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REVIEW ARTICLE

Regulation of Extracellular Matrix Remodeling Associated With Pelvic Organ Prolapse

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Pelvic organ prolapse (POP), like stress urinary incontinence, has a significant impact on women's quality of life. POP results from a defect of the uterosacral/cardinal ligament complex, anterior vaginal wall, and other supportive tissues. However, there is a paucity of information about the etiology and pathophysiology of POP because of its multifactorial and heterogeneous risk factors. Recent reports of women with POP identified changes in the status of the connective tissue, of which the extracellular matrix (ECM) comprises the major component. Accelerated remodeling in patients with POP is caused by biochemical changes of the ECM, e.g., collagen, elastin, and stromal cells. Myofibroblasts play a role in ECM remodeling and can be modulated by matricellular regulators, e.g., transformation growth factor (TGF)- β , thrombospondin (TSP)-1, and matrix metalloproteases (MMPs). The homeostasis of MMPs with the lysyl oxidase family and fibulin ensure ECM integrity. Disturbances in the balance between synthesis/assembly and degradation of ECM proteins in the pelvic floor may result in POP. The high recurrence rate after pelvic reconstructive surgery necessitates the use of an adjuvant synthetic mesh. With the establishment of an *in vitro* model, our study showed that the interplay among the ECM, myofibroblasts, and a synthetic mesh can determine the usefulness of the synthetic mesh in pelvic reconstructive surgery. It was hypothesized that accelerated remodeling in patients with POP is caused by biochemical changes in ECM proteins, myofibroblasts, and their regulators. Further studies are needed to elucidate the following issues: first, whether women with POP have abnormal synthesis and/or degradation of the ECM, and different amounts of stromal cells (myofibroblasts); second, whether myofibroblasts exhibit different ECM protein productions under the regulation of MMP, TSP-1, and TGF- β ; and third, whether ECM matricellular proteins, e.g., TSP-1 and TGF- β , can modulate the biologic responses of host stromal cells to a synthetic mesh used in pelvic reconstructive surgery. This will be very informative for the further advancement of our understanding and treatment of pelvic floor reconstruction.

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1. Pelvic Organ Prolapse is Associated With Abnormal Extracellular Matrix Homeostasis

Pelvic organ prolapse (POP), like stress urinary incontinence (SUI), is prevalent in women, adversely affects their quality of life, and worsens with age. In the Women's Health Initiative study, 41% of women aged 50–79 years showed some degree of POP, including cystoceles (34%), rectoceles (19%), and uterine prolapse (14%).¹ The anterior vaginal wall and the uterosacral ligament/cardinal complex are the main support tissues for the bladder base and uterus (or vaginal stump), respectively. POP and/or SUI can have a significant impact on women's quality of life. Pelvic connective tissue resilience decreases with vaginal delivery, menopause, physical labor, chronic lung diseases, and so on.² The prevalence of POP increases as women age. The lifetime risk of undergoing prolapse or continence surgery is 11.1%, with a high recurrence and a necessity for reoperation of up to 29.2%.³ There are some risk factors for POP recurrence, e.g., poor tissue quality, impaired healing, chronic diseases with persistent high intra-abdominal pressure (due to obstructive pulmonary disease, asthma, or constipation), and age 60 years or above.⁴ POP is caused by mechanical, myogenic, neurological, and connective tissue factors. Although some reports identified changes in the connective tissue status in women with POP and/or SUI, there is a paucity of information about the etiology and pathophysiology.

A possible relationship between POP and connective tissue was indirectly implied by the repeated association of clinically significant POP and connective tissue diseases, e.g., Marfan or Ehlers-Danlos syndrome with joint hypermobility.^{5,6} Normal connective tissue contains relatively few cells with abundant extracellular matrix (ECM). The ECM is made up of water, collagen, elastin, and a ground substance, which are produced by fibroblasts. POP results from ECM alterations, e.g., collagen (types I, III, IV, V, and VI), elastin, and glycoproteins (fibronectin, vitronectin, and laminin), as well as the recruitment of stromal cells, e.g., fibroblasts, endothelial cells, and inflammatory cells.⁷ Collagen fibers form the structural framework and the resisting tensile force of tendons.⁸ Connective tissue alterations might eventually lead to failure of even the most technically sound POP repair.

