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Mechanisms of Regeneration and Fibrosis in the Endometrium

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Abstract

The uterine lining (endometrium) regenerates repeatedly over the life span as part of its normal physiology. Substantial portions of the endometrium are shed during childbirth (parturition) and, in some species, menstruation, but the tissue is rapidly rebuilt without scarring, rendering it a powerful model of regeneration in mammals. Nonetheless, following some assaults, including medical procedures and infections, the endometrium fails to regenerate and instead forms scars that may interfere with normal endometrial function and contribute to infertility. Thus, the endometrium provides an exceptional platform to answer a central question of regenerative medicine: Why do some systems regenerate while others scar? Here, we review our current understanding of diverse endometrial disruption events in humans, nonhuman primates, and rodents, and the associated mechanisms of regenerative success and failure. Elucidating the determinants of these disparate repair processes promises insights into fundamental mechanisms of mammalian regeneration with substantial implications for reproductive health.

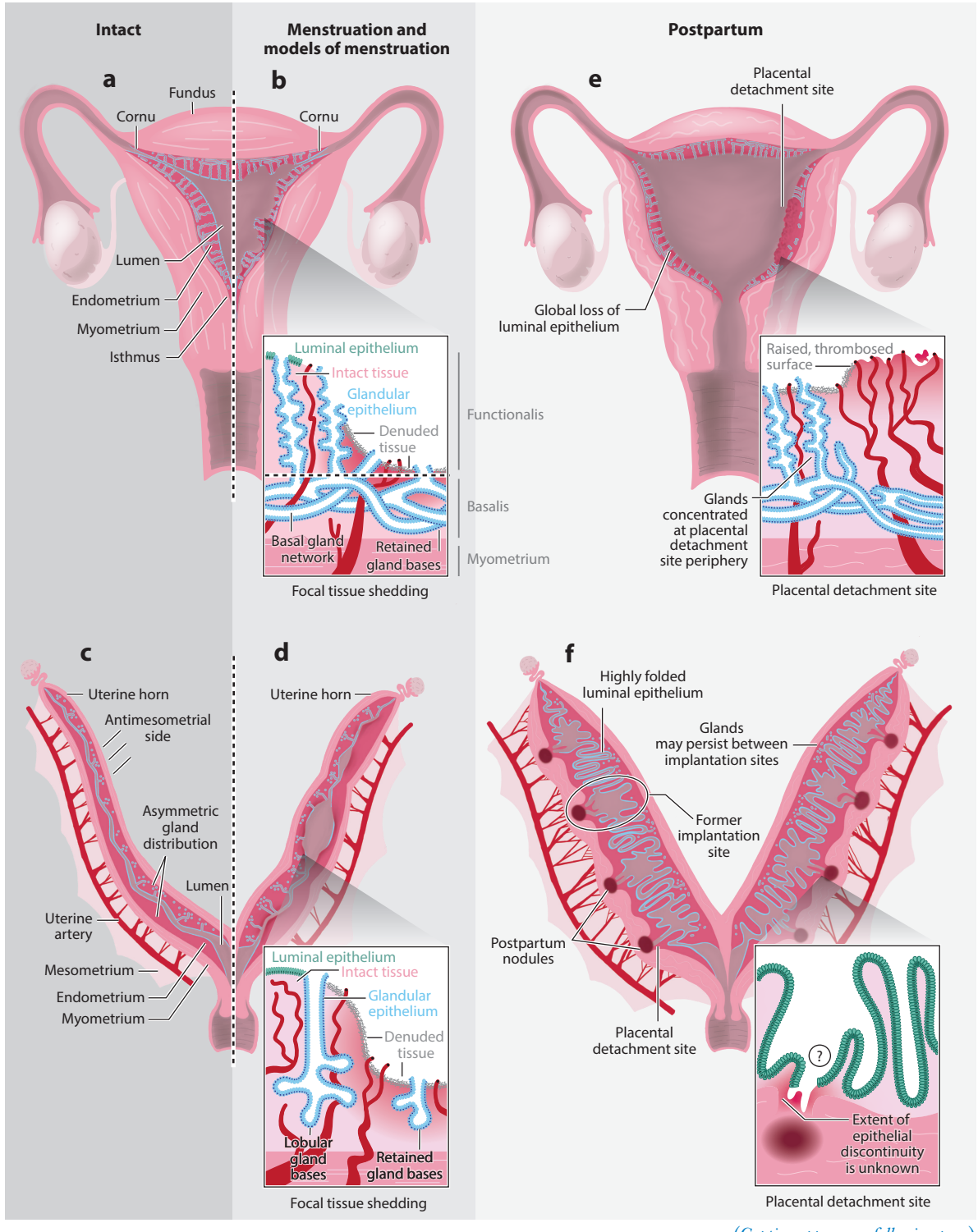
Contents

1. INTRODUCTION

Throughout the human life span, the uterus displays a striking capacity for regeneration. The uterine lining (endometrium) undergoes extensive remodeling before, during, and after pregnancy, as well as programmed shedding and repair during each menstrual cycle. Consequently, the endometrium may regenerate approximately 400 times over the reproductive life span to restore tissue integrity and facilitate future pregnancy. Endometrial dysfunction contributes to infertility and a wealth of poorly understood health conditions, including endometrial cancer, endometriosis, and abnormal uterine bleeding, which respectively affect 1 in 32, 1 in 10, and >1 in 10 people with a uterus in their lifetimes (Howlader et al. 2021, Liu et al. 2007, Zondervan et al. 2020). Thus, unraveling the intricacies of proper endometrial regeneration holds tremendous promise for unlocking fundamental mechanisms of mammalian regeneration and improving the lives of hundreds of millions of individuals worldwide.

Uterine function relies on a complex architecture that must be restored after each menstruation or pregnancy (**Figure 1*a***). The uterine cavity is lined with an epithelial monolayer on top of a supportive mesenchymal compartment (stroma) and underlying smooth muscle layer (myometrium). Glandular offshoots (glandular epithelium) extending from the surface epithelium (luminal epithelium) project into the stroma and merge into a highly branched plexus running parallel to the myometrial border (Tempest et al. 2020, Yamaguchi et al. 2021). Recent single-cell transcriptomic approaches have revealed extensive heterogeneity among endometrial stromal and epithelial populations, illuminating the complexity of this important tissue (Garcia-Alonso et al. 2021; Kirkwood et al. 2021, 2022; Wang et al. 2020; Winkler et al. 2022).

