinoma growth within the uterine cavity is triggered by infiltration of endometrial macrophages [141, 143–146] and is associated with tumor angiogenesis [147, 148]. Macrophages have been linked with both a protective and pathogenic role in various cancers [149]. It is thought that the microenvironment of a tumor has the potential to alter monocyte function [150] to bring antitumor immunity to a halt. Whether this occurs in endometrial cancer has not been studied.

CONCLUDING REMARKS

Available evidence suggests endometrial macrophages play a number of important roles throughout the menstrual cycle, including tissue regeneration, predecidualization of endometrium in anticipation of implantation, initiation of menstruation, and phagocytotic clearance of endometrial tissue debris. Further studies are required to fully understand the mechanisms underpinning these roles. The different phenotypes and regulation of the macrophage within the endometrium at different phases of the menstrual cycle have yet to be fully defined. Furthermore, the interaction between the endometrial macrophage and the many resident cell populations within the endometrium is still poorly understood. Defining the roles of the endometrial macrophage will be an important contribution to knowledge on the functionality of the endometrium throughout the menstrual cycle, as well as disorders associated with endometrial tissue. Given that dysregulation of the macrophage phenotype contributes to aberrant inflammatory responses in many tissues, we propose that the endometrial macrophage has a role in disorders, including abnormal uterine bleeding, endometriosis, and endometrial cancer. Studies on the endometrial macrophage provide a unique model for examination of macrophage function in cyclical repair/remodeling—an important area for future study.

AUTHORSHIP

All authors composed and edited the manuscript.

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