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Mini Review

Extracellular Matrix in Preterm Premature Rupture of Fetal Membranes

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Abstract

Spontaneous preterm birth (sPTB) is a complex health problem that is at the center of intense international collaboration. Detailed understanding of this syndrome is critical to improve related maternal, fetal, newborn health outcomes worldwide. Clinically, the antecedents of sPTB include spontaneous preterm labor (sPTL) or preterm premature rupture of membranes (pPROM), which accounts for one-third of sPTB. The integrity of the amniochorionic membrane is dependent on the extracellular matrix (ECM), which plays a significant role in the function of amnion epithelial cells and the tissue as a whole. ECM proteins mainly include fibronectin, total fibrilar collagens, proteoglycans, hyaluronan, desmoplasia, biglycan and decorin. Abnormalities in the ECM have been related to pPROM, but this link deserves further investigation. In this review, we briefly summarize the components of the ECM, ECM proteins, the functional pathways involving ECM proteins, and their potential role in the pathophysiology of pPROM.

Keywords: Extracellular matrix; Cell adhesion; Preterm birth

Introduction

Preterm birth (PTB) refers to live birth that occurs before 37 completed weeks of gestation. PTB is the principal cause of perinatal mortality and morbidity and the most common cause of death in children under 5 years old. PTB includes spontaneous preterm birth (sPTB) and indicated preterm birth (iPTB) in which birth is induced by medical reasons, such as intrauterine growth restriction, pre-eclampsia or fetal distress. sPTB may follow preterm labor (PTL) and subsequent membrane rupture and expulsion of the intrauterine contents. sPTB may also follow preterm premature rupture of fetal membranes (pPROM), which then leads in turn to labor and preterm birth. A portion of women with pPROM have labor induced for indication, including overt infection or fetal distress. Thus pPROM may lead to PTB along spontaneous and "indicated" pathways (e.g, GM-CSF, TNF-α, TGF-β, IL-1β, IL-6, IL-8, IL-10, etc.) [1].

The primary structure of the fetal membranes is the amnion composed of a monolayer epithelial cells, the basal (bottom, inner) border of which are in contact with amniotic fluid and at the apical (top, outer) border, a fundamentally collagen-rich layer of mesenchymal cells connected in turn to chorion [2]. The primary source of matrix and collagen support for the amnion is the mesenchymal cell layer. The elasticity, integrity and strength of fetal membranes is influenced by mesenchymal extracellular matrix (ECM) proteins and plays an essential role in preventing in pPROM. Dynamic changes of ECM can result in alterations in the components of the stroma, which sequentially affect cellular function mediated via membrane receptors that distinguish specific ECM composition [3]. The unique properties of major ECM proteins also affect the stability of ECM itself. These properties may be a factor not only in pPROM but also disfunction in other intrauterine

environments that lead to, for example, abnormal placentation or cervical insufficiency [4-6]. The catabolism and synthesis of ECM are strictly controlled by cytokines and growth factors, as well as via expression of chaperone proteins, and the function of proteolytic enzymes activators and inhibitors [7-9]. This review describes recent development in the study of ECM metabolism and structure that are relevant to the process of physiological and pathological parturitions.

ECM Composition and Structure

ECM proteins comprise the NC1 domains of basement membrane collagen IV and the C-terminal domains of fibril-forming collagens [10]. Collagen is a plentiful structural protein in humans. It's the most abundant of the ECM, accounts for 3/4 dry weight of skin, comprises 1/3 the total protein. Many proteins include collagenous domains [11,12]. The fibrillin microfibril, along with elastin is present in the elastic fiber. The fibrillin microfibril is a key component of the tissue homeostasis sequestering and storing the potential forms of members of the BMP family and TGF-β [13-15]. Elastic fibers play key role in many tissues including lungs, skin, ligaments and arteries [16-18]. Tumor desmoplasia (fibrosis) is principally constituted of fibrillar collagens, secreted by both co-opted cancer associated fibroblasts (CAFs) and cancer cells into the extracellular space. The desmoplasia decreases vascularity, increases tissue stiffs, and characteristically creates a physical encapsulation in and around the tumor. This fibrosis raises tumor metastasis and growth by activation of intracellular signaling networks at the molecular level [19].