A critical consideration for understanding endometrial regeneration is that the uterus is an organ defined by profound change. Over the menstrual cycle, fluctuations in estrogens



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Working models of physiological disruption of the endometrium (*dark magenta*). The insets illustrate zoomed-in models of the indicated damaged regions, with intact luminal epithelium (*green*) adjacent to exposed glandular epithelium (*blue*) and blood vessel (*red*) remnants. (*a*) Human uterus with an intact endometrium. (*b*) Human uterus undergoing menstruation. (*c*) Mouse uterus with an intact endometrium. (*d*) Mouse uterus undergoing experimentally induced tissue shedding as a model of menstruation. (*e*) Human uterus within 1 day of parturition. (*f*) Mouse uterus within 1 day of parturition. If or how postpartum gland bases connect to the lumen remains unclear. Note that the three-dimensional gland structures in the human and mouse postpartum uterus remain unknown. Mouse, but not human, uteri are approximately to scale across conditions.

(predominantly estradiol), progesterone, and androgens, as well as other hormones, alter cellular proliferation, cell type distributions, and tissue architecture (reviewed in Brenner & Slayden 2012, Gibson et al. 2020). Estrogen drives the expansion of the stroma and epithelium, resulting in thickening of the endometrium during the proliferative phase. Ovulation induces the transition to a progesterone-dominant stage (the secretory phase), during which endometrial glands become more tortuous and secrete products into their lumens (Gray et al. 2001, Tempest et al. 2020). If pregnancy is not established, the demise of the progesterone-producing corpus luteum leads to hormone withdrawal, resulting in focal shedding of the superficial layer of the endometrium (the functionalis) and exposure of the underlying layer (the basalis). If, instead, pregnancy occurs, the endometrium undergoes further remodeling to facilitate implantation and support fetal development. At the end of pregnancy, delivery, placental shearing, and subsequent necrosis remove large portions of the pregnant endometrium, which is termed the decidua (Isley 2021). Thus, endometrial function requires a capacity to regenerate from routine and variable tissue disruption.

Consequently, defining the mechanisms of regenerative success and failure in the endometrium requires interrogating and synthesizing data across the disparate events that compromise endometrial integrity. In this review, we summarize current knowledge about the cellular responses to physiological processes that disrupt the endometrium: menstruation and parturition. We highlight the evidence supporting numerous proposed mechanisms of endometrial regeneration, which may be differentially evoked in response to distinct damage. We provide an overview of a subset of injuries, particularly relating to medical procedures and infections, that are seemingly capable of overwhelming this regenerative repertoire, resulting in fibrosis. The examination of these fibrotic states provides an exciting opportunity to interrogate the determinants of regeneration, with substantial clinical implications. From this perspective, we discuss the possibility that several variables, ranging from the extent of tissue loss to hormone state, may contribute to conditions in which regenerative mechanisms are suppressed or diverted toward nonregenerative healing. A holistic approach to investigations of endometrial repair, considering both the foundational and clinical science of regenerative and nonregenerative healing, is critical to understanding and harnessing the remarkable regenerative potential of this tissue.

2. ENDOMETRIAL DISRUPTION DURING MENSTRUATION AND PARTURITION

The endometrium is rare among mammalian tissues in that it regularly experiences programmed tissue disruption. While both menstruation and parturition breach the endometrium, they differ substantially in the localization and extent of tissue loss, as well as the timescale of regeneration. Interrogating the extent to which diverse compartments are compromised is essential for understanding the regenerative burden imposed on the endometrium by these physiological events. In this section, we review the effects of parturition, menstruation, and menstruation-like tissue shedding on endometrial architecture in primate and rodent models.

2.1. Menstruation

Menstruation is a carefully orchestrated, stepwise process of controlled tissue loss, primarily driven by declining progesterone levels at the end of the menstrual cycle (reviewed in Critchley et al. 2020, Jabbour et al. 2006). This process has been characterized extensively in the endometrium of the rhesus macaque. Just prior to menstruation, the macaque endometrium undergoes a 25–75% regression in size, and specialized uterine arteries constrict to mitigate blood loss (Markee 1940). In the first phase of menstruation, progesterone withdrawal leads to a reversible upregulation of inflammatory mediators, such as interleukins, cytokines, and chemokines (Kelly et al. 2001, Slayden & Brenner 2006, Wang et al. 2013). In the second phase, degradation effectors, including matrix metalloproteinases, are upregulated and begin to break down the extracellular matrix (ECM) (Brenner et al. 1996, Marbaix et al. 1996, Rodgers et al. 1994).

Hysteroscopic observations and examinations of endometrial specimens from menstruating human uteri suggest that menstrual shedding occurs in a piecemeal manner (**Figure 1*b***). Patches of intact, sloughing, and regenerating endometrium can all be found concurrently during menstruation, limiting the amount of exposed stroma at any given time (Ferenczy 1976; Garry et al. 2009, 2010; Nogales-Ortiz et al. 1978; Novak & Te Linde 1924). The newly exposed basalis harbors remnants of the glandular epithelial network and arteries (Ferenczy 1976; Ludwig & Spornitz 1991; Markee 1940; Nogales-Ortiz et al. 1978; Novak & Te Linde 1924; Tempest et al. 2020, 2022; Yamaguchi et al. 2021). Recently denuded stretches of stroma are quickly covered with fibrin, cell debris, and blood cells (Ferenczy 1976, Garry et al. 2009, Ludwig & Metzger 1976, Ludwig & Spornitz 1991), and new surface epithelium is identifiable as early as menstrual cycle day one, with re-epithelialization complete by day five or six (Ferenczy 1976). While the residual glands are commonly attributed as the primary sources of new epithelium (see Section 3), they are not the only reservoirs of unshed epithelium during menstruation. Mature luminal epithelium is retained near the uppermost uterine wall (fundus), utero-cervical junction (isthmus), and utero-tubal junctions (cornua) of the uterine cavity and may re-epithelialize nearby regions (Ferenczy 1976) (**Figure 1*a***).

Outside of primates, very few species have been found to menstruate. Among these are several species of bat, a species of elephant shrew (*Elephantulus myurus*), and a species of spiny mouse (*Acomys cahirinus*), which is the only rodent known to menstruate (Bellofiore et al. 2016, Rasweiler & Debonilla 1992, Van Der Horst 1954). Among many of these species, common features of menstruation include immune cell influx, artery remodeling, and focal tissue shedding (reviewed in Catalini & Fedder 2020). However, there are also numerous differences between species, including the process of tissue shedding itself. For example, in elephant shrews, shedding is compartmentalized to one region of the uterus, as opposed to affecting the entire endometrium (Carter 2018, Van Der Horst 1954).

