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Altering of Collagens in Early Pregnant Mouse Uterus

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착상전 생쥐 자궁에서 콜라겐의 변화

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ABSTRACT : Specific endometrial preparation should occur during periimplantation period. That is a progress of serial differentiation and is absolute in implantation of embryo and successful pregnancy. Remodeling of tissues shown during embryogenesis is regulated by various factors including extracellular matrix (ECM). Marked changes during pregnancy are including embryo migration, decidual response, and differentiation of placenta in placental animals including human. These changes to successful implantation in embryo and uterus have to prepare the competence for attachment of embryo and uterus, and invasion defense of uterus. During these changes, ECM dramatically changes for maintaining the uterine and embryonic functions. The major component of most connective tissue is collagens. It is very complex and hard to explore the mechanisms for ECM modulation. Recently using high throughput methodology, PCR-select cDNA subtraction method, microarray, many candidate genes have been identified. Steroid hormones have fundamental role in implantation and maintenance of pregnancy. Dermatopontin, a regulator of collagen accumulation, is regulated spatio-temporally in the uterus by primarily progesterone through progesterone receptors at the time of implantation. Modulation of extracellular matrix is critically regulated by cascade of gene net-works which are regulated by cascade of sex steroid hormones. Pathological regulation of uterine extracellular matrix reported in diabetic patients. To know the extracellular modulation is essential to understanding implantation, feto-placental development and overcome the paths involved in female reproduction. Though ECM composed with very various components and it is complex, the present review focused on the fate of collagens during periimplantation period.

Key words : Implantation, Extracellular matrix, Collagen, Steroid hormones.

요 약 : 착상기 이전 자궁에서 특이적 자궁내막 준비가 진행되어야 하는데, 이는 자궁 내막의 점진적 분화로 배아의 착상과 성공적 임신에 절대적으로 필요하다. 배아 발생 동안에 관찰되는 조직의 재구성은 세포외 기질을 포함한 다양한 요인에 의해 조절된다. 임신 동안에 관찰되는 극적인 변화로는 배아의 이동, 탈락막 반응, 태반의 분화를 그 예로 들 수 있다. 배아와 자궁간의 성공적 착상을 위한 변화들은 배아와 자궁의 착상을 위한 능력 갖출 수 있도록 한다. 이러한 변화과정 중에, 콜라겐이 주성분인 세포외 기질의 극적인 변화가 진행된다. 이러한 변화는 매우 복잡하여 그 기작을 밝히는 것은 쉽지 않으나, 최근 들어 PCR-select cDNA subtraction 방법, microarry 방법 등 대단위 유전자 동정 방법들을 이용하여 많은 후보 유전자가 동정되었다. 스테로이드 호르몬은 임신과 임신 유지에 중요한 역할을 수행하며, 세포외 기질의 재구성을 엄격하게 성스테로이드 호르몬에 의한 유전자 네트워크를 통하여 조절한다. 자궁의 세포외 기질의 병리적 조절이 당뇨병 등에서 보고되고 있다. 세포외 기질의 재구성은 착상과 태아와 자궁의 발달을 이해하는 데 중요하고, 또한 생식과 관련된 질병을 극복하는 데 중요하다. 비록 세포외 기질의 구성성분이 매우 다양하고 복잡하여 논의할 것이 무척 많으나, 본 종설에서는 착상기를 전후한 시기에 콜라겐의 변화를 중심으로 논하였다.

INTRODUCTION

Simple columnar epithelium and stroma constitute the mucosal layer of the uterine endometrium in primate including human. Epithelial cells are covered with mucose and are ciliated in women that are continuous with many simple glands that extend to the base of the endometrial-myometial border (Ferenczy & Richart, 1973; Ferenc-

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zy, 1977). Stroma is a highly cellular connective tissue with an amorphous extracellular matrix (Deligdisch *et al.*, 1978). In rodent uterus, endometrium is the mucosal layer, consisting of the lamina propria, the lining epithelium, the uterine glands, and many blood vessels. The stromal cells shaped small polyhedral cells exist between epithelium and myometrium (Brenner & Slayden, 1994). Uterus is one of the most dynamic organs that rapidly change structures and functions. There are dramatic changes within both the ECM and the embedded cells of the uterine endometrium during the reproductive cycle.

