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CONCERNING SOME MORPHOFUNCTIONAL ASPECTS OF THE UTERINE CERVICAL RIPENENING

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ABSTRACT — The onset of pregnancy is marked by profound morphological and functional changes occurring in the uterine cervix, the whole combination of which is described by the term *cervical ripenening*. The study of morphological and functional aspects of cervical maturation is both of theoretical and practical importance since many disorders of cervical maturation often lead to premature delivery or the birth of premature infants. The improvement of research methods enabled to study the process of cervical maturation at the molecular and cellular levels of organization. Our paper summarizes current data on the main morphological and functional changes that occur in the uterine cervix during maturation. In the course of the analysis of literature data, it became possible to identify three structural components that play a leading role in the maturation of the uterine cervix: epithelial, immune-inflammatory, connective tissue extracellular matrix component. Understanding the morphofunctional changes that occur in the uterine cervix during its maturation at different levels of organization of living organisms (molecular, cellular, tissue) is crucial for the development and improvement of treatment and prevention strategies.

KEYWORDS — Uterine cervix, pregnancy, maturation, premature delivery, epithelium, inflammation, extracellular matrix.

INTRODUCTION

The uterine cervix is a structure located at the caudal end of the uterus. Its main function is to keep the fetus in the uterus during pregnancy until the onset of labor. The structure of the uterine cervix is represented by the most important components like epithelial tissue, smooth muscle cells, as well as connective tissue, including fibroblast cells and extracellular matrix. With the onset of pregnancy, numerous ultrastructural changes arise in these components of the uterine cervix, the study of which is an important research area that has not only theoretical but also practical importance [14–18, 38]. Thus, the optimal course of the process of the uterine cervix maturation is a prerequisite for a successful natural delivery. Accordingly, a violation of the process of the uterine cervix maturation and its premature dilatation can lead to preterm delivery, which is an urgent problem of modern healthcare. According to statistics, 12.5% of all pregnancies, where any abnormality occur during the maturation of the uterine cervix, end in premature delivery [15, 16]. In this regard, studies aimed at establishing fundamental morphofunctional changes occurring during cervical maturation are essential for the prevention of early delivery and the birth of premature infants.

The purpose of this article is to discuss the main morphological and functional changes that occur in the uterine cervix during maturation. Below, we will sequentially review the role of cervical epithelial cells, components of the extracellular matrix of its connective-tissue stroma as well as immune-inflammatory factors and cells that are activated and/or migrate into the uterine cervix during pregnancy, ensuring the process of its maturation.

ROLE OF THE EPITHELIAL CELLS IN THE UTERINE CERVIX MATURATION

The mucous membrane of the uterine cervix, consisting of the epithelium and the lamina propria, plays an important protective role during pregnancy and delivery, which is to prevent the penetration of infectious agents into the uterine cavity and mechanical damage during the passage of the fetus during labor. It was noted that during pregnancy, epithelial cells actively multiply and differentiate [16, 42, 46]. Differentiation of epithelial cells is accompanied by huge changes in the expression of regulatory genes and products of their transcription (messenger RNA) and translation (protein and enzyme molecules). Due to the improvement of molecular genetic research methods and a series of experiments to study the expression of specific compounds in the epithelial tissue of the uterine cervix, it became possible to obtain interesting data. So, for example, in studies, significant alteration in the expression of aquaporins, fissural junction proteins (contacts) — connexin 26 and 43, enzymes of hyaluronan synthase 2, steroid 5-alpha-reductase type 1

and desmogleins 1α and 1β were found [4, 32, 37, 42]. The data from these studies clearly indicate that during pregnancy there is a carefully regulated expression of specific proteins and enzymes that are necessary to optimize the process of cervical maturation.

Epithelial tissue of the female reproductive tract, including the uterine cervix, is essential in providing protective reactions of innate and acquired immunity, aimed at preventing the development of ascending infection. It has been established that epithelial cells secrete cytokines and chemokines that recruit and activate immune-inflammatory cells and antimicrobial factors that destroy invading pathogens [45]. An increased number of leukocytes is found in the cervical lamina propria in mice during pregnancy, which is recruited by some cytokines and chemokines for immunological surveillance. Additionally, epithelial cells themselves also produce bacterial and viral pattern recognition receptors (Toll-like receptors, antimicrobial factors, and protease inhibitors). Y. Filipovich and colleagues, using an experimental model of preterm labor (induced by infectious agents) in mice, established the important role of the adapter protein MyD88 (TIRAP (toll-interleukin 1 receptor (TIR) domain containing adaptor protein)) in the initiation of preterm delivery. In mice deficient in MyD88, preterm labor did not develop in response to infectious agents [11, 12]. Further study of this mechanism, according to the researchers, is promising in terms of the development of therapeutic and prophylactic medications for the prevention of preterm labor by inhibiting MyD88 and intracellular signaling pathways.

