Role of Microenvironment and Transient Tissue Hypoxia in Regeneration of the Endometrium

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Review

Role of Microenvironment and Transient Tissue Hypoxia in Regeneration of the Endometrium

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During various events in the reproductive period (viz., menstruation and delivery) of a woman, the endometrium displays phenomenal regenerative ability to repeat the cycle of shedding and regeneration. However, the mechanisms responsible for complete inner membrane repair and regeneration remain mostly unexplored. Gynecological diseases, such as placenta accreta and implantation failure, are caused by insufficient repair of the endometrium. However, because the mechanism behind these diseases are unclear, there are no known preventive methods. Changes in oxygen concentration in the endometrium are known to be involved in defense against bacteria and trophoblast invasion for the establishment of pregnancy. Additionally, it is also thought to affect angiogenesis and tissue repair. The difficulty of obtaining human samples, hampers investigation along this line of research. Using a postpartum mouse model and mice with sub-involuted uterus, we have reported that changes in intrauterine oxygen concentration, including hypoxia, due to involution of the uterine smooth muscle are responsible for scarless endometrial repair. Elucidation of the regenerating mechanism of the endometrium provides possibilities to prevent complications in obstetrics and gynecology, and a strong basis for scarless tissue repair through a new approach of generating microenvironments based on oxygen concentration adjustment in normal tissues. In this review, we discuss the role of microenvironment in the process of healing and regeneration of the endometrium.

Key Words: myometrial contraction, hypoxia, regenerative endometrium, macrophage, scarless wound healing

Introduction

The uterus is a mesoderm-derived tissue composed of the uterine smooth muscle and the endometrium. The uterine smooth muscle, with its inherent contractility, can dramatically change its volume during the reproductive period and constantly changes the intrauterine environment to adjust the oxygen concentration in the tissue.[1] The endometrium, on the contrary, has a high regenerative ability, unlike other tissues, and repeatedly cycles through proliferation, differentiation, shedding, and regeneration. The endometrium has drawn considerable attention as the representation of scarless tissue, with its ability to repair without forming scars.[2,3] However, the mechanisms of regeneration in the endometrium are still unknown, and there are several obstetric and gynecological conditions, such as implantation failure, malposition of the placenta, pla-

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centa accreta,[4,5] and excessive bleeding from uterine sub-involution, for which no preventive methods are currently available. Basic research to better understand the mechanism underlying these diseases are imperative. However, factors such as the difficulty of obtaining human samples, and the limitation of animals with similar histology and hormone cycle as humans, hinders progress in this area of research.

To date, there have been reports of infection prevention and trophoblast infiltration associated with transient hypoxia in the endometrium, particularly during the establishment of pregnancy.[6] As a dogma of menstruation mechanism,[2] their relationship to angiogenesis and restorative regeneration under hypoxia has been discussed; however, there have only been a few basic research reports *in vivo*.[2,7,8]

While focusing on uterine volume change before and after parturition in a postpartum mouse model, and while studying a mouse model with sub-involuted uterus, we found that an intrauterine hypoxic environment promotes endometrial regeneration.[9] We also found that a transient hypoxic environment occurs in the uterus because the area of the uterine cavity is sharply reduced after delivery. Immunohistochemical observations revealed that during the repair process, there is transient infiltration of M2 macrophages, primarily in the endometrium-deficient area, with peak infiltration on postpartum day (D) 3. When the normal postpartum mouse model was compared with the sub-involuted mouse model using the β-2 adrenergic receptor agonist, a difference in the time to uterine recovery and hematoma formation was observed. Furthermore, at the transcript level, there were differences in the amounts of hypoxia inducible factor 1a (HIF1a), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGFB). These results show that uterine contraction not only converges the hemorrhage from the vascular stump in endometrial defects, but also induces macrophages by adjusting oxygen concentration in the tissues by creating a transient low oxygen environment, which creates a microenvironment for inner membrane repair and regeneration. With this review, we aim to clarify the mechanism of endometrial repair and regeneration, describe a research approach to investigate scarless tissue repair, and to observe the construction of the microenvironment induced by the regulation of oxygen concentration in normal tissues. These insights are expected to contribute to the development of preventive medicine in the future.