Collagen types I and III are the two main constituents of interstitial connective tissue. Type I collagen is ubiquitous, with large amounts present in the skin, ligaments, fascia, organ capsules, cartilage, and tendons. Type III collagen is abundant in loose connective tissue, e.g., the skin, uterus, aorta, lungs, and ligaments. Type III collagen is the initial collagen laid down in wound healing and is usually replaced by type I collagen over several months.⁸ Types I and III have distinct physical properties and their relative proportions influence tissue functions.

Type I is responsible for the mechanical strength in connective tissues, whereas type III appears to play a role in tissue elasticity and extensibility.⁹ However, changes in collagen subtypes remain controversial according to different literature. Moalli et al reported increased type III collagen in the full-thickness vaginal apex in women with POP relative to those without POP.¹⁰ They suggested that this tissue is actively remodeled under biomechanical stresses associated with POP. Gabriel et al also reported that type III collagen expression in the uterosacral ligament was significantly increased related to the presence of POP ($p < 0.001$) rather than age or parity.⁹ The higher type III expression or the decrease in the type I/III ratio might adversely weaken the tensile strength and elasticity of pelvic tissues, with no difference in collagen I expression.⁹ On the contrary, Lin et al reported that there was significantly less type III collagen in the anterior vaginal wall of women with POP. The quantitative immunoreactivities of collagen types I and III had significant positive correlations with aging, but not with POP itself.⁷ Liapis et al also reported a similar finding after assessing the uterosacral ligament in women with POP.¹¹ Compared to elastin, which allows the tissue to stretch and elongate up to 70% of its length and return to its original contour, unruptured collagen can elongate only 4% prior to failure.⁸ Klutke et al reported altered metabolism and a significant decrease in elastin in the uterosacral ligament of women with POP.¹²

2. ECM Remodeling is Regulated by Matricellular Regulators

Matrix metalloproteases (MMPs) are key regulators of connective tissue degradation, which are involved in physiologic and pathologic processes, including wound healing, tissue remodeling,¹³ tumor invasion, and tumor metastasis.¹⁴ MMPs are a family of highly conserved, zinc-dependent endopeptidases that maintain the turnover of connective tissues throughout the body.¹⁵ They regulate many biologic processes through the release, activation, or sequestration of growth factors, growth factor-binding proteins, cell surface receptors, and cell-cell adhesion molecules.¹⁴ These enzymes are critically involved in the devastating effect of ECM remodeling and in the healing process of injured ligaments.¹⁶ Modulation of the ECM microenvironment can potentially change cell-matrix interactions associated with cell movement. This highlights the importance of ECM remodeling in physiologic and pathologic conditions. Among MMP family members, MMP-2 is a ubiquitous, largely constitutively expressed enzyme, while the expression of MMP-9 tends to be more localized and regulated. Moalli et al found increased activation of MMP-9 expression, but no change in the expressions of proMMP-9, proMMP-2, or active MMP-2, using quantitative zymography in histologically confirmed full-thickness

vaginal specimens in patients with POP.¹⁰ Phillips et al found an increase in proMMP-2 expression but no difference in active MMP-2 or proMMP-9 expressions using zymography in full-thickness vagina in patients with POP.¹⁷ Gabriel et al found increased active MMP-2, but not MMP-1, expression in the uterosacral ligament by immunohistochemistry in patients with POP.¹⁸ The difference in these results most likely reflects the disparate tissues targeted for analysis and different methods of protein quantification. In summary, epithelial specimens showed high MMP-2 levels,¹⁷ while subepithelial, muscularis, and adventitia specimens showed high MMP-9 levels.¹⁰ All of the data point to a condition in which the remodeling of connective tissue is accelerated in the vagina and supportive tissues in women with POP relative to control subjects.¹⁵ The activities of MMPs are regulated by endogenous inhibitors referred to as tissue-derived inhibitors of metalloproteases (TIMPs), transformation growth factor (TGF)- β , and thrombospondin (TSP)-1.¹³ Increased MMP expressions, which parallel significant reductions of TIMPs affect collagen turnover in women with POP.^{19,20} TGF- β transforms epithelial cells and activates MMP production during pathologic conditions.^{21,22} TSP-1 inhibits the activities of MMP-2 and MMP-9 via direct interactions with these proteases in specific regions.^{23,24} Modulation of the ECM microenvironment can potentially change cell-matrix interactions associated with cell movement, which highlights the importance of ECM remodeling in physiologic and pathologic conditions.