The Extracellular Matrix (ECM) is responsible for dynamic structural framework. In addition to that, the ECM of the endometrium interacts with its associated cells to mediate the behavior of cells, i.e. cell adhesion, migration and differentiation, proliferation, and immune response (Aplin, 2002; Chrobak *et al.*, 2004; Haralson & Hassell, 1995; Schutze *et al.*, 2001). Its components are locally produced by the embedded cells, and these cells help the orientation of the matrix which is produced outside the cell. The major macromolecules of ECM of endometrial matrix are collagens, elastin, fibronectin, laminin, nidogen, proteoglycans, glycosaminoglycans (Reichardt, 1999). Defects of ECM are intimately associated with a number of disease including, interstitial pneumonias, cancer, fibrotic disease (Cardin *et al.*, 2007; Donahue *et al.*, 2006; Felicio *et al.*, 2007; Stumpf *et al.*, 2006).

Collagen is one of the major components of the ECM. From the histochemical results, collagen accumulation is dramatically changed during periimplantation in the uteri of mouse. It is mainly localized in the ECM of stromal cells on day 4 of pregnancy, localized in the epithelial basal lamina surrounding the implantation sites on day 5, but it is hard to find the collagens in the decidualized zone (Kim & Cheon, 2006). Collagen concentrations are decreased at the implantation sites compared with interimplantation tissues during early pregnancy (Hurst *et al.*, 1994; Kim & Cheon, 2006; Myers *et al.*, 1990).

CHANGES OF EXTRACELLULAR MATRIX IN THE ENDOMETRIUM DURING IMPLANTATION

Essential function of the ECM has been well known in the uterus with respect to both the development of embryo and the differentiation of the uterine tissue (Kim & Cheon, 2006; Klaffky *et al.*, 2006). Muc-1 (Surveyor *et al.*, 1995), laminin (Church *et al.*, 1996), trophinin (Fukuda *et al.*, 1995), carbohydrate epitopes (e.g. H-type 1 antigen), heparan sulfate proteoglycan, integrins, and the trophinin-bystin/tastin complex (Giudice, 2002) are involved in the generation of a receptive uterine state. Hyaluronan (Brown & Papaioannou, 1992) and decorin (Moscatello *et al.*, 1998) are involved in the regulation of cellular functions, such as the differentiation and proliferation of endometrial cells for the preparation of implantation or decidualization.

Decidual reaction can occur in the implantation competent uterus under the proper hormonal regiments. Decidualization is an epithelial differentiation of the stromal fibroblasts. In rodents, the decidual reaction is a consequence of the blastocyst attachment of non-embryonic stimuli. Endometrial differentiation implies not only the proliferation and the differentiation of the fibroblasts but also a glandular atrophy, a neoformation of the fibrous stromal network, a vascular proliferation and immunological modification (Guillomot *et al.*, 1993; Ono *et al.*, 1989). Physiological changes of uterine endometrium require the degradation of ECM and synthesis of new ECM compounds.

COLLAGENS ARE A MAJOR COMPOUND OF EXTRACELLULAR MATRIX

At least 27 different types of collagen are founded in vertebrates (Baum & Brodsky, 1999; Linsenmayer, 1991; Persikov & Brodsky, 2002). Collagens are found in unique, tissue-specific patterns that arise during development in defined temporal and spatial patterns, and that exhibit different functional properties (Birk & Linsenmayer, 1994).

The most abundant extracellular protein is connective tissue type collagen in uterine endometrium. In the non-pregnant uterus, the best characterized components of the endometrial stroma are fibronectin and types I, III, V, and VI collagen (Aplin *et al.*, 1988; Iwahashi *et al.*, 1996). Content of collagen was increased until day 4 of gestation

and mainly localized in the ECM of stromal cells and basal layer of epithelial cells. Interestingly collagen was totally absent in the apical ECM of the luminal epithelial cells through early pregnancy. On day 5 of gestation, the intensity of the collagen at the implantation site was dramatically decreased in the stromal cells that surround the embryo and mainly localized in the luminal epithelial basement membranes. In decidualization zone, the content of collagen was very low (Kim & Cheon, 2006).