The regulation of the epithelium barrier properties of the uterine cervix mucous membrane is ensured by protein molecules of tight junctions, which, under normal conditions, reliably isolate the spaces between adjacent epithelial cells. According to the results of an experimental study, in mice during pregnancy, there are changes in the content and structure of protein molecules of tight junctions, in particular, in claudin 1 and 2 [43]. Apart from the aforesaid, the expression of desmoglein and a number of keratin proteins increases during cervical maturation and becomes maximal during delivery [13, 43]. The specific functions of tight junction proteins of cervical epithelial cells and their role in epithelial cell differentiation and cervical maturation still remain unclear. However, changes in expression in animals during experimental modeling of preterm birth may indicate that the permeability and, accordingly, the barrier properties of the epithelium are regulated during pregnancy and play an important role in the maturation of the uterine cervix [13, 43, 47].

Rather interesting are reports of additional proteins expressed in the cervical mucosa, such as trefoil factor 1 (TFF1) and the serine protease inhibitor Kazal type 5 (SPINK5/LEKT1). The expression of these proteins increases during cervical maturation and becomes maximal during delivery [9, 25]. The important functions of TFF1 and SPINK5 may be indirectly evidenced by studies on other organs. For example, it has been shown that TFF1 plays an important role in the protection and restoration of the epithelial layer of the gastric mucosa and small intestine [25]. SPINK5 is also expressed in the epithelial layer of the skin and prevents the degradation of desmogleins and some other proteins involved in the formation of the protective barrier of the epithelium [9]. Based on the functions of TFF1 and SPINK5 proteins in the organs of the gastrointestinal tract and skin, it can be assumed that their increased expression in the mucous membrane of the cervix during maturation is also not accidental and, probably, supports the protective properties of the uterine cervix of pregnant women to fight infectious pathogens. In general, a decrease or absence of expression of protective factors can contribute to an increase in susceptibility to infectious-mediated premature birth, and therefore, further study of such mechanisms seems to be a promising research direction.

ROLE OF IMMUNE AND INFLAMMATORY COMPONENTS IN THE UTERINE CERVIX MATURATION

According to one hypothesis, immune and inflammatory cells cause changes in the structure and properties of the uterine cervix extracellular matrix, which can lead to its early maturation and preterm birth [24, 31]. As a result of observations, it was suggested that leukocytes infiltrating the uterine cervix by the time of delivery secrete protease enzymes that contribute to the destruction, loss, and disorganization of the extracellular matrix rich in collagen, which leads to the expansion of the uterine cervix [24, 26, 31, 35, 42, 48] Studies have shown that inflammatory cells (neutrophils, eosinophils, macrophages of the M1 and M2 phenotypes, and others), secreting pro-inflammatory cytokines, are widely represented in the uterine cervix before delivery, both in women and in experimental animals [33, 41]. Also, in the postpartum period, there is a sharp change in the expression profile of macrophage genes. As early as two hours after birth, in mice, M1 macrophages express classical pro-inflammatory markers: interleukin 1 alpha, tumor necrosis factor-alpha (TNF-alpha), monocytic chemotactic protein 1. Alternatively, activated (anti-inflammatory) M2 macrophages express the following markers: chitinase-3-like protein, arginase-1, is an antagonist of the interleukin 1 receptor, which

takes on enormous importance in the immunosuppression and repair of organs and tissues, including the uterine cervix [33, 41, 42]. These data support the theory of preterm labor mediated by infectious and inflammatory processes.