Volume Change and Local Hypoxia Affect Myometrial Contraction in Postpartum Uterus

During pregnancy, the uterus changes its size dramatically through growth and stretching of the uterine smooth muscle. The hemorrhage after delivery is controlled by contraction of the myometrium.[10] Postpartum hemorrhage is one of the major causes of maternal mortality worldwide, and is primarily caused by sub-involution.[4] It is also believed that autolysis and phagocytosis during involution leads to complete tissue repair. Clinically, medical intervention is required for the prevention and therapy of postpartum hemorrhage.

Because of the decrease in the size of the uterus, but not the number of uterine muscles during involution, the uterus of parous women are slightly different from that of non-parous women. Therefore, our study used mice in their first pregnancy to exclude these factors. Changes in uterine size and intrauterine oxygen concentration based on the degree of uterine smooth muscle contraction, were compared in normal postpartum mice (group A), and mice given ritodrine, a β-2 adrenergic receptor agonist, which is used clinically for smooth muscle relaxation (group B). The size of the uterus after delivery was assessed using the ratio of the total area of the uterine cross section in groups A and B. The time to return to their prepregnant size in group B was found to be 4 days later than in group A. In both groups, the rates of involution increased significantly until D2 (**Figure 1**). To assess the ischemic states associated with involution in the postpartum uteri, we examined hypoxia using pimonidazole immunohistochemistry. Pimonidazole in the endometrium was strongly detected on D3, and was more abundant in group A than in group B.[9]

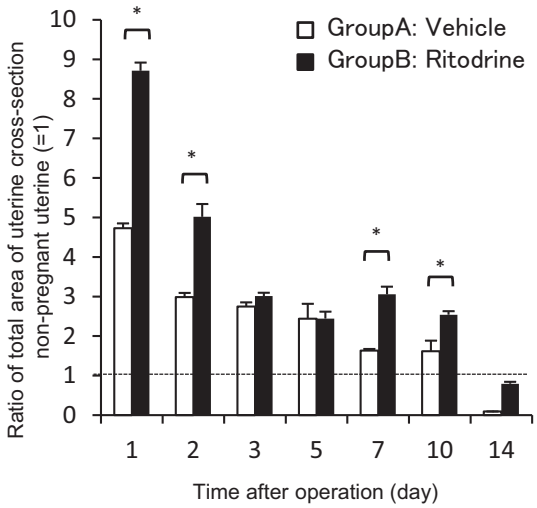

Figure 1 Rates of change in postpartum uterine size. Group A, sham-operated mice, with a mini osmotic pump for administration of saline after caesarean section (CS). Group B, mice treated with ritodrine (10 mg/mL) after CS. The total areas of the cross section, including the lumen space, in group A (white square) and group B (black square) mice were compared with those of the non-pregnant uteri (n = 8; the mean value was scored as 1). The rate of change in the volume was significant until day (D) 2 in both groups. In group A, the size of the uterus returned to its prepregnancy volume by D10 and in group B, this was only attained on D14 (n = 5-8 mice in each column). *p<0.05.

The pimonidazole immunostaining pattern returned to the prepregnant pattern in both groups by D7.

It has been known that hypoxia triggers epithelial-mesenchymal transition (EMT) of endometrial cells.[11,12] Emerging evidence suggests that EMT contributes to wound healing,[13,14] tissue regeneration,[15] the invasion of endometrium[16,17] and implantation of the embryo[15] Furthermore, HIF1a is a transcription factor induced by hypoxia.[18,19] and is responsible for hypoxic stress response in cells. It is also known to be involved in homeostatic mechanisms, such as maintenance of stem cells and control of inflammation, including hypoxic adaptive responses.[20,21] Therefore, to observe hypoxic state in the uterine tissue, changes in HIF1a during the postpartum process was examined. In group A, the amount of HIF1a peaked at D1 after giving birth and rapidly decreased after D2 (**Figure 2b-1**), together with rapid uterine contraction. In addition, secretion of VEGF peaked after D2 postpartum, following the secretion peak of HIF1a (**Figure 2b-2**). It has been reported that hypoxia increases VEGF expression via HIF1a in the endometrial epithelial cells and primary human endometrial stromal cells *in vitro*.[21,22] Our results show a similar relationship