Decidaulizing cells make new components for ECM and new basement membrane. Those are synthesizing laminin, entactin, fibronectin, type-IV collagen, and heparan sulfate proteoglycan (Finn, 1971; Kisalus *et al.*, 1987; Wewer *et al.*, 1986). Modification of collagen is including (1) fibrils, which were arranged in parallel bundles in nonpregnant animals, became organized as baskets around decidual cells; (2) very thick collagen fibrils with very irregular profiles appeared around decidual cells. The modifications of the collagen fibrils show an adaptation of the endometrium to better support the decidual cells while they hold the embryos during the beginning of their development. The deposition of thick collagen fibrils in the decidua may contribute to form a barrier that impedes leukocyte migration within the decidua (Carbone *et al.*, 2006).

1. Collagen Type I

Collagen type I forms the structural support for the endometrium during the establishment of pregnancy (Teodoro *et al.*, 2003). Collagen type I is found to be very little in primary and secondary decidualized tissue in contrast to the outer nondecidualized stroma and myometiral tissue (Clark *et al.*, 1993). During uterine differentiation, decidaulizing cell phagocyte the collagen type I and produce basement membrane components including laminin, collagen type IV (Farrar & Carson, 1992; Zorn *et al.*, 1986). It is one of the hallmarks of normal stromal differentiation to deciduas.

After implantation the thickening of collagen fibrils occurs in the decidualized areas of the endometrial stroma with site specific patterns. The fibrils are heterotyic structures formed at least by type collagens type I, type III, and type V (Spiess & Zorn, 2007).

2. Collagen Type III

Collagen III is a fibrillar collagen with known roles in differentiation and migration (Olsen *et al.*, 1999). It is both secreted and phagocytosed by mouse decidual cells (Zorn *et al.*, 1989). It is localized in interstitial compartments underlying luminal and glandular epithelium and surrounding blood vessels, while the epithelial cells are negative in preimplantation uterus. Metabolism and redistribution of collagen III occur with the onset of endometrial receptivity. Collagen III distribution changes from dense fibrils in the proliferative phase to matrix channels in the secretary phase (Aplin *et al.*, 1988). There is a consistent absence of subluminal collagen III on the antimesometrial side at the time of decidualization in mouse or rat (Hurst *et al.*, 1997; White *et al.*, 2004). It also finds in first trimester deciduas as well as endometrial stroma throughout the menstrual cycle (Aplin *et al.*, 1988; Kisalus *et al.*, 1987). In mouse, the decidualized areas of the endometrial stroma constructed with stromal cells and collagen fibrils formed with type collagens type I, type III, and type V (Spiess & Zorn, 2007).

3. Collagen Type IV

During decidualization, decidualized cells synthesize type IV collagen (Wewer *et al.*, 1986). It expresses in both primary and secondary decidual zones and persists through day 8 of pregnancy in mouse uterus (Farra & Carson, 1992). In baboon and bovine uterus, collagen type IV localize in the basement membrane of glandular epithelium and blood vessels. Its expression also increases at the implantation site (Fazleabas *et al.*, 1997; MacIntyre *et al.*, 2002). In human, collagen type IV also showed similar expression and localization patterns with other mammals. It distribute exclusively in the basement membrane of the endometrial glands and in the wall of blood vessels during the proliferative and secretory phases. In decidualized area strong staining for type IV collagen recognize in the pericellular region of endometrial stromal cells (Iwahashi *et al.*, 1996; MacIntyre *et al.*, 2002). Such a spatio-temporal and site-specific localization suggest that collagen type IV helps to prevent the uncontrolled trophoblast invasion into the uterine wall.

4. Collagen Type V

Amongst interstitial components, collagen type V is present in endometrial stroma throughout the menstrual cycle as well as in first trimester deciduas in human endometrium (Aplin *et al.*, 1988). In mouse, a collagen type V levels are very low in the primary decidual tissue and are not detected in developing secondary decidual tissue (Hurst *et al.*, 1997). Recently it is suggested that collagen type V involve to the rapid increase of the diameter of collagen fibrils of the mouse deciduas (Spiess & Zorn, 2007).

