Collagen Type I/III Turnover

Subjects: Others

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The unique balance between the degradation activity of collagen specific MMPs and their natural tissue inhibitors indicates that TIMPs plays an important role in normal structural uterine changes during healthy pregnancy. Dysregulation of balance between MMPs and their TIMPs occurs in preeclampisa, leading to impaired fibrillar collagen type I and III turnover. This results in pathological changes in uterine structure and abnormal uterine ECM remodeling. MMP-1, MMP-13, TIMP-1, and TIMP-2 are biomolecules, tightly involved in these processes. MMP-1, MMP-13, TIMP-1, and TIMP-2 potential as preeclampsia biomarkers is very promising and possible clinical applications can hopefully be introduced soon.

Keywords: extracellular matrix ; collagen types I and III ; biomarkers ; preeclampsia

1. Collagen Type I Characteristics

Collagen type I is a major connective tissue protein. It increases the strength and stability of the cytoskeleton. The exceptional strength of skin, ligaments, tendons, and vessels requires a long protein chain characterized by repeated amino acid residues and a regular secondary structure.

Type I collagen is fibrillar collagen and a major part of the interstitial membrane's structure. It is the most prevalent type of collagen and a key structural composition of many tissues. It is found practically in all structures involving connective tissue. Type I collagen is the main structural protein of bone, skin, tendon, ligaments, sclera, cornea, and blood vessels, as well as an important component of other tissues. It is gathered in fibers forming a structural-mechanical scaffold (matrix) of bones, skin, tendons, cornea, blood vessel walls, and other connective tissues [1].

The COL1A1 gene produces the pro-alpha1 (I) chain. This chain combines with another pro-alpha1 (I) chain and also with a pro-alpha2 (I) chain (produced by the COL1A2 gene) to make a molecule of type I procollagen. These triple-stranded, rope-like procollagen molecules must be processed by enzymes outside the cell. Once these molecules are processed, they arrange themselves into long, thin fibrils that cross-link to one another in the spaces around cells. The cross-links result in the formation of very strong mature type I collagen fibers.

"Heterotrimers of two α1 (I) and one α2 (I) chains are the dominant isoform of type I collagen. Homotrimers of three α1 (I) chains are found in fetal tissues and some fibrous lesions. The homotrimeric isoform is more resistant to cleavage than collagenases. This may explain its abnormal accumulation and important role in the pathogenesis of tumors and fibrosis" [1].

In vivo, the triple helical fibers are mostly incorporated into a composite containing either type III collagen (in skin and reticular fibers) or type V collagen (in bone, tendon, cornea) [2][3]. Type I collagen provides tensile stiffness in tendons and fascia, while in bone, it defines considerable biomechanical properties concerning load bearing and tensile [4].

2. Collagen Type III Characteristics

Collagen Type III has a unique molecule structure, giving the connective tissue matrix a specific architecture [5]. Collagen molecules contain three identical or similar polypeptide chains called α-chains and contain at least one triplet helix collagen domain with repeating (Gly-X-Y) *n* sequences. Thus, every third amino acid is a glycine residue with frequently repeated proline and 4-hydroxyproline at the X and Y positions. In addition, all collagen contain non-collagen domains. Collagens type III form fibrils [6]. Type III collagen is a homotrimer of three a1 (III)-chains and is widely distributed in collagen I-containing tissues with the exception of bone [7]. It is an important component of reticular fibers in the interstitial tissue of the lungs, liver, dermis, spleen, and vessels. This homotrimeric molecule also often contributes to mixed fibrils with type I collagen and is also abundant in elastic tissues [8].

"Type III collagen is composed of one collagen α-chain, unlike most other collagens. This is a homotrimer containing three α1 (III) chains overlapped in a right triple helix. Type III collagen is secreted by fibroblasts and other types of mesenchymal cells, thus playing a major role in different inflammatory pathological conditions like lung damage, liver diseases, renal fibrosis, and vascular fibrosis diseases". Both collagen type III and type I are the main components of extracellular matrix (ECM). Biomarkers of Type III collagen turnover have been actively studied and different laboratory methods have been used for the detection of fibrosis [9].

3. General Features of Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of MMP (TIMPs)

Matrix metalloproteinases are a complex group of endopeptidases. They are a family of proteolytic enzymes with similar functional domains and a mechanism of action associated with the degradation of ECM components. MMPs are zinc-dependent proteases that can be activated by a number of cytokines and growth factors [10]. Metalloproteinases have the properties to attach to components of the extracellular matrix and in particular to collagen and elastin. MMPs are secreted by activated macrophages in the wall of arterial vessels. The ability of MMPs to change tissues is important from the point of view of normal and pathological physiology. Approximately 20 different types of MMPs are known, classified into groups according to the type of proteolytic substrate (component of the extracellular matrix) against which they act and degrade, respectively. The MMP group includes collagenases (MMP-1 and MMP-13), stromelysins such as MMP-3, gelatinases such as MMP-2 and MMP-9, and membrane MMPs. This classification based on the substrate of action was particularly useful years ago. With the accumulation of additional knowledge about the enzymatic activity of MMP, the benefit of this classification is questioned, as the substrate profile of the enzyme is more relative than absolute [11].

