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Title
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Permalink
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Journal
Biology of Reproduction, 104(2)

ISSN
0006-3363

Authors
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Publication Date
2021-02-11

DOI
10.1093/biolre/ioaa220

Peer reviewed

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Biology of Reproduction, 2021, 104(2), 252–254
doi:10.1093/biolre/ioaa220
Commentary
Advance Access Publication Date: 10 December 2020

OXFORD

Commentary

Vascular smooth muscle cells during spiral artery remodeling in early human pregnancy†

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†**Grant Support**: The present study was supported in part by National Institutes of Health grants HD102451, HD097498, and HL70562 (DBC); HL117341 (to RRM). The content is solely the responsibility of the authors and does not necessarily present the official views of NIH.

Received 23 November 2020; Accepted 28 November 2020

Post-implantation human development *in utero* depends completely upon the nutrients and oxygen in the mother's blood delivered via the uterine arterial vascular tree in which the smallest distal branches are called spiral arteries (SA), which are embedded in the decidua in direct contact with stromal cells. In the non-pregnant uterus, SAs develop through angiogenesis during the secretory phase of the menstrual cycle under the influence of progesterone and estrogens via enhanced production of angiogenic factors such as vascular endothelial growth factors and hydrogen sulfide [1–3]. They arise from the radial arteries at the endometrial and myometrial border, having a muscular wall with well-developed elastic lamina which diminishes as the artery penetrates the endometrium. In the absence of an implanted blastocyst, these vessels regress and are ultimately lost during menstrual shedding [4]. Following implantation and from about week 10 until 22 weeks' gestation, these vessels expand massively via angiogenesis [3], and undergo significant structural, cellular, molecular and functional changes; the cells of SA wall, including vascular endothelial cells (ECs) and smooth muscle cells (VSMCs), morphologically disappear and seem to be replaced by the invading extravillous trophoblast cells (EVTs) of placenta origin, leading to a complete reconstruction or remodeling of these arteries [5, 6]. This process is referred to as SA remodeling, which results in at least 10-fold increase in the vessel diameter and a 3–4 fold increase in total blood volume delivered to the intervillous space with an accompanying significantly reduced pressure [5, 7, 8]. Therefore, these uterine SAs are remodeled into very low-resistance high-capacity distal branches of the expanding uterine artery network, adjacent to the intervillous spaces within each "functional cotyledon" to ensure sufficient nutrient- and oxygen-rich maternal blood perfusion [9]. The process occurs in early placentation, but prepares a transport system for the entire gestation mandatory for delivering the growing volume of maternal blood, via increase in uterine blood flow, to the intervillous space, which is necessary for enhancing placental perfusion for the bi-directional maternal-fetal exchanges so that the demanding needs of nutrients and oxygen for fetal and placental development can be met and the fetal metabolic wastes and respiratory gases can be exhausted. Normal pregnancy is associated with a substantial increase in uterine blood flow with advancing gestation, reaching as high as 20-fold in the third trimester in a singleton pregnant women, proportionally to the growth rate of the fetus [7, 10]. SA remodeling is essential for pregnancy health, exemplified by the reports that defective SA remodeling is a leading etiology of certain pregnancy disorders due to placental ischemia, notably miscarriage [11, 12] and early-onset preeclampsia that is associated with fetal growth restriction and normally needs premature delivery prior to week 34 of gestation [9, 13, 14].

The literature describing the process of SA remodeling has primarily focused on differentiation and invasion of EVTs to replace vascular cells and the role of decidual immune cells [i.e., natural killer (dNK) cells and macrophages]; VSMCs have, for the most part, been understudied and description of the detailed changes in VSMCs itself in human SA remodeling is lacking. Dr Yan-Ling Wang's group at the Chinese Academy of Sciences in Beijing recently conducted an elegant study that examines the phenotypic changes of SA-VSMCs in 6–12 weeks' gestation normal decidua samples collected from electively terminated human pregnancies without known complications [15]. They observed that in a given early human gestation decidua sample, SAs displayed multiple forms of remodeling; some (~20–30%) are not remodeled as they are not surrounded by EVTs and uniformly express typical contractile smooth muscle cell (SMC) markers, including smooth muscle (SM) α-actin (αSMA), SM22a, and calponin [16, 17], similar to the VSMCs of un-remodeled SAs in non-pregnant endometrium [15]. Although ~70% of SAs are remodeled by EVTs, but at varying

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rates; they referred to SAs with EVTs surrounding VSMC and intact EC lining as "early remodeled," those with partial intact ECs as "active remodeled," and those with complete loss of VSMCs and ECs lining as "fully remodeled." With this nomenclature in mind, they also meticulously described the phenotypic changes of these cells in all forms of SAs, displaying asymmetric alterations including separation, rounding, misaligning, and loss of SMC markers, thus indicting progressive differentiation of these cells during SA remodeling. Nonetheless, the asynchronous remodeling of SAs implies that specific microenvironments are involved in the remodeling of individual SA, similar to SMC differentiation adaptive to pathological microenvironment as reported in other organs [18–20]. Indeed, the types of cells that surround each SA vary greatly, and VSMCs tend to differentiate more intensively in SAs surrounded by both EVTs and immune cells than that not surrounded by EVTs [15], pointing to an important role of the surrounding niche cells in SA-VSMC differentiation. Their results and many others also show that not all SAs are equal in early gestation decidua [4, 15, 21, 22], raising many interesting questions regarding SA remodeling during human placentation. For instance, what is the trigger of SA remodeling? Are the embryo and its proximity required during interstitial invasive implantation? And which one(s) are selected to be remodeled first, and why? Human endometrium and decidua samples around the time when the blastocyst implants would be ideal to address these important questions; however, these samples are nearly impossible to obtain due to ethic issues.