5. Collagen Type VI

ECM of undifferentiated uterine tissue of rats has abundant of collagen type VI. However after initiation of decidual response, collagen type VI essentially disappears from the matrix of the antimeometrial stomal compartment (Mulholland *et al.*, 1992). Collagen type VI expression and localization patterns are similar with rat in mouse. High levels of collagen VI protein and mRNAs are present in the endometrium and myometrium of the uterus up to Day 4.5 of pregnancy. No collagen type VI protein or mRNAs present in any tissue layers of the embryo on Days 5.5 or 6.5 of gestation (Dziadek *et al.*, 1995). In human endometrium, collagen type VI is abundant in endometrium in the proliferative phase, but is progressively lost in the secretory phase and decidua, in which it is retained only in blood vessel walls (Aplin *et al.*, 1988).

ECM MODELING PROTEINASES AND PROTEINASE INHIBITORS

Proteinases involved degradation of ECM are to be a key modulator during implantation and decidualization (Cheon *et al.*, 2004; Vu & Werb, 2000). Those do many things during pregnancy in several ways: 1) to degrade the ECM molecules and make a space for cell migration or division, 2) to alter the ECM micro-environment and result in alteration in cellular behavior, 3) to modulate the activity of biologically active molecules by direct cleavage, release from bound stores, or the modulating of the activity of their inhibitors. Therefore the remodeling of ECM by proteinase is essential to the uterine differentiation, embryo development, and implantation processes. Proteinase activity is controlled by decidua formation and specific proteinase inhibitors. The balance between proteinases and those inhibitors are critical factor for tissue remodeling.

1. Matrix Metalloproteinases and Matrix Metalloproteinase Inhibitors

The matrix metalloproteinases (MMPs) are a family of ECM-degrading enzymes that share common functional domains and activation mechanisms. These are Ca^{2+} - and Zn^{2+}-dependent endopeptidases, and are synthesized as secretion form or transmembrane form. There are now many families more than 20 members. There are several distinct subgroups based on preferential substrates or similar structural domains: Collagenases that are activity against denatured collagens, gelatinases that have high activity against denatured collagens, stromelysins that degrade noncollagen components of the ECM, membrane-type MMPs (MT-MMPs) that are transmembrane molecules, and other less characterized members (Sternlicht *et al.*, 2000; Vu & Werb, 2000).

Matrix metalloproteinases and its inhibitors (tissue inhibitors of matrix metaloproteinases) are thought to be key mediators for matrix degradation during implantation and decidualization (Behrendtsen *et al.*, 1992; Cross *et al.*, 1994). It also thought to play important roles during embryonic development, as ECM remodeling is a critical for morphogenesis, or influence many cellular functions. During embryonic invasion, trophoblasts show MMP activities and express high level of MMP-9, and improve the trophoblast from invading and degrading ECM (Lei *et al*, 2007; Behrendtsen & Werb, 1997). Substrates for gelatinases include type IV collagen and gelatin. Ets2 is essential for placental function, mediating growth factor signaling to key target genes including MMP-3 (stromelsin-1), MMP-9, and MMP-13 (collagenase 13) in different cell types. In trophoblsts, MMP-9 expression is under the control of Ets-2. Ets-2-null mice is embryo lethal because the insufficient MMP-9 activity (Yamamoto *et al.*, 1998). TIMP-1 overexpressing mice also showed similar placental phenotypes with Ets-2-null mice (Alexander *et al.*, 1996). It is revealed that other MMPs and/or other metaloproteinases

contribute to ECM remodeling, but there is limit to understanding the role of MMPs.

2. Serine Proteinases

It has been suggested that serine proteinases are involved in implantation. Urokinase type plasminogen activator (uPA) requires for the embryo implantation to the uterine endometrium through activation of ECM-degradation (Grevin *et al.*, 1993; Teesalu *et al.*, 1996). uPA activity increased toward the blastocyst stage (Aflalo *et al.*, 2004) and high level of uPA localize in invasive trophoblast cells, while the same cells do not synthesize plasminogen activator inhibitor type 1 (PAI-1) (Teesalu *et al.*, 1996). uPA and PAI-1 co-localized with the expression domains of uPAR and alpha 2MR/LRPO (Teesalu *et al.*, 1996).