ECM components are frequently oligomeric and large multidomain molecules [20]. The non-collagenous composition of the ECM includes proteoglycans, fibronectin, laminin, decorin, biglycan, hyaluronan, fibrinogen, plasminogen, and integrins [21-23]. Progeoglycans (PGs) are a common component and the key constituents of ECM [24,25]. These proteins also attach to the lipid membrane of the cell and interact with many morphological factors, proteins and receptors from the ECM. They mediate a variety of biological reactions such as cell adhesion, proliferation, migration and differentiation [26]. Proteoglycans exist on nearly all animal cell surfaces to maintain cell adhesion [27].

Fibronectin (FN) is a 230~270kDa glycoprotein that is present in most ECM. The single FN gene transcript encodes 20 isoforms in humans. FN exists as a protein dimer consisting of two antiparallel monomers covalently bonded at their C-termini by a pair of disulfide bonds [28]. FN is comprised of repeating type I, II, III units. FN domains or units mediate ligand binding and self-assembly for gelatin/collagen, heparin, fibronectin, integrins, and other extracellular molecules [29]. FN is extensively expressed in embryos as well as adults, especially in areas of cell migration, active morphogenesis and inflammation.

Laminin is a 500-800kDa heterotrimeric glycoprotein located in the basement membrane. The sixteen trimeric isoforms which have been found in human and mouse tissues show both cell and tissue specificity [30-32]. Laminins contribute to the ECM structure and contribute to cellular differentiation, adhesion, phenotype stability, resistance to apoptosis, and migration.

Decorin is an ECM proteoglycan that contains a single-chain aminopoly saccharide and a core protein [33,34]. It is an archetypal Small Leucine Rich Proteoglycans (SLRP) structurally composing of single glycosaminoglycan (GAG) chain, either dermatan sulfate (CS) or chondroitin sulfate (DS), which is connection with the N-terminal of core protein [35]. It is secreted in the ECM by stromal cells like endothelial, myofibroblast and fibroblast [35]. Decorin is a natural ligand for insulin like growth factor-1R (IGF-1R), receptor tyrosine kinase especially epidermal growth factor receptor (EGFR), c-met (hepatocyte growth factor receptor (HGFR)), fibroblast growth receptor (FGFR), transforming growth factor-β (TGF-β), toll like receptors (TLR) [35-37]. Decorin makes receptor tyrosine kinase c-met inactivate and lead to inhibition of downstream β-catenin signaling which reduces cancer metastasis [38]. Biglycan, a 42 kDa core protein, is class I SLRP that is similar structure with decorin [39]. It is broadly expressed in ECM where it plays an important role as an essential signaling molecule and a key matrix component [39]. Biglycan mediates TLR activation and consequent NF-κB expression to influence cancer migration. Recombinant Biglycan has revealed to prompt gastric cancer cell migration by TLR- NF-KB-HIF-1α-VEGF mediated axis [40].

Hyaluronan (HA) is a ubiquitously expressed glycosaminoglycan. Although HA structure is simple, with repeating glucuronic acid and disaccharide chains of N-acety1-Glucosamine, its biology is wonderfully complex [41,42]. HA plays an essential role in approximately all areas of biology. Its interactions with extracellular binding partners or cell receptors are important in cell and organ development and, the cellular response to migratory signals, tissue inflammation and injury, cancer formation and resistance of cancer [43-45].

Fibrinogen is a 340-kDa fibrous glycoprotein made up of ~3000 amino acids. Two pairs of three-peptide (alpha, beta, gamma) molecular units connected by five symmetric disulfide bridges comprise the structure of this molecule [46], which depends on bound calcium for its structure and function.

The plasminogen activator system includes binding proteins, a proteolytic cascade of serine proteases and active broad-spectrum serine protease plasmin of inhibitors which control the spatial and

temporal generation [47]. The physiological roles of this system includes ECM degradation, fibrinolysis, cell signaling, and wound healing [48]. The plasminogen and associated proteins contribute to inflammation, and there has been a recent focus on the role that plasminogen has in the development, progression, and regulation of diseases with an inflammation component.