Another research field is the homeostasis between the lysyl oxidase (LOX) family and fibulin.²⁵ LOXs are extracellular copper-dependent monoamine oxidases, secreted by fibroblasts and smooth muscles. LOXs catalyze a key step in the posttranslational cross-linking of elastin and an element of the scaffold to ensure spatially defined deposition of elastin. Fibulin is a calcium-dependent elastin-binding protein, and it determines the elastic fiber organization. LOX-like 1 (LOXL1) protein specifically localizes to sites of elastogenesis and interacts with fibulin-5.²⁵ The failure of elastic fiber homeostasis leads to POP.²⁶ Reductions in the mRNA and protein expression levels of LOX family enzymes were noted in women with POP.²⁵ Collectively, these alterations in ECM proteins may play specific biochemical roles in the etiology of POP.²⁶ MMPs, as well as TIMPs, are in homeostasis with the LOX family and fibulin to ensure the ECM's integrity. Disturbances in the balance between the synthesis/assembly and degradation of ECM proteins in the pelvic floor during aging and parturition may result in POP.

3. Myfibroblasts Play Important Roles in ECM Remodeling During POP Processes

Fibroblasts are the major cellular component of the ECM. Their biologic behaviors significantly affect

ECM remodeling. Alpha-smooth muscle actin (α -SMA)-containing contractile fibroblastic cells, i.e., myofibroblasts and activated fibroblasts, were identified as playing possible roles during healing processes by restoring tissues *in situ* via ECM contraction.²⁷ The appearance of differentiated myofibroblasts may have multiple origins in different pathological situations.²⁸ Myofibroblasts are involved in maintaining tissue homeostasis in both the intact and remodeled anterior cruciate ligament.²⁹ It is generally accepted that modulation of fibroblastic cells towards the myofibroblastic phenotype, with acquisition of specialized contractile features, is essential for connective tissue remodeling during normal and pathological wound healing.³⁰ Yet myofibroblasts still remain one of the most enigmatic of cells, because of their transient appearance in association with connective-tissue injury and difficulties in establishing their role in the production of tissue contracture.³⁰

Myofibroblasts can be regulated by ECM matrix-cellular regulators, e.g., TGF- β and TSP-1. TGF- β is a potent fibroblast activation and transdifferentiation factor.³¹ Myofibroblast contraction can activate latent TGF- β from the ECM.³² In our previous study, TGF- β activated fibroblasts with migratory ability, as well as the α -SMA expression level, a typical marker of myofibroblasts.³³ TSP-1 potently exerts an inhibitory effect on the migration and invasion of myofibroblasts, but has little effect on the α -SMA expression level.³³ In addition to the inhibitory effects on myofibroblasts, TSP-1 inhibits the activities of MMP-2 and MMP-9 via direct interactions with these proteases in specific regions.^{23,24} Therefore, TSP-1 can potentially affect ECM remodeling via two aspects, by inhibiting fibroblast migration³⁴ and modulating MMPs.³³

4. The Biological Response of Host Stromal Cells to a Synthetic Mesh is Unclear

The high recurrence rate after pelvic reconstructive surgery necessitates the development of more-refined reconstructive surgical methods.³ Although the use of synthetic prostheses for sacrocolpopexy is well established, the use of prostheses for repair of isolated anterior and posterior compartment defects remains controversial. Several lines of research have suggested that autologous tissues used in pelvic reconstructive surgery are themselves altered and weakened in women with POP.^{35,36} Whether those tissue alterations are primary or secondary to the pelvic floor disorder remains unknown. There are no long-term studies with sufficient patient numbers to draw conclusions as to which current prosthesis, either synthetic or biological, is superior for vaginal surgery. Tension-free vaginal meshes (TVMs) with procedural kits which include disposable insertion needles, retrieval devices, and large pieces of

polypropylene mesh are increasingly being adopted. The available products at present include intravaginal slingplasty (IVS) (Tyco Healthcare, Norwalk, CT, USA), Prolift (Ethicon, Somerville, NJ, USA), Perigee, Apogee, Elevate (American Medical Systems, Minnetonka, MN, USA), and Avaulta (Bard, Gainesville, VA, USA). Some authors have already described their success performing this type of repair,³⁷ nevertheless, great care and consideration should be devoted to actual and theoretical short- and long-term risks, many of which have not been fully elucidated.