Macrophages have a heterogeneous phenotype, the change of which at different stages of cervical maturation plays a role in creating optimal conditions for pregnancy and facilitating the effective recovery of the uterine cervix after delivery. In general, a mixed population of macrophages serves two main purposes: 1) macrophages of the M1 phenotype protect the reproductive tract from the threat of microbial invasion and provide postpartal clearance of extracellular matrix molecules necessary during cervical maturation, and 2) macrophages of the M2 phenotype suppress hyperactivation of pro-inflammatory reactions and promote restoration of the structure of the uterine cervix to its original (non-pregnant) state, which is necessary after childbirth [33, 41].

It is also notable that the role of inflammation in cervical maturation, according to a series of studies, can be controversial. Some studies have reported a slight increase in the expression of genes encoding pro-inflammatory proteins during cervical maturation [19]. In another study, on the contrary, there was a significant increase in the expression of proinflammatory factors in the uterine cervix during maturation and during vaginal delivery [19, 20]. Many researchers believe that infections and inflammatory responses are triggers for premature cervical maturation, significantly increasing the likelihood of preterm birth. Thus, according to some data, infection-mediated premature deliveries account for approximately 25–40% of all causes of preterm births [6, 15].

The ability of inflammation to induce preterm labor is clearly demonstrated by an experimental study in which the administration of a Toll-like receptor 4 antagonist to non-human primates reduces the risk of preterm labor caused by infectious pathogens [1]. In another experimental study, it was shown that mice with a deficiency of receptors for pro-inflammatory markers (interleukin 1-alpha and tumor necrosis factor-alpha) are more resistant to preterm labor induced by exposure to one of the key pathogenicity factors of gram-negative microbes — lipopolysaccharide (LPS). LPS is very often used for experimental modeling of preterm delivery in animals [21, 22].

ROLE OF EXTRACELLULAR MATRIX COMPONENTS IN THE UTERINE CERVIX MATURATION

The components of the extracellular matrix, due to their high content in the uterine cervix, make an invaluable contribution to the process of its maturation. Changes in the uterine cervix, characterized by its significant softening in women in early pregnancy, were described by the German researcher A. Hegar back in 1895. The results of these initial studies provided the first evidence for structural changes occurring in the uterine cervix during the first trimester of pregnancy, characterized by increased cervical compliance in response to mechanical stress [10]. A subsequent more detailed study of the biomechanical properties of the uterine cervix at different stages of pregnancy confirmed that the compliance or distensibility of the uterine cervix increases in the early stages of pregnancy and becomes maximal by the time of delivery [10, 23]. Changes in the biomechanical properties of the uterine cervix play a significant role in maintaining a normal pregnancy [10].

The development of research methods made it possible to establish that the biomechanical properties of the uterine cervix are closely related to its structural components, among which the proteins of the extracellular matrix should be specially noted [14–16, 29, 30, 40]. Collagen is the most abundant protein in the entire human body, including individual organs such as the uterine cervix. Fibrillar collagen is considered to be the main structural protein that affects such biomechanical properties of the uterine cervix as strength and distensibility [14–16]. The properties of collagen are partially affected by changes in its synthesis, post-translational (post-synthetic) modifications (folding, glycosylation, etc.), assembly of synthesized collagen chains into fibers, and degradation of its fibers. In the literature, there are conflicting data on the role of collagen in cervical maturation [14–16, 29, 30, 40]. Some researchers believe that different types of collagen significantly affect the biomechanical properties of the uterine cervix as it matures. There is an opinion, that this assumption is the most convincing. So, in the non-pregnant uterine cervix and the early stages of its maturation (pregnancy), type 1 collagen prevails. It determines the increased stiffness of the uterine cervix and got cleaved by proteases when the uterine cervix is mature. At the same time, along with the processes of the breakdown of type 1 collagen during the maturation of the uterine cervix, there is an increase in the synthesis of type 3 collagen, the functional properties of which differ from type 1 collagen. Based on statistical analysis, a positive correlation was noted between type 3 collagen synthesis and gestational age. The maximum content of type 3 collagen is observed at birth and, according to the previous studies, is associated with an increase in the distensibility of the uterine cervix [15, 16]. Consequently, different types of collagen, changing during the maturation of

the uterine cervix, provide changes in its biomechanical properties as needed. However, further research is needed to clarify the specific mechanisms of collagen involvement in this process.

