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Review

Cervical etiology of spontaneous preterm birth

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SUMMARY

The cervix functions as a barrier between the uterus and vagina and keeps the uterus closed until term so that the fetus can develop. For delivery the cervix must soften and dilate, and finally reconstitute to close the uterus. This complex process involves precisely timed activation of molecular and microstructural events. Spontaneous preterm birth (sPTB) can result from aberrant timing of these events in the cervix. Unfortunately, the pathophysiology of sPTB due to cervical causes remains unclear and thus our treatment options remain limited – even if all appropriate candidates were identified and correctly treated with currently available interventions, the rate of sPTB would only be reduced by 5%. Very recent molecular and microstructural investigation is challenging prevailing concepts about cervical remodeling in pregnancy. We believe that progress toward novel, targeted solutions for the diverse pathways to sPTB entails a paradigm shift in which the overlapping and complex interactions between the cervix, uterus, membranes, fetus, placenta, and surrounding (structural and molecular) environment are suitably honored.

1. The role of the cervix in pregnancy

In normal pregnancy, despite progressive softening, the cervix keeps the uterus closed until term, and then softens/dilates further to allow for delivery of the fetus. Within minutes after birth, this remarkable structure reconstitutes to close the uterus. The entire complex process involves an elegant concert of molecular and microstructural events, including precisely timed activation of biochemical pathways and interactions between resident and immune cells and the extracellular matrix (ECM). Our understanding of this multifaceted process is rapidly changing as an explosion of molecular and microstructural information is adding to the body of knowledge about cervical remodeling in pregnancy. Below we provide a brief overview of cervical tissue architecture and cervical remodeling, as well as an introduction to emerging concepts in this rapidly growing field.

2. Cervical tissue architecture

The prevailing viewpoint is that the cervix is (i) relatively homogeneous, (ii) composed mainly of ECM/collagen (90%) with minimal cellular content (10–15%; e.g. fibroblasts, smooth muscle cells, glandular cells, vascular cells and immune cells), and (iii) structurally and physiologically distinct from the uterus [1,2]. However, recent investigation is rapidly expanding our understanding of human cervical tissue architecture.

Cervical tissue ECM contains proteins (mostly collagen, some elastin) and proteoglycans (e.g. hyaluronic acid and decorin) that serve as a scaffold and govern biochemical and mechanical tissue properties such as strength and elasticity [2,3]. In the 1970s, studies postulated that the cervical collagen network in the ECM consists of three relatively homogeneous and distinct zones: inner and outer zones of collagen fibers oriented parallel to the endocervical canal (theoretically to prevent the cervix from tearing off the uterus during dilation), and a circumferential middle layer that may serve as a ratchet to control cervical dilation (Fig. 1) [4,5]. Although this theory remains generally relevant, we now know that the cervical collagen network is highly heterogeneous, with interweaving zones of collagen that change along the cervix from the internal to external os (Fig. 2) [6]. Further, the strength of the collagen network (and thus the tissue) depends on the degree and type of collagen crosslinks between each collagen microfibril [3,7–10] and recent studies show that the internal os has significant collagen crosslink heterogeneity compared to the external os [11]. In other words, the cervix is not homogeneous, nor are the zones as distinct as previously thought. Also, because structure relates to function, it is logical that architectural differences in the internal os compared to

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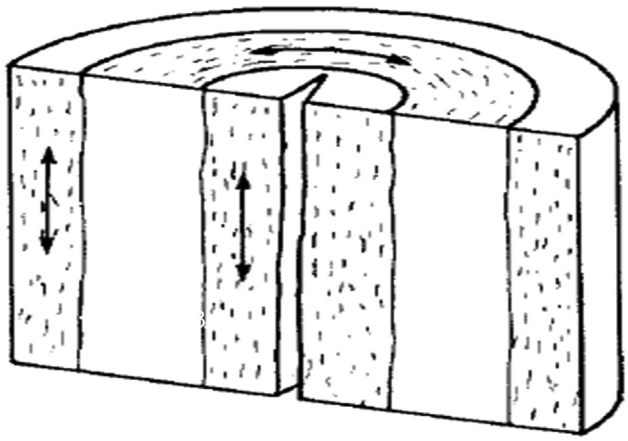

Fig. 1. The three-zone theory of the cervical collagen network: inner and outer zones contain mostly collagen fibers that are oriented parallel to the endocervical canal, and a middle zone contains collagen fibers that are circumferentially oriented around the endocervical canal.

the external os are due to functional/physiological differences. A critical concept illuminated by these findings is that "location matters" when studying the cervix.