Our recent review showed that patients with primary and those with recurrent POP may benefit from the use of adjuvant materials in pelvic reconstructive surgery.³⁸ Different prostheses, either synthetic (absorbable, non-absorbable, or mixed) or biologic (autologous, allograft, or xenograft donor tissue), have emerged as adjuvant materials for the purpose of integrating with host tissues and supporting attenuated areas.³⁹ However, ideal materials to achieve the goals of being sterile, durable, non-carcinogenic, inexpensive, easily applied, and causing no antigenic response but able to withstand remodeling by body tissue are not yet available.^{38,40} A successful material can decrease the operating time and morbidity in vaginal surgeries and decrease the higher hospital costs and higher risks of abdominal procedures. Some issues in the use of prostheses in pelvic floor reconstructive surgery are still being debated. Knowledge of the mechanism between the host response and a prosthesis is still limited at present. A recent study revealed that fibroblasts surrounding mesh material displayed strong MMP-2 gene transcription, whereas fibroblasts without close contact to the mesh material had low MMP-2 synthesis rates. *In vitro* studies support a cellular crosstalk concept between fibroblasts and the ECM. The zonal and cell-specific regulation of MMP-2 gene transcription illuminates an intimate cellular crosstalk in a foreign-body reaction that may provide a new approach for mesh modification.⁴¹ Fibroblast proliferation, neovascularization, and remodeling occur with a graft. No evidence of an inflammatory reaction or graft degeneration was detected.⁴² Therefore, the usefulness of a mesh is dependent on the ingrowth of fibroblasts and other stromal cells. The establishment of *in vivo* and *in vitro* study models is important to understand the pathophysiology of POP and synthetic meshes and biologic grafts used in pelvic floor reconstruction.

5. Different *In Vitro* or *In Vivo* Models Have Been Developed to Elucidate the ECM Microenvironment

Different animal models are being used to characterize the biomechanical properties of the pelvic support, including non-human primates, rodents, rabbits, and

sheep.⁴³ The organization of the extracellular components, i.e., ECM, myofibroblast, and endothelial cell co-culture system can distinguish characteristics of different synthetic materials that are associated with constructive tissue remodeling.⁴⁴ Common features of this ECM-assisted tissue remodeling include angiogenesis, recruitment of circulating progenitor cells, and constructive remodeling of damaged tissue structures.⁴⁵ To elucidate the biological behaviors of host stromal cell responses to different synthetic meshes, we established an *in vitro* Matrigel multicellular co-culture system with an embedded synthetic mesh,⁴⁶ which was modified from a report by Walter-Yohrling et al⁴⁷ and our previous work.³³ We used NIH3T3 to represent myofibroblasts because of its characters of high α -SMA expression and MMP-2 activity compared to normal primary fibroblasts. NIH3T3 cells, endothelial cells, or both cells were dispersed in the Matrigel multicellular co-culture system with or without different meshes being embedded. NIH3T3 cells and endothelial cells grew into the interstitials of the mesh and formed a tube-like structure. Many more NIH3T3 cells and/or endothelial cells were recruited into the pores of the type I Prolift (J&J) mesh than in the type III IVS (Tyco) mesh embedding system (Figure 1).⁴⁶ The presence of a synthetic mesh may also hinder stromal cell recruitment. The impaired recruitment and tube-formation ability of myofibroblasts and endothelial cells into the type III mesh, compared to the type I mesh, may account, at least in part, for the limitations of these meshes. Establishment of this *in vitro* Matrigel co-culture system is therefore important for understanding the pathophysiology of POP and synthetic meshes and biologic grafts used in pelvic reconstructive surgery. Gaining a better understanding of the complexities of ECM-myofibroblast interactions will improve our prospects for developing more effective pelvic reconstructive surgical techniques.