2.2. Modeling Menstruation

Due to the technical limitations and ethical considerations associated with the study of naturally menstruating species, substantial work has been done to model hormone-driven endometrial shedding in lab mice (*Mus musculus*) (reviewed in Liu et al. 2020). Mouse and human uteri display key anatomical differences (**Figure 1*a*,*c***). Whereas the human uterus is composed of a single cavity with glands throughout the whole endometrium, the mouse uterus consists of two tubular horns (**Figure 1*c***). Glands reside along one side of each horn, which is termed the antimesometrial side, as it is opposite a supportive ligament (mesometrium) that encloses the uterine artery. Despite these differences, endometrial biology in the mouse shares many common features with humans. For instance, mice undergo a similar hormonal cycle to humans, termed an estrous cycle, which is broken into two estrogen-dominant stages (proestrus and estrus) and two progesterone-dominant

stages (metestrus and diestrus). As in humans, the mouse endometrium undergoes substantial remodeling across the hormonal cycle, albeit without a menstruating stage (Wood et al. 2007). Thus, the mouse provides a tractable model for the mechanistic dissection of endometrial biology.

Efforts to model menstruation in mice derive from observations that human menstruation follows a spontaneous stromal differentiation process called decidualization. In mice, natural decidualization only occurs in response to embryo implantation, but it can be artificially induced in nonpregnant mice by combining estrogen and progesterone priming with physical or chemical manipulations of the uterine lining, such as oil injection (Finn & Pope 1984). Following hormone withdrawal, the artificially decidualized mouse endometrium recapitulates key aspects of primate menstruation, including uterine bleeding, focal tissue shedding that preserves gland bases near the myometrial border, and the expression of menstruation-associated molecular markers (**Figure 1*d***) (Brasted et al. 2003; Cousins et al. 2014; Finn & Pope 1984; Kaitu'u-Lino et al. 2007, 2010; Rudolph et al. 2012; Xu et al. 2013). To achieve precise hormonal control, mice may be ovariectomized and receive cyclic estrogen and progesterone injections and/or progesterone-releasing implants before the induction of decidualization (Brasted et al. 2003). Other models rely on the natural progesterone fluctuations associated with mating an intact female with a vasectomized male (this induces a physiological state called pseudopregnancy), which may be paired with progesterone signaling inhibitors or ovariectomy to control bleeding onset (Patterson & Pru 2013, Rudolph et al. 2012).

In addition to mouse models of induced menstruation, alternative approaches are emerging to accommodate the experimental manipulation of human endometrial tissue. In xenograft models, human endometrial tissue fragments or dissociated cells are transplanted under the kidney capsules of ovariectomized, immunodeficient mice, which are then treated with estrogen and progesterone to promote graft growth (reviewed in Kuokkanen et al. 2017). Additionally, technological breakthroughs in three-dimensional tissue culture models and bioengineering techniques have led to the development of modular cocultures integrating multiple endometrial compartments, including epithelium, stroma, and vasculature (Abbas et al. 2020, Ahn et al. 2021, Cheung et al. 2021, Jamaluddin et al. 2022, Young & Huh 2021). Efforts are ongoing to build increasingly sophisticated in vitro models of the human endometrium, particularly with the goal of modeling human embryo implantation (reviewed in Li et al. 2022). Such models also hold great promise for recapitulating other complex aspects of human uterine regeneration, including menstruation, in vitro.

2.3. Parturition in Humans

Gestation and parturition also result in substantial remodeling of the endometrium, which is then restored to its prepartum state through a process called uterine involution. Much of what is known about this process comes from a study of postpartum uterine samples that were obtained through ethically fraught sterilization procedures (Williams 1931; for commentary, see Haig 1995). These samples and others revealed that the placental detachment site exhibits a distinct pattern of damage and timeline of repair compared to the neighboring endometrium (Anderson & Davis 1968, Williams 1931) (**Figure 1*e***). Although the surface epithelium is lost from both regions, the placental detachment site sustains deeper damage that appears to preserve fewer gland remnants than surrounding areas (Anderson & Davis 1968, Benirschke et al. 2012, Sharman 1953, Williams 1931). As in menstrual shedding, an irregular meshwork of fibrin and erythrocytes rapidly covers denuded areas (Ludwig 1971). In contrast to postmenstrual regeneration, uterine involution takes place over weeks rather than days. Within the first week, islands of luminal epithelium begin to emerge at nonplacental peripheries, where remnant gland density is highest.

By the fourth week, these nonplacental regions are completely re-epithelialized, and the underlying endometrial structure is restored (Anderson & Davis 1968, Williams 1931). In contrast, macroscopic endometrial irregularities can be observed at the placental detachment site until at least 7 weeks postpartum, and microscopic differences persist beyond this point (Anderson & Davis 1968, Benirschke et al. 2012, Friedländer 1870, Williams 1931). Rounds of new tissue growth and subsequent exfoliation at the perimeter of the detachment site may contribute to the gradual restoration of the superficial endometrial architecture, but it is unclear whether this process fully returns the placental site to its pregravid state (Williams 1931).

2.4. Parturition in Common Rodent Models

Despite differences between rodent and human implantation and placentation (Aplin & Ruane 2017, Hemberger et al. 2020), the tissue disruption arising from parturition appears to share some common features in both species. As in humans, mouse placental detachment sites exhibit substantial tissue loss, with the placental detachment cleavage plane forming partway through the mesometrial decidua (Deno 1937). Placental detachment sites are gradually restored through epithelial outgrowth from peripheral regions, mirroring placental site recovery in humans (Brandon 1994, Deno 1937). However, architectural differences between rodents and humans may necessitate different reparative processes in the postpartum uterus. For example, in humans, the luminal epithelium is disrupted throughout the uterine cavity, but a comparable extent of loss is unlikely in the mouse, as the endometrial epithelium is largely intact 1 day after parturition, with the exception of discontinuities at placental detachment sites (Strug et al. 2018) (**Figure 1*f***). However, relatively little is known about uterine architecture on the day of parturition in rodents, and the degree of epithelial discontinuity remains an important avenue for future work.

Analyses of rodent models throughout pregnancy have revealed that alterations observed immediately postpartum not only reflect damage incurred during parturition but also encompass preceding remodeling that occurred during gestation. For example, the expansion of the decidua surrounding the embryo appears to displace the gland bases into the regions between implantation sites (Yuan et al. 2018). Whether these glands persist throughout gestation or are degraded is unclear. In addition, the luminal epithelium undergoes a variety of degradation and remodeling processes throughout pregnancy (Arora et al. 2016, Welsh & Enders 1983, Yuan et al. 2018). For example, a gap in the mesometrial luminal epithelium (termed the mesometrial aperture) forms to accommodate the placental vascular supply and persists up to parturition (Welsh & Enders 1983). Thus, postpartum involution requires the resolution of a subset of gestational alterations in addition to the acute tissue damage associated with parturition.