Related to the importance of location, previous studies suggest that the average cellular content in the cervix is about 10–15% but recent data show that the area of the internal os is significantly more cellular than the external os and contains around 50–60% smooth muscle cells (SMCs). More intriguing is that these SMCs (i) are generally circumferentially oriented around the endocervical canal, possibly similar to a "sphincter," (Fig. 3), (ii) express contraction-associated proteins (i.e. gap junctions), and (iii) are functional (i.e. when treated with oxytocin ex vivo, they are contractile like uterine SMCs) (J. Vink, N.M. Zork, H. Feltovich, et al., unpublished data). In fact, there is a foundation for direct communication between them (via gap junctions on SMCs). These findings suggest that the uterus and cervix are less structurally and functionally distinct than previously believed. Adding to the complexity, a layer of epithelial cells surrounds the cervical stroma, forming an active gateway and communication pathway to the external vaginal environment [12,13].

This brief overview of emerging concepts highlights three important and evolving concepts about the cervix: (i) its architectural heterogeneity means that properties of the external os are likely not generalizable to the internal os; (ii) the internal os may actually resemble a sphincter – thus "sphincter failure" may explain why the internal os dilates/funnels first in premature cervical remodeling; and (iii) the structural/physiological continuity between the cervix and uterus suggests that the cervix may play a much more active role during pregnancy than previously appreciated.

3. Normal cervical remodeling

Three essential elements are required for spontaneous delivery of a fetus: cervical remodeling/ripening, decidual activation, and uterine contractions (Fig. 4) [14–16]. To date, neither the way in which these elements interact nor any of their underlying molecular mechanisms have been fully elucidated. That said, the pathway to birth seems to begin and end with the cervix: human and animal studies suggest that softening begins just after conception, and the cervix obviously dilates completely just before birth.

"Cervical remodeling" is the collective term for progressive cervical change and recovery during pregnancy and involves four overlapping phases: a long, progressive softening phase; an accelerated phase of marked softening and increasing compliance near the end of pregnancy (ripening); active dilation just prior to delivery; and postpartum repair [17]. Remodeling has been studied predominantly in rodents because of inherent difficulties with obtaining tissue from pregnant women. In rodents, the softening phase is characterized by an increase in collagen solubility (decreased collagen crosslinking) [17] and a decrease in enzymes which form collagen crosslinks [18]. Recent study has also

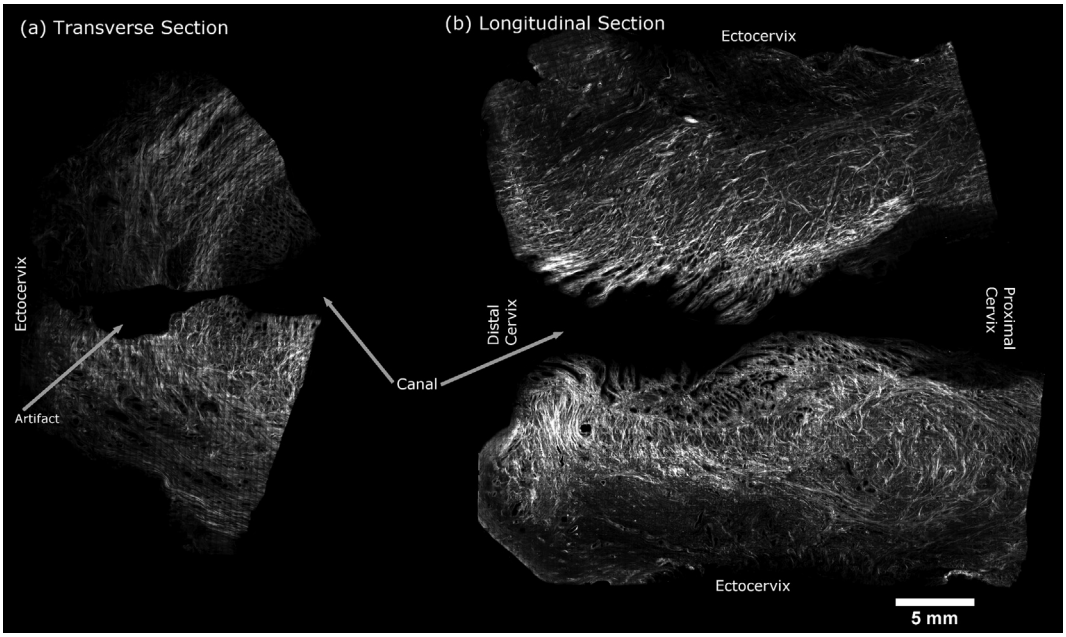

Fig. 2. Second harmonic generation microscopy image of human cervical tissue showing the complex collagen network. The right side of the image shows longitudinal sections taken from the endocervical canal, with the distal cervix on the left and proximal on the right. The left side of the image shows transverse sections taken from midway between the distal and proximal ends of the cervix (upper: anterior cervix; lower: posterior cervix).