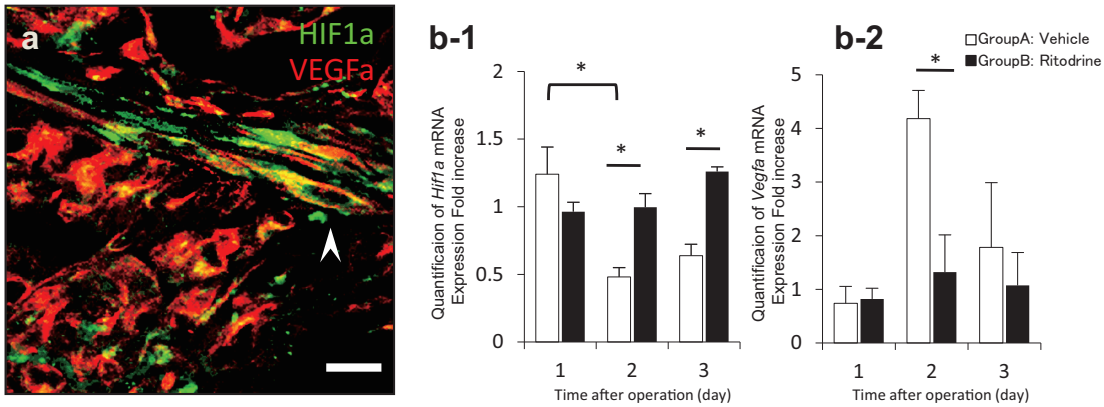

Figure 2 Expression of HIF1a and VEGFa related to postpartum tissue repair.
(a) Double positive cells for HIF1a and VEGFa were seen in the healing endometrium (arrow head). Scale bar, 25 μm. (b-1,2) Expression of *Hif1a* and *Vegfa* transcripts are shown as fold increases compared to the control (untreated samples) after normalization to expression of hypoxanthine phosphoribosyltransferase. The *Hif1a* transcript level peaked on day (D) 1 in group A, and was later for group B. The *Vegfa* levels peaked on D2 in group A (p<0.05). However, no significant change was seen in the *Vegfa* levels over a period of 3 days in group B. *p<0.05. Data are presented are mean ± SD.
HIF1a, hypoxia inducible factor 1a; VEGFa, vascular endothelial growth factor a.

between HIF1a and VEGF *in vivo* (**Figure 2**), suggesting that uterine contraction promotes angiogenesis.

HIF1a is also known to be associated with decreased TGFB1 production. Some studies have suggested that fibrosis can develop in a TGFB1-independent manner.[23] TGFB1 is a pleiotropic factor that is important in stimulating wound contraction and acts as a chemoattractant for monocytes, macrophages, and fibroblasts. Murray and Wynn demonstrated models of idiopathic pulmonary fibrosis in which the pro-fibrotic function of macrophages had been attributed to their production and activation of the pro-fibrotic cytokine TGFB1.[23] Conversely, TGFB3 stimulates fibroblast cell migration into healing wounds, resulting in marked improvement or absence of scarring.[24] Low levels of TGFB1 and high levels of TGFB3 have been described as key factors in scarless wound healing. In our study, the ratio of TGFB3 to TGFB1 was significantly higher in the normal postpartum group and the hypoxic environment owing to uterine contraction played a crucial role in scarless wound healing. In group B, *HIF1a* transcript levels increased after D2, which suggests that uterine contractions up to D1 after birth, immediately after parturition, is important for hemostasis and regeneration.