TIMPs, consisting of 184–194 amino acids, are inhibitors of MMPs. They are subdivided into an N-terminal and a C-terminal subdomain. Each domain contains three conserved disulfide bonds and the N-terminal domain folds as an independent unit with MMP inhibitory activity. TIMPs inhibit all MMPs tested so far, but TIMP-1 is a poor inhibitor for membrane-type (MT)1-MMP, MT3-MMP, MT5-MMP, and MMP-19 [12].

4. Matrix Metalloproteinases and Tissue Inhibitors of MMPs in Preeclampsia

4.1. MMP-1 Structure and Function

Collagenases (MMP-1, MMP-8, and MMP-13) cleave interstitial collagens I, II, and III into characteristic 3/4 and 1/4 fragments, but they can digest other ECM molecules and soluble proteins [13][14]. MMP-1, also known as collagenase-1, was the first MMP identified by Gross and Lapiere in 1962 [15]. "Humans express MMP-1 while rodents have two MMP-1 isoforms—namely, MMP-1a and -1b. MMP-1 cleaves both ECM and non-ECM substrates such as collagen, gelatin, laminin, complement C1q, IL-1β, and TNF-α, suggesting a crucial role in inflammatory and fibrotic responses" [16]. MMP-1 can also activate MMP-2 and -9, initiating an activation cascade. MMP-1 is an important member of MMP family, which particularly degrades interstitial collagen and is abundant in tissues of the placenta and decidua. TIMP-1 is a natural inhibitor of MMP-1 [17][18]. "The invasive capacity of trophoblasts has been associated with their secretion of MMP-1. The zymolytes of MMP-1 are collagen and metagelatin, which play major roles in trophoblast invasion" [13].

4.2. MMP-13 Structure and Function

MMP-13 plays a role in the degradation of extracellular matrix proteins including fibrillar collagen and fibronectin. It cleaves triple helical collagens, including type I, type II, and type III collagen, but has the highest activity with soluble type II collagen. "Can also degrade collagen type IV, type XIV and type X. Plays a role in wound healing, tissue remodeling, may play a role in cell migration and in tumor cell invasion" [19]. MMP-13 also play role in tissue repair and in progression of diseases such as cancer, arthritis, atherosclerosis, and aneurysm.

4.3. TIMP-1 Structure and Function

TIMP-1 is a glycoprotein, member of the TIMPs family [20]. It is expressed by several tissues [21]. This protein serves as natural inhibitor of the matrix metalloproteinases, which are involved in extracellular matrix degradation [14]. While TIMP-1 potently inhibits the activity of most MMPs, with the exception of MMP-2 and MT1-MMP, TIMP-2 is a potent inhibitor of most MMPs, except MMP-9 [22].

4.4. TIMP-2 Structure and Function

TIMP-2 inhibits specific types of MMPs, thus involving degradation of the extracellular matrix. TIMP-2 has ability to directly suppress the proliferation of endothelial cells. This leads to critical possibility for the encoded protein in the maintenance of tissue homeostasis by suppressing the proliferation of quiescent tissues in response to angiogenic factors, and by inhibiting protease activity in tissues undergoing remodeling of the extracellular matrix [23]. While TIMP-1 inhibits MMP-7, MMP-9, MMP-1, and MMP-3 better than TIMP-2, TIMP-2 inhibits MMP-2 more effectively than other TIMPs.

5. Collagen Type I and III Turnover in Normal Pregnancy

Collagen types I and III are the main proteins involved in the structure of the uterine wall. As the uterus grows during pregnancy, there is an intensified collagen turnover. It is well known that the uterine collagen structure has been shown to be disturbed in women with pre-eclampsia. Amino-terminal and carboxy-terminal propeptides of collagen type I and III play a central role in this process [24]. The human uterus is composed of a fibrous tissue framework consisting mainly of collagen types I and III [25]. It is, therefore, possible that in hypertensive disorders in pregnancy these collagens (which are mainly responsible for the coherence and supportive strength of the uterus) could be affected. Controlled collagenolysis and/or changes in collagen cross-linking will be needed to meet the demand of the growing uterine content to expand. As the uterus grows during pregnancy there is a high production and turnover of collagen proteins [26].

Collagen types I and III are major components of human cervical uterine connective tissue. During pregnancy, a remodeling of the cervical connective tissue takes place, with decreases in the concentrations of collagen and proteoglycans concomitant with an increase in the collagenolytic activity [27][28][29]. 70% decrease in the amount of collagen and the change in its organization is observed [30][31]. In abnormal conditions such as preeclampsia and gestational hypertension, the blood flow to both placenta and foetus is disturbed, favouring a microcirulatory ischaemia. Altered extracellular matrix turnover with MMP/TIMP dysbalance play a crucial role in these pathological processes [32][33].

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