6. Future Directions

It was hypothesized that accelerated remodeling in patients with POP is caused by biochemical changes in ECM proteins, myofibroblasts, and their regulators. Further studies are indicated to elucidate the following issues: first, whether women with POP have abnormal synthesis and/or degradation of the ECM, and different amounts of stroma cells (myofibroblasts); second, whether myofibroblasts from women with POP have different ECM protein productions under regulation of MMP, TSP-1, and TGF- β ; and third, whether ECM matricellular proteins, e.g., TSP-1 and TGF- β , can modulate the biologic responses of host stromal cells to synthetic meshes in pelvic reconstructive surgery. The interplay of the ECM, myofibroblasts, and synthetic meshes can determine the usefulness and development

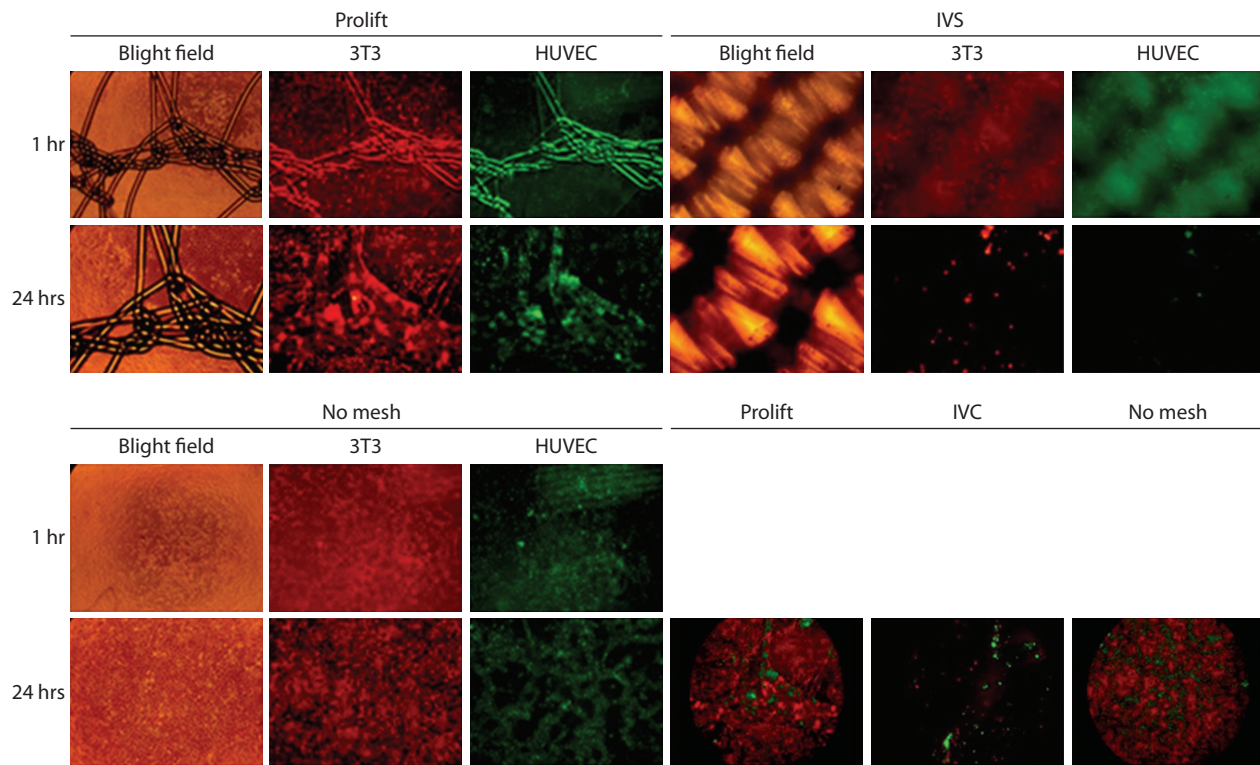


Figure 1 Myfibroblasts (NIH3T3), endothelial cells (human umbilical vein endothelial cells; HUVECs), or both cells of same number were dispersed in a Matrigel co-culture system with or without different embedded meshes for 1 and 24 hours. Many more NIH3T3s were recruited into the pores of the type I mesh, e.g., Prolift (J&J), than into the type III mesh, IVS, (Tyco) embedding system at 24 hours. Similar phenomena were also found in both HUVECs and stromal cells (merged image shown in the right lower panel). Matrigel without a mesh was used as a positive control. The presence of the synthetic mesh may also hinder the recruitment of stromal cells (unpublished data, presented at The 34th Annual Meeting of the International Urogynecology Association, Como, Italy).⁴⁶

of synthetic prostheses in pelvic reconstructive surgery. This will be very informative for the further advancement of our understanding and treatment using pelvic floor reconstruction.

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