Tissue Repair and Local Microcirculation in the Postpartum Uteri

Ferenczy et al.[25] reported that endometrial regeneration from stromal cells occurs within 48 h after endometrial peeling in humans, whereas in rats it occurs 60 h after endometrial peeling. Regeneration of the stromal tissue begins after the endothelial epithelium is regenerated, which is similar to the process of normal wound healing in other tissues. In addition, Ludwig and Spornitz[26] report that the endometrial vascular vessels are repaired on day 5 of menstruation.

Furthermore, during the endometrial regeneration process, the presence of the estrogen progesterone receptor in the uterine glandular epithelium was reported, and the stromal cell is known to be hormone-dependent in the endoplasmic regeneration following completion of epithelial repair.[27,28] Interestingly, even in cases lacking ovarian hormonal support, hemorrhage from the endometrium stops and endometrial regeneration is completed, suggesting that there is another regeneration-promoting factor that is different from the hormone.[2] Endometriosis is an estrogen-dependent gynecological disease where endometrium-like tissue grows outside the uterine cavity. The pathogenesis of endometriosis is multifactorial, and factors such as genetics, environment, the immune system, and intrinsic abnormalities in the endometrium play an intrinsic role.[29-31]

In our study, we performed bilateral salpingo-oophorectomy during delivery and observed regeneration in the absence of the ovarian hormone.[9] During endometrial regeneration after placental abruption, massive hemorrhage and defects in the endometrium were seen on D1. The leakage of lectin from the edge of the vessels and the extravasation of lectin gradually reduced and ceased by D3. The reduction of uterine size and hemostasis occurred concurrently and the epithelium was repaired by D 5. Type IV positive continuous epithelium was seen on D5 (**Figure 3d-f**). Although the speed of recovery and degree of hematoma formation of the postpartum uterus are different, the endometrial epithelial regeneration was completed by D5 in both the normal postpartum and sub-involuted mouse models. As previously reported, the endometrium regenerates without the ovarian hormone, thereby returning to its initial point for the next cycle.

Scarless Wound Healing and Role of Inflammatory Cells, Including M2 Macrophages

The wound healing process consists of the four phases, hemostasis, inflammation, proliferation and remodeling, which involves complex interactions between the epithelium, immune cells, and extracellular matrix components.[32,33] The endometrium is particularly abundant with cells of the myeloid lineage, including neutrophils, eosinophils, macrophages and monocytes. The changes in the endometrium can be regarded as an inflammatory process.[2] Macrophages differentiated from monocytes play critical roles in regulating a wide range of processes, in all stages of repair. Although early

