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REVIEW ARTICLE

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Some Molecular Mechanisms of Cervical Ripening

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Abstract

Cervical remodeling is an active dynamic process that begins long before the onset of labor. The optimal course of the cervical ripening/remodeling processes is a prerequisite for successful vaginal delivery. Cervical remodeling is a slow progressive process that begins early in mammalian pregnancies, and can be loosely divided into four overlapping phases termed softening, ripening, dilation/labor, and postpartum repair. This review discusses some aspects of structural changes in the cervix at different stages of cervical ripening. In particular, the role of cervical epithelia, immune-inflammatory factors/cells, and components of the cervical extracellular matrix in cervical ripening is considered. A better understanding of the molecular-biochemical and histophysiological processes occurring during cervical remodeling is critical for the development of novel approaches to treat cervical insufficiency, preterm labor, and postpartum cervical disorders associated with its integrity. (**International Journal of Biomedicine. 2020;10(4):324-329.**)

Key Words: cervical ripening • extracellular matrix • histophysiological processes

Abbreviations

AP-1, activator protein 1; **HA**, hyaluronic acid; **GAGs**, glycosaminoglycans; **mRNA**, messenger RNA; **NF-kB**, nuclear factor-κB; **PG**, prostaglandin; **TNFα**, tumor necrosis factor alpha

Introduction

The uterine cervix performs two critical functions during pregnancy. First, the primary biomechanical function of the cervix is to maintain the fetus within the uterus until the appropriate time for delivery. Second, at the end of pregnancy, the cervix prepares for labor and delivery and begins to soften (ripen), thin out, and open (cervical ripening). Studying the ultrastructural processes of cervical remodeling is critical for the prevention and management of preterm delivery.[1-4]

The optimal course of the cervical ripening/remodeling processes is a prerequisite for successful vaginal delivery. The premature cervical opening can result in preterm birth, which occurs in 12.5% of pregnancies and is the leading cause of neonatal morbidity as well as the cause of later health problems.[5] In this regard, understanding the fundamental biochemical and histophysiological processes occurring during cervical ripening is essential in the prevention of preterm labor and birth. This review discusses some aspects of structural changes in the cervix at different stages of cervical ripening. In particular, the role of cervical epithelia, immune-inflammatory factors/cells, and components of the cervical extracellular matrix in cervical ripening is considered.

Distinct Phases of Cervical Remodeling

The transformation of the cervix from a closed rigid structure in a soft and distensible structure, which opens sufficiently for birth, is an active dynamic process that begins at the early stages of gestation. A better understanding

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of the molecular-biochemical and histophysiological processes occurring during cervical remodeling is critical for the development of novel approaches to treat cervical insufficiency, preterm labor, and postpartum cervical disorders associated with its integrity. Although biopsy material from pregnant women before term is limited, experimental studies in rodents have facilitated a comparative evaluation of the cervical remodeling process.

Cervical remodeling is a slow progressive process that begins early in mammalian pregnancies, and can be loosely divided into four overlapping phases termed softening, ripening, dilation/labor, and postpartum repair.[6-9]

Cervical softening (Phase 1)

Cervical softening (Phase 1) can be defined as a change in the biomechanical properties of the cervix when compared with the nonpregnant cervix and is characterized by a progressive decrease in tissue stiffness without loss of tensile strength.[7,10] From a restrictive and rigid barrier before pregnancy, the cervix grows and softens during Phase 1 of remodeling under the trophic influences of a variety of hormones and ovarian steroids.[11] Experimental studies in mice indicated that the softening phase begins by day 12 of a 19-day gestation.[5,7-9,12,13]

Cervical softening begins early in mammalian pregnancies. In 1895, Hegar first described the 'softening' of the lower uterine segment in association with human pregnancy at 4–6 weeks. Phase 1 is a relatively slow and incremental process. This phase takes place in a progesterone rich environment. Yoshida et al.[14] reported that in the early softening period mature cross-linked collagens decline and are replaced by immature collagens to facilitate increased tissue compliance. Increases in collagen solubility in Phase 1 is one of the earlier events in the remodeling process. Akins et al.[15] showed that early changes in tensile strength during cervical softening result in part from changes in the number and type of collagen cross-links and are associated with a decline in expression of two matricellular proteins thrombospondin 2 (THBS2) and tenascin C (TnC).