The integrin family of type I transmembrane adhesion receptors are principally responsible for mediating cell-matrix attachments, but integrins can also be participated in cell adhesion, signaling and migration in disease and health [49-51]. Integrins play key roles in epithelial cells. Integrins in epithelial cells have been confirmed to vital components of the signaling that serves to both establish and control epithelial adhesion to the basement membrane [52]. Integrins are adhesion receptors which mediate communication between the intracellular and extracellular environments and are vital for universal tissue.

ECM Structural Components of the Fetal Membrane

Collagen is the main structural component of fetal membrane ECM [53] and the distribution of ECM collagen types, includingI, III, IV, Vand VI, has been examined by immunohistochemistry [21]. The key component of fetal membrane ECM, type IV collagen, provides a holder for assembling other structural proteins for maintaining the tensile strength of fetal membranes. Types V and VII are minor fibrillar collagens, which afford an extra anchoring function for the basement membrane together with type IV collagen. Types VI and VII represent a small fraction of the collagen in the fetal membrane ECM. However, in conjunction with types Iand III, they form a critical anchoring fibrillar structure. The different types of fibrillar collagens (types, II, III, XXIV and XXVII) have different with their vulnerability to cleavage by matrix metalloproteinases (MMPs). MMPs participate in the action of physiological degradation and extracellular proteases [54]. Some MMPs family member have been found in the fetal membranes [55]. For example, type I collagen is less efficiently cleaved by MMP-1 than type III collagen [56,57]. ECM proteins affect cell morphology behavior through signaling by cell surface receptors, mainly by MMPs [9]. The presence of specific memebrane ECM molecules is determined by the velocity of their synthesis and their degradation.

ECM and Associated Signaling and Cytokine Expression Pathways

Cells can sense ECM stiffening via integrins through cytoskeletal filaments that induce changes within the cell and manage cell migration. So, stiffer ECM can provoke manufacture of heparin sulfate proteoglycans, fibrin and from the other side to integrins, fibronectin as a glycoprotein of the ECM binding from one side to extracellular collagen [58]. ECM stiffening can also enhance cytoskeletal tension by Rho/ROCK signaling activation and increase cell-ECM adhesion connecting the ECM to the cytoskeleton by local adhesion proteins [59,60]. Fork head box O (FoxO) proteins regulate ECM remodeling, inflammation and apoptosis. FoxO1, FoxO3, and FoxO4 belong to the FoxO subfamily of Forkhead transcription factors [61]. These related subfamily members are vital physiologic targets of protein kinase B (PKB)/phoshpatidylinositol-3 kinase (PI3K) signaling [62,63]. PI3K signaling can influence matrix stiffness and cell movement by integrin-mediated activation of FAK [64]. FoxO3 can reduce tissue inhibitor of MMP1 in human umbilical vein endothelial cells and induce MMP-3, MMP-9 and MMP-13 activity and expression in cancer cells [65, 66].

cytokines regulate MMP expression in fetal membranes. Research studies suggested that the pro-inflammatory cytokine TNF-α can activate the c-Jun N –terminal kinases (JNK) stress signaling pathway and, in turn, help nuclear import and subsequent activation of FoxO4 thus leading to the enhancement of MMP-9 gene transcription and enzymatic activity [67,68]. In contrast, *in vitro* studies with amnion cells showed that either tumor necrosis factor-α（TNF-α）or interleukin-1β (IL-1β) can increase secretion of the MMP-9 proenzyme but not activation [69]. TNF-α binding to its receptor can activate caspases, degradation of ECM, and apoptosis in fetal membranes, which in turn promotes pPROM [70]. An increase expression of MMP-2 and MMP-9, and a decrease of expression of tissue inhibitors of TIMP-1 and TIMP2 can increase the risk of pPROM. This is likely important as some studies have shown that the overexpression of MMP-1 and MMP-9 can be mediated by IL-1β release from activated macrophages. An important cellular source of prostaglandins (PGs) in intrauterine tissues is the amnion [71]. PG, by upregulating MMP-9, also may participate in membrane rupture [72]. MMP-9 is likely a critical mediator in degradation of the ECM of fetal membranes in normal parturition [73]. MMP-9 preferentially targets basement membrane elastin, collagen (collagen IV), and fibronectin [74,75] and may also participate in fetal membrane rupture through degradation of type IV collagen. I