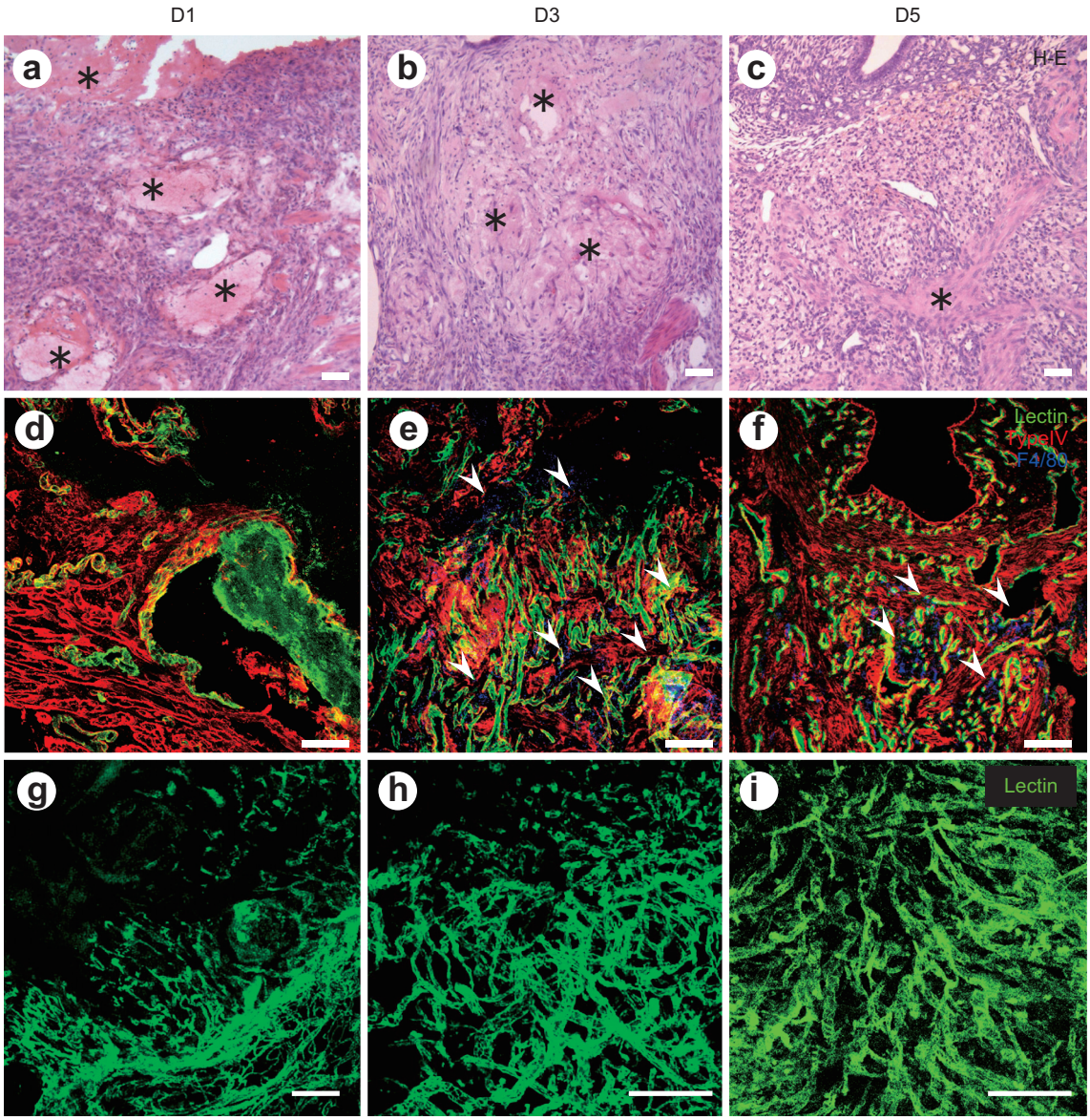

Figure 3 Morphological time course of postpartum uteri.
(a-c) Hematoxylin and eosin staining. (d-f) Immunohistochemical staining for lectin (green), type IV basement membrane (red), and F4/80 (blue). (g-i) Whole mount observed under a confocal laser microscope for tomato lectin-labeled vascular architecture. Massive hemorrhage and fibrin deposits (marked with *) were seen on day (D) 1 (a), which gradually diminished in accordance with uterine size reduction (b, c). The continuous type IV positive basement membrane showed that the epithelium regenerated within D5 of postpartum (d-f). Infiltrated F4/80 positive macrophages were seen in the repairing endometrium and quickly disappeared after D5 (d-f). To characterize microcirculation in postpartum uteri, FITC-labeled tomato lectin was administered. Tomato lectin-labeled vascular architecture can be seen in the uteri and microvascular repair occurs rapidly in the endometrium. The * indicate the location of fibrin. Arrowheads indicate the infiltrated macrophages. Scale bars; 50 μm (a-f), 200 μm (g-i).

research focused on the role of macrophages as scavenger cells in wound healing, the complex roles of monocytes and macrophages in tissue repair, and mechanisms of fibrosis and tissue regeneration are being investigated.[34] If macrophages are depleted in early stages of injury, the inflammatory response is often diminished.[35] Their removal can also result in decreased wound debridement and lead to delayed