M. Mahendroo[16] highlights that the gradual replacement of mature cross-linked collagen with collagen harboring reduced cross-links along with the decline in THBS2 and TnC in the cervix is key to modulating collagen architecture within the extracellular matrix during softening and initiating the incremental fall in cervical mechanical strength while maintaining tissue integrity.

Gene expression studies performed by Read et al.[7] revealed a potentially important role of cervical epithelia during softening and ripening in the maintenance of the immuno-mucosal barrier that protects the stromal compartment during matrix remodeling. Expression of two genes involved in repair and protection of the epithelial permeability barrier in the gut (trefoil factor 1, Tff1) and skin (serine protease inhibitor Kazal type 5, Spink5) was increased during softening and/or ripening. Expression of the Pcp4 gene encoding Purkinje cell protein 4 (a neuronal-specific calmodulin regulatory protein that inhibits apoptosis) decreased as remodeling progressed. These results indicate that cervical softening during pregnancy is a unique phase of the tissue remodeling process characterized by increased collagen solubility, maintenance of tissue strength, and upregulation of genes involved in mucosal protection.[7]

A marked proliferation of the mucosal epithelia occurs in the latter half of rat pregnancy.[17] By gestation day 16 and 17 as the softening phase merges into the ripening phase, the epithelium becomes laden with mucin-secreting vacuoles important in immune surveillance and lubrication.[16] During softening and ripening, the cervical epithelia maintain fluid balance and permeability barrier via regulated expression of aquaporins, gap junction proteins connexin 26 and 43, hyaluronan synthase 2, desmogleins (1 alpha and 1 beta), and claudin proteins.[18-21]

In contrast to the later phases of cervical remodeling, major inflammatory events do not mediate the softening process. In Phase 1, only little changes in the distribution of macrophages or neutrophils are revealed.[7]

Cervical ripening (Phase 2)

Following softening, cervical ripening (Phase 2) occurs in the weeks or days preceding birth. The transition to Phase 2 is mediated by a decline in progesterone synthesis, increased cervical progesterone metabolism, and increased synthesis of estradiol and relaxin.[5] The results obtained by B. C. Timmons,[22] evident that cervical ripening requires downregulation of collagen assembly genes; increased synthesis of glycosaminoglycans that disrupt the matrix, such as hyaluronan; increased metabolism of progesterone; and changes in epithelial barrier properties. Cervical ripening is characterized by an increase in the content of hyaluronic acid, loosening of the collagen matrix, increased collagen solubility,[23,24] changes in the distribution of inflammatory cells, increased tissue growth and hydration, and loss of tensile strength.[25-28] Thus, this phase is characterized by maximal loss of tissue compliance and integrity.

During cervical ripening, alterations in collagen structure and packing are influenced by the composition of glycosaminoglycans (GAGs) in the extracellular matrix. Osmers and al.[29] showed that the clinical features of cervical ripening and dilatation were characterized by variation in the total glycosaminoglycan content and changes in the proportions of the different glycosaminoglycans (HA, dermatan sulfate, chondroitin sulfate, and heparan sulfate). The studies performed by Ruscheinsky et al.[30] suggest that HA has multiple, cell-specific functions in the cervix that may include modulation of tissue structure and integrity, epithelial cell migration and differentiation, and inflammatory responses. Increased hyaluronan synthase 2 expression and the subsequent increase in HA is a distinct feature of cervical ripening and dilation.[27] Proteoglycans containing sulfated GAG chains modulate collagen fibril size, spacing, and access to proteases.[31,32]

Several studies have suggested that normal cervical ripening may be a sterile inflammatory state characterized by an influx of immune cells into the cervix.[33-38] M. Mahendroo [16] and other authors [39,40] consider that immune cells are present but not activated during cervical ripening.

Cervical dilatation /labor (Phase 3)

According to Mendelson,[41] both term and preterm labor in humans and rodents are associated with an inflammatory response. If in preterm labor, intraamniotic infections may provide the stimulus for increased amniotic fluid interleukins and inflammatory cell migration,[42] at term, the stimulus for this inflammatory response is unknown.

Increasing evidence suggests that at term labor mechanical stretch [43,44] caused by the growing fetus, as well as hormonal signals produced by the developing fetus near term,[45-48] promote the production of chemokines leading to macrophage migration and up-regulation of inflammatory response pathways with the release of cytokines and activation of inflammatory transcription factors, such as NF-kB and AP-1, which also is activated by myometrial stretch.