L-1β is usually undetected in amniotic fluid during normal pregnancy, while IL-1β levels in amniotic fluid in preterm birth with and without infection is range from 100 to 2000 pg/ml [76, 77]. IL-1β plays a key role in inducing expression of MMP-9 in amniochorion in response to lipopolysaccharide (LPS) stimulation [78]. Further, LPS provokes immune system cells via binding cell-surface Toll-like receptor 4 (TLR4) and activating protein kinase, such as p38 kinase and NF-κB, leading to an overexpression of pro-inflammatory cytokines, increased production of matrix-degrading enzymes and adhesion molecules [79]. TLR4 is generally expressed via the fetal membranes, placental trophoblasts and the female

reproductive tract [80-82]. In some cases, elevated levels of MMP-8 are thought to be the result of increased proinflammatory cytokine IL-6 in the context of infection-induced inflammation [83,84]. In other cases of such inflammation, the observed increase in intra-amniotic lactic acid in the amniotic membrane suggests that an increase in anaerobic glycolysis may raise the production of MMP-8 thus weakening the maternal membrane [85]. However, the association between MMP-8 and IL-6 levels was unclear [85].

Pathophysiological Role of ECM in pPROM

Degradation of amniotic membrane ECM components, structural alterations in ECM and resulting biomechanical changes in the membranes [6] are hypothesized to participate in the pathway leading to membrane rupture at term and in pPROM. In addition, anomalous disruption of the ECM at the trophoblast layer may relate to a regional thinning or absence of decidua and an increase in trophoblast apoptosis [86-88]. Down regulation of ECM-receptor interactions has also been documented [89]. Several lines of evidence suggest a direct relationship between infection or inflammation and pPROM. This evidence includes the increased expression or activity of inflammatory mediators such as IL-1β, IL-2, IL-6, IL-12, IL-18, TNF-α, interferon γ (IFNγ), epidermal growth factor (EGF), C-reactive protein (CRP), soluble intercellular adhesion molecule I (ICAM-I) in pPROM [90-99]. It is likely that these molecules work participating in pathways and leading to disruption of ECM protein interactions.

Epigenetic Regulation of Long non-coding RNAs on the ECM in pPROM

Long non-coding RNAs (lncRNAs) are long single-stranded RNAs with no translational potential. LncRNAs function in regulating epigenetic and cellular processes through various mechanisms. By analyzing the present available studies of lncRNA transcripts within the reproductive system and the current understanding of the biology of lncRNAs, the important diagnostic and therapeutic roles of lncRNAs in the etiology of reproductive disorders have been illustrated [100]. LncRNA is a mediator of the outcomes of interaction at the maternal–fetal interface and in the biological mechanisms underlying trophoblast differentiation [101,102]. In addition to miscarriage, intrauterine grown retardation, preeclampsia, and gestational diabetes mellitus [103,104], a pathogenic role for lncRNA has been observed in human sPTB, wherein the epigenetic regulatory function of lncRNA was found to link social and environmental exposures and the outcome of pregnancy [105,106]. Down-regulation of lncRNAs on laminin, collagens, VLAα10, OPN, α6β1, and α/βDG, which also implied that these lncRNAs may be significant for the decreased synthesis of mRNA and leaded to weakening of the ECM. Several co-differentially expressed pairs of lncRNA–mRNA sharing the same genomic loci in sPTB were recognized as being associated with the infection-inflammation pathway and ubiquitine-proteasome system [107].

Conclusion

The above experimental and clinical data have identified the causal nature of intrauterine infection and cervix vaginal infection in explaining the progress of sPTB and pPROM. The inflammatory response can lead to the activation of mechanisms and resulting in labour. But in some cases, pregnancy with the infection can maintain to term without complications. In other cases, the major event is activation of myometrial movement, leading to the risk of sPTB. In other cases, the primary outcome is the secretion of MMP from fetal membranes, resulting in pPROM. Therefore, a better understanding of the relationship between the ECM and the pPROM remains limited and is elucidated to shed light on effective strategies to provide opportunities to prevent the potential risk of pPROM during pregnancy.

Conflict of Interest

No conflict of interest declared.

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