Although uterine involution in rodents reverses many of the remodeling events of the pregnant state, traces may remain. The gross morphology of postpartum uterine horns readily reveals regularly spaced, darkly pigmented, macrophage-rich foci, termed postpartum nodules—one for each pup in a litter (**Figure 1*f***) (Brandon 1994, Deno 1937, Tàl et al. 2021). These nodules are not composed of fibrous scar tissue but nonetheless denote areas of altered endometrial function in many mammals, as subsequent implantation events primarily occur between postpartum nodules, and the tissue surrounding these features exhibits a decreased capacity for decidualization (Brandon 1990, 1994; Deno 1937). Macrophages have also been noted to occasionally form conspicuous pigmented nodules in the human basalis after parturition, but little is known about their functional significance in uterine involution (Anderson & Davis 1968). Thus, although the endometrium regenerates after parturition, postpartum nodules highlight the possibility of persistent irregularities. Further studies are needed to fully understand the extent and duration of functional impairment at these sites.

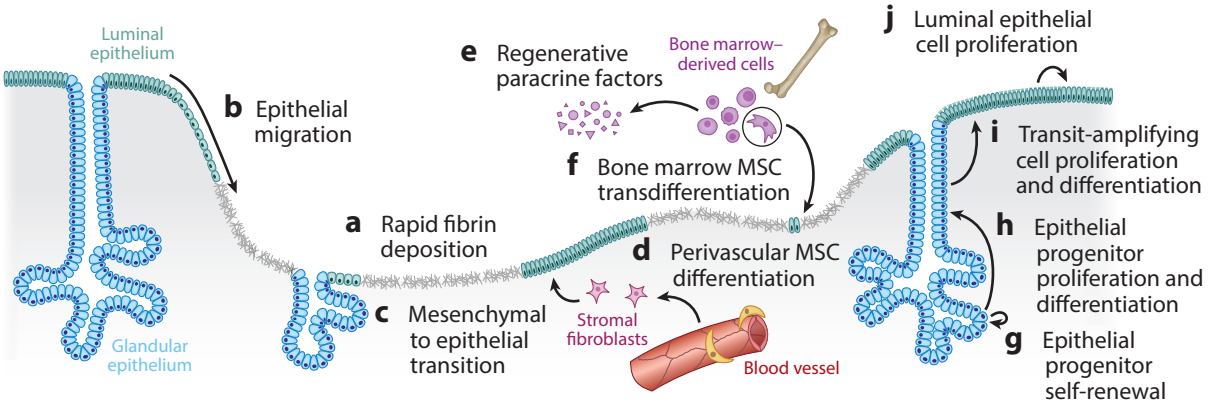


Figure 2

Proposed mechanisms of endometrial regeneration following physiological tissue damage. The mechanisms presented here derive from both human and mouse studies, although the endometrial architecture depicted is from the mouse. The relative timing and extent of the contributions of each mechanism remain to be elucidated. (*a*) Injured sites are rapidly covered with the fibrinous extracellular matrix. (*b*) Epithelial migration from nearby intact luminal epithelium (*green*) or glandular epithelium (*blue*) covers the denuded areas. (*c*) In the stromal compartment, fibroblasts (*magenta*) undergo a mesenchymal to epithelial transition to contribute to new luminal epithelium. (*d*) Perivascular MSCs differentiate to restore stromal fibroblasts. (*e*) Paracrine signaling factors from bone marrow–derived cells (*purple*) and other sources promote regenerative outcomes. (*f*) Bone marrow–derived MSCs (*circled*) transdifferentiate to make minor contributions to the endometrial epithelium. (*g*,*h*) Long-lived epithelial progenitors residing in the gland bases self-renew and give rise to transit-amplifying cells residing higher up in the gland. (*i*) Transit-amplifying cells proliferate and differentiate to form short-lived, luminal epithelial cells. (*j*) The local proliferation of luminal epithelial cells also sustains the surface epithelium. Abbreviation: MSC, mesenchymal stem cell.

3. PROPOSED MECHANISMS OF ENDOMETRIAL REGENERATION

Menstruation and parturition extensively disrupt both the epithelial and stromal compartments of the endometrium, necessitating substantial cellular proliferation and differentiation to enable continued tissue function. In this section, we outline the cell types that have been proposed to repopulate the tissue (**Figure 2**). Much of this work has relied on lineage tracing experiments in mice, which frequently use a recombinase (e.g., Cre recombinase) to induce the heritable expression of a genetically encoded reporter in a cell of interest and all its descendants. By assessing changes in the abundance, distributions, and identities of labeled cells over time, these methods reveal the contributions of specific cell lineages to tissues undergoing routine turnover and/or regeneration (reviewed in Hsu 2015). As lineage tracing is difficult to implement in humans, the capacity of isolated cells to self-renew and/or differentiate into multiple lineages in vitro has been used as a proxy for stemness. In addition, naturally occurring mutations have been used to deduce common cellular ancestry (clonality) between endometrial components, revealing, for example, that endometrial glands in humans, as in mice, are primarily monoclonal (Fu et al. 2020; Lipschutz et al. 1999; Moore et al. 2020; Tanaka et al. 2003; Tempest et al. 2020, 2022). Together, these approaches have revealed a diverse array of potential cellular sources that may contribute to tissue turnover and/or repopulate endometrial compartments following menstruation and parturition.

3.1. Epithelial Progenitor Cells

Lineage tracing studies in mice have provided extensive evidence that epithelial progenitors play critical roles in repopulating the epithelium under various conditions (Fu et al. 2020, Jin 2019, Seishima et al. 2019, Syed et al. 2020). For instance, two studies performed with the pan-epithelial

marker *Pax8* showed that the proportion of labeled cells remained constant over the entire reproductive life span of the cycling mouse, as well as after recurrent pregnancies or following mechanical denudation, suggesting that the labeled epithelium is largely self-renewing in diverse contexts (Fu et al. 2020, Syed et al. 2020). This aligns with longstanding speculation in humans, where the conspicuous gland remnants dotting the denuded endometrium after menstruation and parturition have been proposed to supply new surface and glandular epithelium. Updated models reflecting the three-dimensional structure of human endometrial glands illustrate how the interconnected architecture of the gland plexus, which remains after tissue loss, could enable efficient re-epithelialization by multiple epithelial progenitor pools (Tempest et al. 2022). Both the proliferation and migration of preexisting epithelial cells have been proposed as possible mechanisms for re-epithelialization (Cousins et al. 2014, Ferenczy 1976, Ludwig & Metzger 1976, Ludwig & Spornitz 1991, Markee 1940, Nogales-Ortiz et al. 1978, Novak & Te Linde 1924).