Proprotein convertase subtilisin proprotein convertase (SPC)-6 expressions involve in uterine ECM remodeling. SPC-6 is induced during the decidual cell response (Wong *et al.*, 2002). In E6.5 section, proprotein convertase SPC-6 locaized in differentiated deciduas, and it is overlapping and extending beyond the region previously described for the metalloproteinase inhibitor TIMP-2 or TIMP-3 (Rancourt & Rancourt, 1997; Wong *et al.*, 2002).

Implantation serine proteinases (ISP1 and ISP2) are co-expressed in mouse uterine endometrium throughout the peri-implantation period, under the positive influence of progesterone (O'Sullivan *et al.*, 2002). It localizes to the site of embryo invasion during implantation (Huang *et al.*, 2004; Sharma *et al.*, 2006). A tryptase inhibitor, gabexate mesylate, inhibits the ISP activity, and arrest implantation in utero (Sharma *et al.*, 2006).

3. Cystein Proteinases

Cystein proteinases play a regulator of normal development for embryonic development and decidual differentiation. It is suggested that cystein proteinases can activate latent proteinase activity from the basement membrane and thus initiate a novel proteolytic cascade (Guinec *et al.*, 1993). Cathepsin L activates pro-uPA and cathepsin B activates the metalloproteinase, stromelysin (Goretzki *et al.*, 1992; Murphy *et al.*, 1992). Cathepsin B and cathepsin L are capable of digesting matrix molecules, including laminin, collagen IV and fibronectin (Guinec *et al.*, 1993; Mason *et al.*, 1986). Cathepsin B and cathepsin L protein are localized to the mature, invasive trophoblast giant cells (Afonso *et al.*, 1997). Cathepsins expression and localization changes related with the phase of the cycle in human endometrium. Cathepsins H and K are significantly lower in secretory phase endometrium in comparison with proliferative phase endometrium. Cathepsins B, H. K and S distribute in the surface epithelium of the endometirum (Jokimaa *et al.*, 2001).

Cystatin C, the main inhibitor of cathepsins, is a major product of the decidualizing stroma and locating closely to the embryos during implantation. Inhibition of cysteine proteinase activity during early implantation causes abnormal embryo development and uterine decidualzation (Afonso *et al.*, 1997; Hamilton *et al.*, 1991). Interestingly, cathepsin L, which is expressed in giant trophoblast cells, is one of the targets of cytotoxic T lymphocyte antigen-2 β (CTLA-2 β), a cystein proteinase inhibitor. Expression of CTLA-2 β in uterine stroma during PR-mediated decidualization plays a critical role in regulation of embryo implantation through interaction with cathepsin L (Cheon *et al.*, 2004).

4. Collagen Synthesis Regulating Gene Expression

Cell proliferation and endometrial remodeling are based on synthesis and degradation of some molecular of the extracellular matrix. Therefore collagen accumulation or disappearing is critically regulated by very complex net-work of various factors. All of these events are orchestrated by a precise sequence of ovarian steroid hormones and cytokines.

TGF β and PDGF stimulate collagen synthesis by fibroblasts whereas glucocorticoids inhibit its synthesis. It is known that progesterone regulate expression of ECM in the pregnant rat myometrium (Shynlova *et al.*, 2004). Serotonin regulate the collagen type I mRNA expression in rat uterine smooth muscle cells. It down regulate the gene for type I collagen and other extracellular matrix proteins (Passaretti *et al.*, 1996).

Downstream targets of IL-II receptor α (IL-11 R α) include extracellular matrix proteins; collagen III α 1, se-

creted acidic cysteine-rich glycoprotein, biglycan and nidogen-1 (entactin) (White *et al.*, 2004). Biglycan interacts with collagens. IL-11 induces the tissue inhibitor of metalloproteinases (TIMP)-1 (Hermann *et al.*, 1998). These genes are suggested to involve in decidual differentiation because IL-11 Rα null mice are infertile due to disrupted decidualization (Robb *et al.*, 1998).