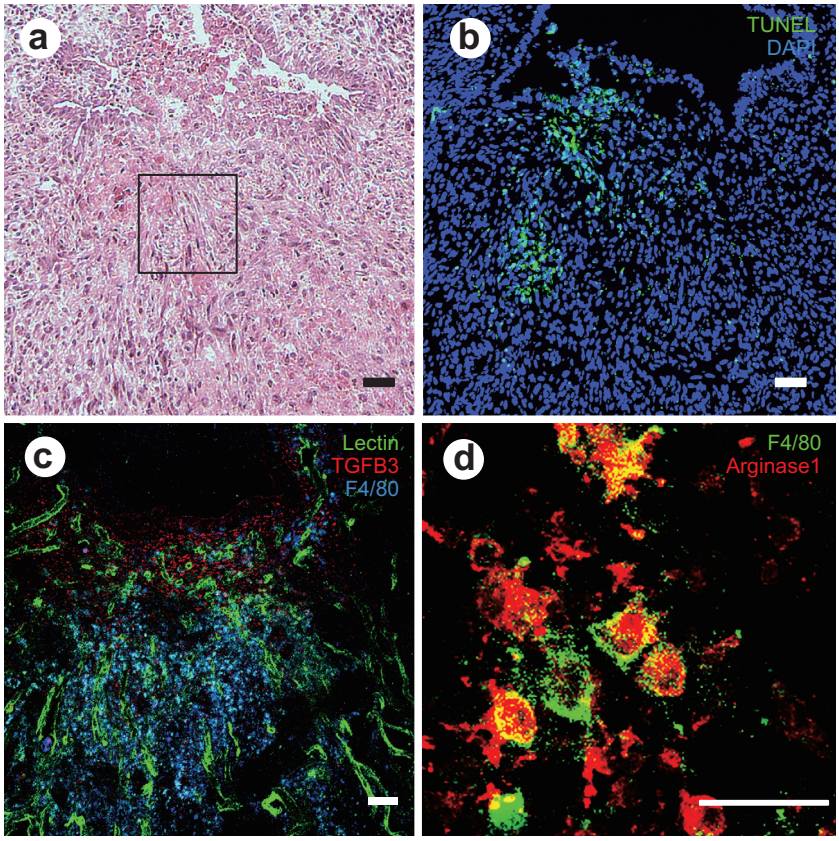

Figure 4 Microscopic changes in the uterine tissue on postpartum day 3.
(a) Hematoxylin and eosin staining. (b) TUNEL (green) and Dapi (blue) staining. (c) Immunohistochemical staining for lectin (green), TGFB3 (red), and F4/80 (blue). (d) Enlarged hematoxylin and eosin staining of (a). F4/80 (green) and Arginase 1 (red). Many F4/80 positive macrophages are seen beneath the epithelial defect. Scale bar, 50 μm (a-d).

rates of structural and functional recovery.[36] Recent research suggested two phenotypes of macrophages, M1 and M2, based on their gene expression profile in response to specific stimuli.[23,37] M1 cells are classically activated macrophages, comprised of immune effector cells with an acute inflammatory phenotype for host defense, and M2 cells are alternatively activated macrophages that regulate the maintenance of tolerance and tissue repair. Hesse et al.[38] and Briken and Mosser[39] demonstrated that alternatively activated macrophages play important roles in the clearance of helminthic parasites. M2 macrophages synthesize arginase, an enzyme that inhibits nitric oxide production, which kills cellular pathogens and allows them to produce ornithine, a precursor of hydroxyproline and polyamines. In our previous study, we showed that M2 macrophages increased in ischemic sites in early phase of healing, with a rapid response to hypoxia, which involved alteration in expression of a wide array of genes[9] **(Figure 4)**. We suggest that the balance of M1 and M2 macrophages is controlled by transient hypoxia with uterine contraction, which plays a predominant role in scarless endometrial healing.

Conclusion

We propose that uterine contractility promotes scarless endometrial regeneration, with infiltration of inflammatory cells under transient hypoxia. Understanding the normal endometrial healing process provides greater insight into several obstetrical and gynecological complications resulting from endometrial defects caused by its inadequate repair. Furthermore, these results are useful in the prevention and management of various healing disorders involving other tissue.

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組織内酸素濃度変化を背景とした子宮内膜再生における微小環境変化

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