Consistent with the existence of endometrial epithelial progenitors, a subset of isolated human endometrial cells expressing the epithelial marker EPCAM exhibit high clonogenic, self-renewal, and proliferative capacities in vitro (Chan et al. 2004, Gargett et al. 2009, Schwab et al. 2005). Several molecular markers have been proposed to demarcate progenitor populations in humans, although a clear consensus has not been reached (Gil-Sanchis et al. 2013, Nguyen et al. 2017, Spooner et al. 2021, Tempest et al. 2018, Valentijn et al. 2013). The molecular markers, localization, and lineage potential of endometrial epithelial progenitors in mice have also been subjects of debate. Importantly, the contributions of different epithelial progenitor populations may change throughout the life span. For instance, while *Lgr5* marks endometrial epithelial progenitors in neonatal mice, *Lgr5*-positive cells provide minimal contributions to the endometrial epithelium in adulthood (Seishima et al. 2019). Instead, emerging evidence in adult mice points to a model in which long-lived, potentially damage-responsive progenitors (marked with *Axin2*) reside at the gland bases and give rise to quickly dividing, transient populations that contribute to short-term epithelial maintenance, akin to the transit-amplifying cells in the intestine and skin (Kaitu'u-Lino et al. 2010, Syed et al. 2020) (**Figure 2**), although other models have been proposed (Jin 2019).

3.2. Lineage Plasticity in Resident Mesenchymal Populations

A growing body of literature suggests that the endometrium contains highly plastic mesenchymal populations capable of producing multiple cell types. Human endometrial *SUSD2*-positive perivascular cells exhibit characteristics of mesenchymal stem cells (MSCs), particularly the ability to give rise to adipocytes, myocytes, osteocytes, and chondrocytes in vitro; these cells can also contribute to connective tissue in a xenograft model (Dimitrov et al. 2008, Gargett et al. 2009, Masuda et al. 2012, Schwab & Gargett 2007). Additionally, side population cells, which include mesenchymal and epithelial cells identified by their ability to efflux Hoechst dye, can produce both hormone-responsive stroma and epithelium in vitro and when transplanted subrenally (Cervelló et al. 2010, 2011; Golebiewska et al. 2011; Kato et al. 2007; Tsuji et al. 2008). While it remains to be seen whether these cell types make significant contributions to the adult endometrium as a normal part of uterine physiology, their multilineage potential in these experimental contexts underscores the many cellular sources the human endometrium may have at its disposal during tissue repair.

Lineage tracing studies in the mouse have further implicated mesenchymal cells in regenerating the epithelium through a mesenchymal to epithelial transition (MET). However, debate about the contribution of this mechanism is ongoing. Many studies have taken advantage of *Amhr2* gene expression in endometrial stromal cells, and therefore used mouse models in which Cre recombinase is expressed from the *Amhr2* locus for lineage tracing. In contrast to the *Pax8* lineage tracing described above, which suggests self-renewal of the epithelium (Fu et al. 2020, Syed et al. 2020),

lineage tracing using *Amhr2-Cre* showed that labeled cells give rise to variable proportions of epithelial cells at various stages of the estrous cycle (Spooner-Harris et al. 2022) and following parturition (Huang et al. 2012, Patterson et al. 2013). However, recent work using two different mouse models revealed that widespread expression of *Amhr2-Cre* during early embryonic development may account for the labeled endometrial epithelium in the adult, rather than bona fide MET (Dickson et al. 2023). Similarly, the coexpression of epithelial and mesenchymal markers in the mouse embryonic endometrial epithelium may be a confounding factor in lineage tracing studies using mesenchymal Cre promoters that are active in the embryo (Ghosh et al. 2020). Nonetheless, evidence from an alternative approach using a different stromal cell promoter (*Pdgfrα-CreERT2*) and an inducible Cre, where recombination is restricted to adulthood, has provided further support for MET (Kirkwood et al. 2022). Using this approach in a mouse model of menstruation, the authors detected fibroblast-derived luminal epithelial cells after bleeding onset, bolstering earlier studies reporting MET in this model (Cousins et al. 2014, Patterson et al. 2013, Yin et al. 2019). In human menstruation, evidence for or against MET is technically challenging to acquire and therefore limited. A small number of studies have claimed that the lack of proliferation in the glandular epithelium during early menstruation, and the presence of growing epithelial islands free from remnant gland stumps, supports a role for MET in human epithelial regeneration (Baggish et al. 1967; Garry et al. 2009, 2010). Altogether, the conditions under which MET occurs in the endometrium are still under investigation, and how epithelialization through MET intersects with tissue restoration from preexisting epithelial populations remains to be determined.

3.3. Bone Marrow–Derived Mesenchymal Cells as Additional Contributors to Endometrial Regeneration

Finally, it has been proposed that bone marrow–derived stem cells (BMDSCs), particularly MSCs, differentiate into endometrial tissue in humans and mice (Du & Taylor 2007, Du et al. 2012, Taylor 2004). However, bone marrow transplant studies have found that rates of bone marrow–derived cell engraftment are often low or negligible in the endometrium (Bratincsák et al. 2007, Du & Taylor 2007, Du et al. 2012, Morelli et al. 2013, Ong et al. 2018, Tal et al. 2016, Wolff et al. 2013), and these cells do not appear to expand within the human endometrium once established (Cervelló et al. 2012, Ikoma et al. 2009). These observations suggest that these cells are unlikely to constitute major endometrial progenitors under most circumstances. However, human and mouse bone marrow MSCs can be cultured to take on decidual phenotypes, which raises the possibility that bone marrow MSCs may play a transient role in pregnancy and/or involution (Aghajanova et al. 2010, Tal et al. 2019). Unfractionated bone marrow can also differentiate into short-lived murine endometrial epithelium during pregnancy before becoming senescent and dying in the days following parturition, although the functional significance of such a contribution remains unknown (Tal et al. 2021). Emerging evidence suggests that BMDSCs may not directly restore lost cellular populations long-term but rather may provide paracrine factors that stimulate regenerative remodeling (Alawadhi et al. 2014, Cervelló et al. 2015).

4. NONREGENERATIVE HEALING OF THE UTERUS

Despite the tremendous regeneration that occurs after most physiological disruptions of the endometrium, more than a century of clinical gynecological observations reveal numerous instances in which the endometrium fails to regenerate and instead develops fibrosis (Fritsch 1894, Johnson 1900) (**Figure 3**). In some cases, fibrotic lesions may span the uterine walls, forming intrauterine adhesions (IUAs), or synechiae, capable of partially or completely obstructing the

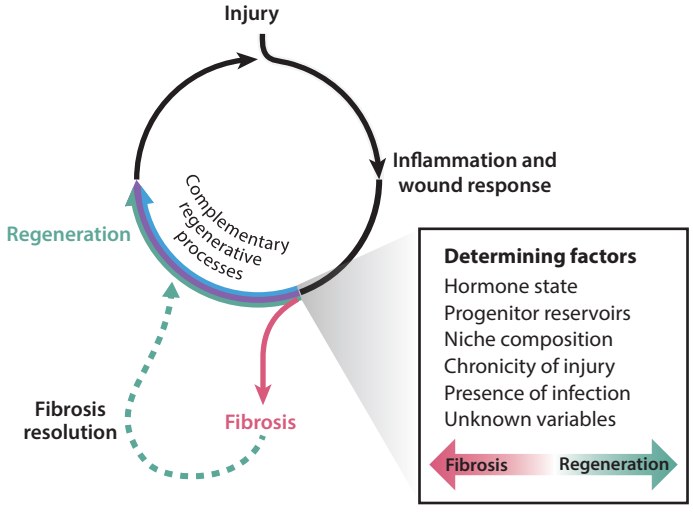


Figure 3

Wound healing outcomes in the endometrium. Both physiological and nonphysiological endometrial disruptions induce an acute inflammatory/wound response, which can be resolved via complementary regenerative processes (outlined in **Figure 2**) to restore tissue architecture prior to subsequent injury. If coincident with underlying predisposing conditions, which may involve a number of known and unknown determining factors, this inflammation may, instead, progress to fibrosis. Without intervention, fibroses can be terminal or, at some frequency, undergo spontaneous reversion through poorly understood processes to restore functional endometrial tissues.