Ovarian sex steroid hormones have fundamental role during pregnancy. Estrogen control the ECM integrity of uterus through ER and expression regulation of a number of genes involved in collagen turnover (Cox & Helvering, 2006; Pastore *et al.*, 1989). In ovariectomized rat, collagen bundles do not appear to be as densely packed as in control tissues and large clear spaces are evident in the ECM. Administration of estrogen results in reappearance of collagen bundles (Pastore *et al.*, 1989). Progesterone also involved in the modulation of uterine endometrial ECM (Anthony *et al.*, 2003; Cheon *et al.*, 2002; Ghosh *et al.*, 1996; Kim & Cheon, 2006).

Dermatopontin plays a key role in collagen fibril organization (Cooper *et al.*, 2006). During early pregnancy, dermatopontin mRNA is expressed both in the luminal epithelial cell and stromal cells in highly spatio-temporal manner. It is well known that the function of dermatopontin is the acceleration of collagen fibril formation *in vitro* and *in vivo* (Takeda *et al.*, 2002; MacBeath *et al.*, 1993). Interestingly the spatio-temporal patterns of dermatopontin shifted from luminal epithelial cell to stromal cells during periimplantation period. Dermatopontin expression and localization pattern overlaps with the collagen accumulation pattern. Unlike the genes involved in embryo attachment, based on this study, the data support the hypothesis that dermatopontin has a role in the preparation or the matrix preparation through ECM accumulation and reorganization for the uterine stroma and epithelial cells (Kim & Cheon, 2006).

COLLAGEN ASSEMBLY

The synthesis of fibril-forming collagen is complex and involves many steps. The essential steps including, synthesis of collagen chains in endoplasmic reticulum, post-translational modification to glycosylation, helix formation proceeds from the carboxyl-terminus as an intrinsic property, and fibril formation. The fibril forming collagens (FFCs) that constitute collagen thin fibrils contains a long, continuous, uninterrupted-Gly-X-Y-repeat amino acid sequence. In that portion of the molecule, the three chains are wound into a compound triple helix structure with a high axial ration. The aggregation of the fibrils into fibers and fiber bundles regulated both by the collagen-secreting cells and by the presence of other matrix macromolecules, including fibril-associated collagen (Gordon & Olsen, 1990; Birk & Linsenmayer, 1994). The molecular mechanisms by which cells insure that fibrils form in the right place, with the right shape, and at the right time must be determined (Prockop *et al.*, 1993).

PATHOLOGICAL PHENOMENON

Defects of ECM are the reason of pathological phenotype in cell, tissue and organs. Mutation of collagens causes the imperfects of organogenesis including osteogenesis (Cabral *et al.*, 2006; Makareeva *et al.*, 2006). In here just few types will be discussed.

Pro-inflammatory agents' overproduction is observed in the uterus during implantation from experimental models of diabetes. These pro-inflammatory agents lead to the intrauterine activation of matrix metalloproteinases, proteases involved in remodeling the extracellular matrix during implantation and feto-placental development, and result in disfunction of the embryo-uterus interaction (Garris & Smith, 1983).

Classical or vascular type Ehlers-Danlos syndrome is a genetic disorders caused a defect in collagen synthesis. Pregnancy can be life-threatening caused by rupture of uterus in classical or vascular type Ehlers-Donlos syndrome variant (Lane, 2006; Rudd *et al.*, 1983).

In addition, abnormal distribution of collagens during preimplantation is observed in habitural abortion women (Kuznetsova *et al.*, 2002). Altering of the ECM components during implantation causes the defective decidualization (White *et al.*, 2004). In normal fertile women collagen type IV is localized as mentioned previously, but it is ab-

sent from all endometrial regions in the women suffering from unexplained infertility (Bilalis *et al.*, 1996).

CONCLUDING REMARKS

To keep the successful pregnancy, the uterus has to modulate itself ECM. Previously known genes, however, cannot account for the full range of physiological and biochemical events in the ECM in the periimplantation uterus. Recently using PCR-select cDNA subtraction method, microarray, many candidate genes have been identified ECM. However, remodeling mechanisms are still unmasked and are the subject of intense investigation.

Evidences discussed here suggest that modulation of ECM during implantation is orchestrated through a series of trafficking events. Many unanswered questions remain regarding the appropriateness of generalizing processed observed during implantation. It would be interesting to know how modulate the ECM of uterine endometirum. The innovation of new technologies for investigation ECM remodeling presents an opportunity to solve the clues for the complex ECM remodeling for pregnancy.

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