Mendelson [41] postulates that the increased inflammatory response and NF-kappaB activation promote uterine contractility via 1) direct activation of contractile genes (e.g. COX-2,[49] oxytocin receptor,[50] and connexin 43)[51] and 2) impairment of the capacity of progesterone receptor to mediate uterine quiescence.

After the onset of regular uterine contractions, the ripened cervix is dilated sufficiently (Phase 3) to allow the passage of the full-term fetus through the birth canal. Given the short duration of the ripening and dilation phases, it is difficult to identify processes that distinguish these two overlapping phases of cervical remodeling. Just before birth, the final remodeling of the cervix is driven through the secretion of prostaglandins by the fetoplacental unit. Upon the increased secretion of cortisol by the fetal adrenals, prostaglandin synthase (PGHS)-2 gene expression in the placenta is up-regulated, resulting in increased production of PGE2 in the cervical region and subsequent matrix remodeling. [52]

According to Hassan et al.,[53] cervical dilatation in term labor is associated with a stereotypic gene expression pattern determined by microarray, which is characterized by overexpression of genes involved in neutrophil chemotaxis, apoptosis, extracellular matrix regulation, and steroid metabolism. The dilation phase has been well-studied in women due to the availability of cervix biopsies.

Postpartum repair (Phase 4)

Accumulating evidence suggests that human parturition represents an inflammatory process and the infiltrating leukocytes are a major source of pro-inflammatory mediators. Macrophages appear to play a more crucial role in the onset of parturition.[54] Macrophages account for around 20% of the decidual leukocyte population[55] and there is an influx of macrophages into the myometrium, fetal membranes, decidua, placenta, and cervix during spontaneous term labor [56, 57] and in preterm labor.[58]

Osman et al.[56] found that parturition was associated with a significant increase in IL-1beta, IL-6, and IL-8 mRNA expression in cervix and myometrium, IL-6 and IL-8 mRNA expression in chorio-decidua and IL-1beta and IL-8 mRNA expression in amnion. Histological analysis demonstrated that leukocytes (predominantly neutrophils and macrophages) infiltrate the uterine cervix coincident with the onset of labor. In a study performed by Young et al.,[37] such pro-inflammatory cytokines as IL-6, IL-8, and TNFα have been identified in the cervix during labor.

Characteristics of inflammation during the dilation phase are supported by the increased presence of inducible nitric oxide synthetase (iNOS) in the cervix stroma of women at term, whether or not in labor.[59, 50] Overall, these findings raise the possibility that some balance of immune cell products guides extracellular remodeling to promote softening, ripening, and the capability to dilate. [61]

During postpartum repair (Phase 4), the integrity and competence of cervical tissues are recovered to ensure a normal cervical function for subsequent pregnancies. Postpartum remodeling is characterized by decreased HA content, increased expression of genes involved in the assembly of mature collagen, synthesis of matrix proteins that promote a dense connective tissue, and inflammation.[22,30]

Matricellular proteins (SPARC, thrombospondin 1, thrombospondin 2, and tenascin C) modulating interactions between cells and the extracellular matrix[62] are expressed and regulated during cervical remodeling, but their specific function during postpartum repair remains to be elucidated.[63-66] A variety of factors, including metalloproteases, extracellular matrix proteins, and genes governing epithelial differentiation pathways, are all upregulated in postpartum,[22,39,67] as well as the expression of neutrophils, eosinophils, and both M1 and M2 macrophages.[5,16,37] The postpartum activation of M1 macrophages and neutrophils generate pro-inflammatory molecules that are important in matrix cleanup, whereas the alternatively activated M2 macrophages prevent overactivation of the inflammatory process and promote tissue repair.[5] Thus, the postpartum repair is characterized as a pro-inflammatory wound-healing response. [16,22,68,69]

Conclusion

Cervical remodeling is an active dynamic process that begins long before the onset of labor. The optimal course of the cervical ripening/remodeling processes is a prerequisite for successful vaginal delivery. Much more information about in vivo human tissue is necessary for a comprehensive understanding of the complex process of cervical remodeling. A better understanding of the fundamental biochemical and histophysiological processes occurring during cervical ripening is essential in the prevention of preterm labor and birth.

Competing Interests

The authors declare that they have no competing interests.

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