uterine cavity (Deans & Abbott 2010). IUAs exhibit a wide range of histological and clinical manifestations (Foix et al. 1966, Sugimoto 1978). While some IUAs may go undiagnosed due to a lack of symptoms, those resulting in uterine cavity obstruction or loss of functional endometrium may contribute to pelvic pain, menstrual disruption, and fertility complications (Schenker & Margalioth 1982). IUAs manifesting in a substantial reduction or cessation of menstrual bleeding (hypomenorrhea and amenorrhea, respectively) and infertility are characteristic of Asherman syndrome (AS) (Asherman 1948, Stamer 1946). The true incidence of IUAs remains unknown, but IUAs likely represent a significant health burden as prevalence strongly correlates with gynecological dysfunction (March 2011b).

Injuries inflicted during medical interventions (iatrogenic injuries) are the most cited cause of IUA formation. The vast majority of cases are attributed to curettage of the endometrium for abortion or the removal of remnants of conception. However, infections and other procedures, including diagnostic curettage, myomectomy, cesarean section, and uterine artery embolization, also contribute (Asherman 1948, Hanstede et al. 2015, Schenker & Margalioth 1982). Moreover, interventions intended to induce fibrosis of the uterus (endometrial ablation) have been exploited since the late nineteenth century for the treatment of heavy menstrual bleeding (reviewed in Wortman 2017). Despite this storied clinical history, the basic mechanisms underlying nonregenerative healing in the uterus remain poorly understood.

4.1. Causal Factors of Uterine Fibrosis

Clinicians have long posited that physical trauma is the leading cause of IUAs, with the depth of injury playing an important role (Asherman 1948, Stamer 1946). In humans, this model has most compellingly been explored in the context of endometrial ablation, where the efficacy of ablation and extent of fibrosis can be examined following treatment. Early case studies of cauterization in

the uterus indicated that extensive injury correlated with more dramatic compositional changes to the endometrium; following the most potent treatments, a complete loss of mucosa and uterine patency can be observed (Johnson 1900).

In the context of incidental fibroses, the majority of studies implicating physical trauma and injury depth in IUA formation are correlative. Human endometrium obtained from patients following curettage after abortion or within the immediate postpartum (puerperal) period often reveals myometrial components, with a higher incidence of IUAs and/or amenorrhea correlating with samples containing what the authors describe as "plentiful" myometrium, suggesting that deep tissue removal may contribute to fibrosis in iatrogenic contexts (Eriksen & Kaestel 1960, Hald 1949, Jensen & Stromme 1972). Additionally, evidence suggests that interventions in which the uterine cavity is opened, for example, during some types of fibroid removal, may increase the potential for IUA formation (Capmas et al. 2018). However, significant endometrial regeneration has also been reported following many instances of physical trauma. For example, signs of endometrial regeneration are evident within days of curettage of the nonpregnant human uterus (McLennan 1969). Similarly, nonhuman primates subjected to consecutive endometrial resections recovered a healthy endometrium capable of implantation and, in some cases, carrying viable offspring to term (Hartman 1944). A comparable resilience to traumatic injury has been observed in a variety of nonprimate laboratory models (Schenker et al. 1971, 1973a,b). Importantly, correlational studies of uterine fibrosis in humans rarely involve examination of the uterine cavity prior to medical interventions or other suspected inciting incidents. As a result, these studies preclude the identification of preexisting IUAs or other uterine abnormalities. Studies in which endometrial health metrics are obtained prior to curettage, for example, in cases where the endometrium has been previously assessed as part of infertility treatment, could provide crucial opportunities to determine whether iatrogenic injury per se plays a causal role in IUA formation (Gilman et al. 2016).

In addition to iatrogenic trauma, some infections are now appreciated as important contributors to uterine fibrosis (Netter et al. 1955, Sharma et al. 2008). Among these, female genital tuberculosis (FGTB) is highly correlated with IUAs and AS, particularly in regions with a high incidence of tuberculosis infection, as most cases of FGTB arise as a secondary manifestation of pulmonary tuberculosis (Schaefer 1976). FGTB is often discovered incidentally during investigation for infertility and/or amenorrhea, with lesions frequently accompanied by inflammation, extensive fibrotic tissue, and the loss of endometrium in advanced stages, despite no history of iatrogenic injury (Bazaz-Malik et al. 1983, Schaefer 1976). Patterns of tissue destruction mirror the spread of tuberculosis infection, which often originates in the fallopian tubes and spreads to the uterus, suggesting a causal relationship between pathogenic damage and fibrosis (Schaefer 1976). Pelvic schistosomiasis has also been implicated in several cases of AS (Acosta Go & Ibrahim 2022, Krolikowski et al. 1995), suggesting that the role for infectious agents in uterine fibroses extends beyond FGTB.

4.2. Factors That Predispose the Uterus to Fibrosis

A survey of clinical studies on IUAs and AS suggests that uterine fibrosis most often arises when an inciting injury occurs alongside additional risk factors. Pregnant and postpartum uteri appear to be particularly susceptible to IUA formation following trauma (Hanstede et al. 2015, Schenker & Margalioth 1982, Xiao et al. 2014). In one of the largest clinical studies of IUA incidence, researchers attributed 90.8% of 1,856 cases to trauma incurred during pregnancy or the puerperium. In contrast, only 3.7% of cases were attributed to comparable interventions independent of pregnancy (Schenker & Margalioth 1982). Parturition coincides with dramatic changes in the hormonal milieu, including sudden decreases in estrogens and progesterone,

which may contribute to the fibrotic outcome (Barkley et al. 1979, Lewis et al. 1987). Based on these observations, hormone supplementation has become a common peri-operative treatment for the prevention of IUA reformation after resection, with estradiol administration, in particular, intended to promote regeneration. However, the efficacy of this treatment remains debated (Farhi et al. 1993, Johary et al. 2014), and the precise contributions of hormones to endometrial regeneration are still being elucidated. Studies in which rhesus macaques and mice were depleted of sex hormones reported complete endometrial regeneration after menstruation and induced endometrial shedding, respectively (Hartman 1944, Kaitu'u-Lino et al. 2010), suggesting that sex hormones may be dispensable for regeneration in some contexts. Progesterone may hinder regeneration in some cases, as human samples subjected to curettage during the progesterone-dominant secretory phase exhibit delayed endometrial regeneration (Johannisson et al. 1981, McLennan 1969). Similarly, in the mouse, defective healing is associated with injury to the diestrus uterus (Zhang et al. 2022). Further study of the role of hormones in endometrial regeneration after diverse injuries will provide valuable information to inform clinical practice.