There is evidence that changes in the structure and packaging of collagen also depend on the composition of glycosaminoglycans (GAGs) in the extracellular matrix of the uterine cervix. The total GAG content in the uterine cervix increases during pregnancy. In addition to this, there have been significant changes in the composition of GAGs in the uterine cervix [36]. GAGs include unsulfated GAGs, hyaluronan, and sulfated GAG chains, which, in combination with proteins, form proteoglycans. Proteoglycans perform various functions in the uterine cervix, one of the most important of which is the binding of growth factors, regulation of the size of collagen fibrils, the distance therebetween, and, as a consequence, the action of protease enzymes [2, 3]. According to a study by G. Westergren-Thorsson et al, numerous proteoglycans, such as versican, decorin, fibromodulin, and others, are present in significant quantities in the uterine cervix, and their composition may change during pregnancy [44]. The function of proteoglycans is regulated by both the protein part of the molecule and the carbohydrate part, namely, the composition, length, and degree of sulfation of the GAG carbohydrate chain, which occurs in the endoplasmic reticulum and the complex at the stage of post-translational modifications. Thus, changes in the structure of GAG chains can regulate the function of proteoglycans in the uterine cervix during its maturation [39, 44]. However, the specific mechanisms underlying these processes remain unexplored.

Other additional components of the extracellular matrix, even though they are present in the uterine cervix in a rather small amount, also somewhat affect its biomechanical properties. Elastic fibers, which give the uterine cervix the property of distensibility, account for an average of 0.9–2.4% of the total volume of the uterine cervix connective tissue [29, 30]. Although the content of elastic fibers does not change during pregnancy, they may also play an important role in cervical maturation. Thus, it was shown that in women with mutations in genes encoding fibrillin proteins and components of elastin microfibrils, the content of elastic fibers and cervical elongation decrease [5].

Matrix proteins such as secreted cysteine-rich acidic protein (SPARC, osteonectin), thrombospondin 1, thrombospondin 2, and tenascin C are also some of the most important structural components of the connective tissue extracellular matrix. These proteins play important roles in regulating the interaction of cells with the extracellular matrix, wound healing, and cell migration within the connective tissue of many organs of the human body [34]. Given these functions of matrix proteins, they have attracted the attention of researchers studying the morphological and functional aspects of cervical maturation. For example, several studies have found a change in the expression of genes encoding thrombospondins 1 and 2, tenascin C during maturation, and postpartum repair of the uterine cervix in experimental animals and humans [19, 42, 46]. In experimental studies on pregnant laboratory mice with a deficiency of each of these proteins, numerous disturbances in the production and interaction of components of the uterine cervix extracellular matrix were noted, which led to a change in its biomechanical properties [7, 8, 27, 28]. For example, in mice with thrombospondin 2 deficiency, premature softening of the uterine cervix occurred, and the risk of developing premature birth increased [27]. Thus, a change in the expression of these matrix proteins has a significant effect on the process of cervical maturation.

CONCLUSION

Thus, the process of cervical maturation is complex and affects many structural components of the uterine cervix: epithelial, immune-inflammatory, extracellular matrix elements. With the maturation of the uterine cervix, epithelial cells actively proliferate and differentiate, they significantly increase the expression of some types of protein molecules (connexins, desmogleins, claudins, and several others) aimed at increasing the barrier properties of the mucous membrane. Besides, cervical epithelial cells play an important role in providing protective reactions of innate and acquired immunity by increasing the formation of cytokines, chemokines, and adapter protein MyD88, which can serve as therapeutic targets for the development of pharmaceutical preparations. Immune and inflammatory components of the uterine cervix regulate the structure and properties of the extracellular matrix. Increased activity of pro-inflammatory factors leads to disorganization of the extracellular matrix and contributes to premature birth. Infectious agents, predominantly gram-negative bacteria, are triggers for the early maturation of the uterine cervix. Moreover, during the maturation of the uterine cervix, profound structural changes occur in its extracellular matrix, independently from the factors indicated above. The expression of different types of collagen changes, in particular, type 1 collagen is replaced by type 3 collagen. The composition and properties of glycosaminoglycans, the expression of genes encoding matrix proteins (thrombospondin 1, thrombospondin 2, tenascin C and osteonectin) also change. There are certain conflicting data on the role of individual

components in cervical maturation, and there is also insufficient knowledge of specific mechanisms. Further study of the role of individual components in cervical maturation and clarification of the underlying mechanisms will be critical for the development of diagnostics as well as treatment and prophylactic strategies to handle violations of the process of cervical maturation.

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