Likewise, decidualization of stromal cells is necessary for preparing the endometrium receptive of embryo implantation; it initiates in the mid-secretory phase of the menstrual cycle even in the absence of an embryo, occurring first around terminal SAs in the superficial endometrial layer and ultimately expands the entire endometrium [23, 24]. Decidualization is initiated by increased adenosine 3′,5′-cyclic monophosphate (cAMP) signaling to sensitize endometrial stromal cells to progesterone prior to embryo implantation [25], and once conceived, it is further boosted with the formation of a functional placenta by trophoblast-produced human chorionic gonadotrophin that activates cAMP signaling [26]. By using immunofluorescence microscopy analysis and *in vitro* co-culture studies of stromal cells and VSMCs, Dr Wang's group provided new evidence that the signals from the embryo initiate the decidualization of stromal cells, and the decidualized stromal cells in turn release soluble factors (although yet to be determined) to initiate VSMC dedifferentiation in the early phase of SA remodeling [15]. This adds a new concept into human placentation in that SA remodeling begins much earlier before the functional placenta is formed; it is likely initiated early around embryo implantation by decidual stromal cells to start VSMC differentiation, whereas the progression and completion of SA remodeling is facilitated by EVT invasion along with the formation of a functional placenta. Recent studies have revealed a role of matrix metallopeptidase 9, angiopoietin-1 and angiopoietin-2, interferon-γ, vascular endothelial growth factor-C released by dNK cells [27, 28], Interferon gamma-induced protein 10 produced by EVTs [29], and the phagocytotic function of macrophages [27], in disrupting the integrity of VSMCs. To this end, further studies are needed to identify the decidual stromal cell-derived soluble factors that trigger SA remodeling.

The common denominator of the literature on SA remodeling is the replacement of VSMCs and ECs by EVTs once SA is fully remodeled, which is confirmed in the study from Dr Wang's group [15]. SA remodeling is associated with increased apoptosis in ECs [21] and VSMCs [22]. However, it is very likely that not all ECs and VSMCs are cleared by apoptosis or other death pathways once SAs are fully remodeled. This raises a question regarding the fate of the vascular cells of SAs during remodeling, which has not been explored hitherto. The plasticity of SMCs has been reported in previous studies in which SMCs can dedifferentiate into macrophages, osteochondrocytes, and adipocytes under diverse conditions [19, 30, 31], whereas VSMC transformation toward NK lineage has not been reported. VSMCs specifically exhibit H3K4dime modification on the promoter of *MYH11* gene that encodes SM myosin heavy chain 11 [19, 32, 33]. Interestingly, data presented by Dr Wang's group demonstrate that approximately 5% of human $CD56^{+}$ dNK cells in early gestation human decidua contain H3K4dime modification in *MYH11* promotor, indicating that dNK cells might be originated from SA-VSMCs [15]. Because dNK cells play a key role in SA remodeling and pregnancy health in humans [28], the findings of Dr Wang's group have therefore provided intriguing evidence not only suggesting an potential origin of dNK cells (a topic of hot debate for a long time) but also implicating a novel feed-forward mechanism involving VSMCs and dNK cells for remodeling SAs during human placentation.

In summary, in order to set the foundation for maternal nutrient and oxygen delivery to the placenta for fetal growth, early gestation SA remodeling begins with the implanting blastocyst into the uterine interstitium that greatly enhances decidualization of stromal cells. These decidualized stromal cells release as yet to be determined specific soluble factors that appear to initiate VSMC differentiation into dNK cells and the dNK cells, together with decidual macrophages, in turn greatly elevate the timing and degree of SA remodeling processes. This novel idea is supported by the existing literature and the study from Dr Wang's group [15], although conclusive proof will need additional studies, such as *in vitro* differentiation models for inducing "authentic" dNKs from SMCs and *in vivo* studies utilizing cell lineage tracing in murine models. Nonetheless, further investigations of VSMCs are warranted to better comprehend our understanding of SA remodeling, which will assist in the development of new strategies to mitigate pregnancy complications due to dysfunctional SA remodeling such as miscarriage and early-onset preeclampsia with fetal growth restriction.

Disclosure statement

The authors have nothing to disclose.

Acknowledgment

The authors wish to thank Dr Yan-Ling Wang in the Institute of Zoology at the Chinese Academy of Sciences, Beijing, China, for insightful discussions.

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