Recurrent or chronic injury may also predispose uterine healing toward fibrosis. This is supported by the relatively high prevalence of IUAs reported in patients undergoing repeated curettages for incomplete or missed abortion (Westendorp et al. 1998). Several retrospective studies also show a higher prevalence and severity of IUAs in patients with a history of repeat miscarriage/abortion and curettage (Friedler et al. 1993, Römer 1994). While these reports are consistent with the interpretation that repetitive iatrogenic injury may compound the risk for fibrosis, determining cause and consequence is challenging. For instance, recurrent pregnancy loss or the necessity for repeat curettage may reflect undiagnosed fibrosis or other uterine factors (i.e., thin endometrium, placental retention) that may themselves predispose the uterus to fibrosis. In line with this possibility, elevated IUAs have been reported in patients with a history of pregnancy loss, irrespective of iatrogenic factors (Ventolini et al. 2004).

Infection has also been posited as a predisposing factor for uterine fibrosis. Acute inflammation is frequently considered a risk factor for IUA, based on reports that the risk of IUA is relatively high in patients undergoing curettage following missed abortion (Adoni et al. 1982, Schenker & Margalioth 1982, Toaff & Ballas 1978). This observation, though not reported in all cases (Römer 1994), has been attributed to the fact that delayed intervention in cases of missed abortion may permit persisting remnants of conception to become necrotic and promote inflammation (Adoni et al. 1982, Schenker & Margalioth 1982, Toaff & Ballas 1978). Previous work has also reported histological signs of acute and subacute inflammation in the majority of puerperal curettings taken in the postpartum window associated with fibrosis risk (Smid & Bedö 1978). In addition to acute infection (for example, septic abortion), chronic endometritis has also been proposed to play a role in IUA formation (Rabau & David 1963). However, the proposed relationship between chronic endometritis and IUAs has been met with opposition due to inconsistent diagnostic criteria and mixed reports of the prevalence of endometritis in patients presenting with IUAs or AS (Jensen & Stromme 1972, Liu et al. 2019). Nonetheless, inflammation appears to compound the effects of injury to promote uterine fibrosis in some contexts.

4.3. Persistent Regenerative Potential in the Fibrotic Uterus

The endometrial response to iatrogenic injury mirrors that observed following menstruation, including moderate immune infiltration, the deposition of a provisional ECM, and the subsequent emergence of an epithelium from persisting progenitors (Johannisson et al. 1981, Wyss et al. 1996). In general, fibrosis is widely regarded as a consequence of the dysregulation of normal healing processes, as many of the effectors and pathways involved in inflammation and scarring play fundamental roles in regenerative wound healing (reviewed in Henderson et al. 2020, Nathan

& Ding 2010). In the endometrium, the diversion of healing towards a fibrotic outcome is often attributed to the obliteration of the stem cell reservoir during injury. However, this model is complicated by the possibility that diverse cell populations may contribute to re-epithelialization of the endometrium (see Section 3) and that epithelial compartments may persist even after extensive, catastrophic injury. Specifically, menstruation may be reduced but not eliminated following endometrial ablation in a subset of patients, consistent with the persistence of functional endometrium after the procedure. Further, endometrial glands may be observed in up to 80% of patients after ablations considered to be clinically successful (Onoglu et al. 2007, Taskin et al. 2002).

The notion that regenerative potential can be maintained in the fibrotic uterus is further underlined by late-onset endometrial ablation failure (LOEAF), a common outcome of ablation characterized by the continuation or restoration of menstruation >1 month after treatment (Wortman 2017). LOEAF is attributed to the persistence and/or regeneration of hormone-responsive endometrial tissues, which may arise from incomplete ablation in uterine regions with limited instrument access (Lisa et al. 1954, Turnbull et al. 1997) or from the persistence of basal glands. Intriguingly, the probability of LOEAF increases over time after treatment (Longinotti et al. 2008, Shavell et al. 2012), suggesting that the fibrotic uterus can retain the ability to regenerate and, remarkably, reverse the fibrotic course. In light of the data on uterine fibrosis and its reversion, it is tempting to speculate that the regeneration of the endometrium depends less on a singular mediator than on a tenuous balance between pathways underlying both regenerative and nonregenerative processes (**Figure 3**). In this regard, dissecting uterine regeneration requires understanding how changes associated with injury and fibrosis predisposition—injury timing, depth, and chronicity, among others—compromise or divert existing regenerative mechanisms.

4.4. Mechanisms of Uterine Fibrosis

The anatomy of the uterus ensures that deep tissue damage disproportionately impacts stromal and myometrial compartments, which contribute to the formation and maintenance of the niche in which progenitors reside. Clinical studies have revealed substantial alterations of uterine compartments in patients presenting with IUAs and AS, including increases in fibrotic tissue in the muscle (Yaffe et al. 1978) and stroma (Bergman 1961), reduced myometrial blood flow, and widespread vascular occlusion (Polishuk et al. 1977). Such changes may impact tissue mechanics and perfusion—factors that are known to contribute to diverse fibrotic disorders (Darby & Hewitson 2016, Van De Water et al. 2013). Furthermore, necrotizing granulomas and other immune cell infiltrates are frequently observed in postablation specimens (Ashworth et al. 1991, Silvernagel et al. 1997, Tresserra et al. 1999), and could conceivably contribute to a profibrotic tissue environment. Together, these observations highlight potential avenues by which the extensive injury and remodeling of the endometrium and adjacent compartments may impact cellular interactions to disrupt the balance of regenerative and nonregenerative healing processes.

Disentangling the complex interactions between endometrial progenitors and their niche factors requires experimental models of uterine fibroses. Attempts to develop such animal models using a variety of approaches associated with IUA formation in humans have had varying success, with few studies reporting the presence of bona fide IUAs or obstruction of the uterine cavity (Liang et al. 2022; Schenker & Polishuk 1972, 1973; Schenker et al. 1971, 1973a,b). Comparisons of existing experimental models are complicated in many cases by the use of different diagnostic criteria, ranging from functional measures (such as fecundity) to histological and molecular readouts. Challenges in developing uterine fibrosis models may further arise from interspecies variation related to fundamental differences in reproductive biology and/or the necessity to

incorporate additional predisposing factors. Particularly compelling rabbit models of IUAs and AS have arisen from dual injury approaches in which mechanical trauma is compounded with inflammatory [e.g., bacterial lipopolysaccharide (Liu et al. 2013)] or profibrotic stimuli [e.g., fibroblast- and collagen-enriched sponges (Schenker et al. 1975)], underscoring the potential role of predisposing physiological states in promoting uterine scarring.

Experiments in animal models have explored a wealth of molecular factors that contribute to uterine fibrosis (reviewed in Leung et al. 2020), many of which converge on signaling pathways underlying global injury responses, immune activation, fibroblast mobilization, and tissue remodeling. Unsurprisingly, among these are a number of effectors that have been implicated in fibrosis in other organs. For instance, rabbit and rat models of induced IUAs exhibit elevated activation of TGF-β and NF-κB pathways, which are also reported in human IUAs (Ning et al. 2018, Salma et al. 2016, Wang et al. 2017, Xue et al. 2015). NF-κB represents a family of transcription factors regulating critical pathways in immune signaling and inflammation (reviewed in Liu et al. 2017). TGF-β is well established as a driver of fibrosis in many organs, where its transcriptional activities contribute to an array of processes, including ECM accumulation and fibroblast recruitment, activation, and differentiation into myofibroblasts (reviewed in Budi et al. 2021, Rockey et al. 2015). Consistent with this, experimental hyperactivation of the TGF-β pathway in the mouse uterus promoted myofibroblast differentiation (Gao et al. 2015). The development and refinement of additional experimental models of uterine fibroses will play a critical role in facilitating further gain- and loss-of-function studies of these pathways.

Modern single-cell transcriptomic approaches offer additional opportunities to construct an unbiased portrait of nonregenerative healing in the uterus. For example, recent work compared single-cell expression profiles from a human endometrium atlas to those from patients with moderate and severe AS (Santamaria et al. 2022, Wang et al. 2020). This study reported profound changes in the composition and function of AS uteri, including unique epithelial and smooth muscle cell populations, a proinflammatory immune cell state, fibrotic stroma, and compromised vascularity. Moreover, the authors' analyses of ligand-receptor pair expression suggested alterations to cell-cell communication in AS uteri, including a decrease in epithelial-stromal communication and an increase in autocrine stromal signaling and endothelial-immune communication. Such approaches hold great promise for both basic mechanistic and therapeutic discoveries in uterine biology.

4.5. Therapeutic Management of Uterine Fibrosis

Treatment of IUAs and AS primarily focuses on adhesiolysis, the resection of scar tissue under hysteroscopic visualization, often augmented with hormone treatment or the placement of physical barriers to prevent adhesion reformation (e.g., a Foley catheter) (March 2011a). However, the efficacy of these interventions is variable, and adhesions have been reported to recur in up to two-thirds of patients (reviewed in AAGL 2017). Nevertheless, the success of adhesiolysis in enhancing menstrual flow and fertility in some cases provides an additional tantalizing indication that latent regenerative potential may persist in a fibrotic uterus.

Experimental models of uterine injury have also been harnessed to explore a remarkable breadth of therapeutic strategies for preventing and treating IUAs. These include a variety of biocompatible materials that may be transplanted into the injured uterus to serve as cellular scaffolds or enable the release of proregenerative factors (Jonkman et al. 1986, Li et al. 2011, Taveau et al. 2004; reviewed in Yin et al. 2023). Additionally, considerable effort has gone toward developing approaches to transplant putative stem/progenitor cells or enhance their homing to the target tissue (Sahin Ersoy et al. 2017). Bone marrow–based therapies have gained notable traction, with the transplantation of unfractionated bone marrow, a putative source of BMDSCs,

improving fecundity in a mouse model of traumatic AS (Alawadhi et al. 2014). This improvement likely occurs through the modulation of the uterine niche, as opposed to substantial cellular repopulation, as human CD133$^+$ BMDSCs transplanted into the same AS mouse model engraft around endometrial vessels and promote glandular epithelial proliferation (Cervelló et al. 2015). BMDSC-based approaches have since been translated to phase I/II clinical trials for the treatment of AS and endometrial atrophy, and shown to partially reverse AS-associated transcriptional signatures following treatment (Santamaria et al. 2016, 2022). A variety of other cell-based therapies have been explored in similar models, including MSCs from adipose tissue, umbilical cord, or amniotic membranes (Gan et al. 2017, Kilic et al. 2014, Tang et al. 2016); uterine- or menstrual blood-derived cells (Hu et al. 2019, Liu et al. 2018); and human embryonic stem cell–derived endometrium-like cells (Song et al. 2015). All report some improvements in uterine regeneration and/or reproductive performance. The efficacy of these diverse interventions suggests that many strategies, ranging from resupplying component parts to niche priming with paracrine signals, may suffice to bias healing toward regenerative outcomes. Furthermore, this work offers hope for positive health and reproductive outcomes for diverse patients, as orthogonal therapeutic approaches may be necessary to address the poorly defined variability in uterine fibroses.

5. OUTLOOK

Efforts to synthesize information from basic science and medicine hold great promise for advancing our understanding of uterine biology. In summarizing how the endometrium responds to menstruation, parturition, iatrogenic injury, and infection, this review underscores the plethora of factors that may determine regenerative versus fibrotic outcomes. These factors include the spatial heterogeneity of damage across the organ, which cell types survive the breach (both progenitors and their niche components), the extent and duration of inflammation, and the speed of repair processes. Each of these may be further modulated by the tissue state, including hormone levels or prior tissue history. Our inability to robustly predict the outcomes of many uterine injuries in a clinical setting or to understand pathological responses to physiological injuries, such as abnormal uterine bleeding, reveals that many important variables remain to be defined.

The true breadth of change to which the endometrium is exposed extends far beyond the conditions we have reviewed here. Endocrinological disorders, other disease states, and contraceptives provide additional variables that may modify endometrial architecture and regenerative capacity within the reproductive years. In addition, the reproductive life span, bounded by menarche and menopause, reflects only half of the total life span (Appiah et al. 2021, Martinez 2020, Stewart et al. 2022). Outside of the reproductive window, endometrial remodeling and regeneration also unfold in ways that remain exceedingly poorly understood. For example, some newborns exhibit a sparsely studied withdrawal bleed (neonatal uterine bleeding) upon removal from the hormone-rich in utero environment at parturition (reviewed in Benagiano et al. 2021). In addition, there is much to discover about the endometrium during childhood, perimenopause, and menopause, which may evoke different regenerative strategies and vulnerabilities compared to the reproductive years (Metcalf et al. 1981, Swain & Kulkarni 2021). While much remains unknown about the balance between regenerative and nonregenerative healing in the uterus, uncovering the secret to the remarkable resilience of this organ holds the potential to inform far-reaching fields, from wound healing and regeneration to inflammation and beyond.

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