DERLEME REVIEW

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Matricellular Proteins and Related ADAMTS Genes in Infertility

İnfertilitede Matrisellüler Proteinler ve İlişkili ADAMTS Genleri: Review

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ABSTRACT The human reproductive system is more sensitive than other species to functional disorders. Each organ in the system should function properly in the process of fertilization. Data of recent genetic studies suggest a critical role of multiple genes in various reproductive organs and tissues. Even though scrutinizing studies about all macro- and microprocesses in fertility are yet being held, and the system is trying to be untangled, the pathophysiology of infertility remains an appealing subject to research, which encircles the known sieged by unknown. The extracellular matrix (ECM) is not only a structural support for the cells, but also is a functional mesh which has determining role in cellular shapes, behaviors, differentiation, proliferation, gene expressions, and their life cycles. Matricellular proteins are members of extracellular matrix which functions in regulation of cellular reactions, cell-to-cell and cell-matrix interactions via providing the interplay among structural macromolecules, growth factors, cytokines, and proteinases. A Disintegrin-like And Metalloproteinase with Thrombospondin type-1 motif (ADAMTS) proteins are a group of zinc-dependent metalloproteinases responsible for degradation of ECM structures, which significantly act in many physiologic and pathologic processes. We aimed, in this review, to pose a broad view about the pathophysiology of infertility gathering the studies pertaining to matricellular proteins and ADAMTS enzymes which participate in the riddle of matrix breakdown and renewal.

Keywords: Infertility; extracellular matrix proteins; ADAMTS1 protein, human

ÖZET İnsan üreme sistemi işlevsel bozukluklara diğer türlere kıyasla daha duyarlıdır. Fertilizasyon sürecinde kadın reprodüktif organlarından her biri görevini tam olarak yerine getirmelidir. Güncel genetik çalışmalarından elde edilen bilgilere göre pek çok gen çeşitli üreme organ ve dokularında hayati rol oynamaktadır. Fertilitenin tüm makro- ve mikro-süreçlerinde yoğun araştırmalar devam etmesine ve sistem çözülmeye çalışılmasına rağmen, infertilite patofizyolojisi halen tüm bilinmezliğiyle karşımızda durmaktadır. Ekstraselüler matriks (ECM) hücreler için yapısal bir destek olmasının yanısıra hücrenin şekli, davranışı, diferansiasyonu, proliferasyonu, gen ekspresyonu ve hayatiyetleri üzerinde belirleyici rolü olan fonksiyonel bir dokudur. Matrisellüler proteinler ECM'ye ait elemanlardır; görevleri yapısal makromoleküller ile büyüme faktörleri, sitokinler ve proteazların etkileşimini sağlayarak hücre fonksiyonunu, hücreler arası etkileşimi ve hücre-ECM etkileşimini regüle etmektir. "A Disintegrin-like And Metalloproteinase with Thrombospondin type-1 motif" (ADAMTS) proteinleri, ECM yapılarının yıkımından sorumlu, vücutta birçok fizyolojik ve patolojik süreçte önemli rolleri olan çinko bağımlı proteinazlardır. Bu derlemenin amacı infertilite patofizyolojisinde matrisellüler proteinlerin ve ilgili ADAMTS'lerin rolleri üzerine yapılmış çalışmaları biraraya getirerek konuyla ilgili geniş bir perspektif sunmaktır.

Anahtar Kelimeler: İnfertilite; ekstraselüler matriks proteinleri; ADAMTS1 protein, insan

Female reproduction tract, unlike other mucosal structures, is an unique system that has genetic and immunologic versatility in a wide spectrum of tissues spreading from the vagina thru ovarian follicles.

The system widely variates not only among individuals, but also between and in cycles. Besides cellular and interstitial local regulator factors, endocrine changes in the body affect the system significantly.[1,2] Data of recent genetic studies suggest a critical role of multiple genes in various reproductive organs and situations.[3] These genes might quite possibly be expressed within an organ, or throughout the reproductive tract. How the regulator cytokines interact amongst and stamp out the target tissue, their cellular loci and concentrations, and how they maintain the overall harmony of the network requires future elucidation.

FERTILIZATION AND PATHOPHYSIOLOGY OF INFERTILITY

The human reproductive system is more sensitive than other species to disorders. Each organ in the system should function properly in the process spanning from the zygote formation until labor. For an accomplished pregnancy, basic steps of the fertilization including folliculogenesis and ovulation in the ovaries, union of two gametes and formation of the zygote in the fallopian tubes, transportation of the zygote to uterus, ensuring the receptivity in uterus, decidualization, implantation and placental formation should optimally take place in harmony in concerning tissues. Besides, a normal genital anatomy, functioning of the hypothalamic hypophyseal ovarian axis, engaged neuroendocrine tasks, optimal sperm function is involved, as well. The equilibrium among these factors is under control via complicated interactions of multiple paracrine, autocrine, immunologic, genetic, and even psychologic systems. A provided undesirable defect in any of these participants may inhibit the function, which consequently leads to infertility.[2,4] Even though scrutinizing studies about all macro- and microprocesses in fertility are yet being held, and the system is trying to be untangled, the pathophysiology of infertility remains an appealing subject to research, which encircles the known sieged by unknown.

We aimed, in this review, to pose a broad view about the pathophysiology of infertility gathering the studies pertaining to matricellular proteins and A Disintegrin-like And Metalloproteinase with Thrombospondin type-1 motif (ADAMTS) enzymes which participate in the riddle of matrix breakdown and renewal.

MATRICELLULAR PROTEINS

The extracellular matrix (ECM) is not only a structural support for the cells, but also is a functional mesh which has determining role in cellular shapes, behaviors, differentiation, proliferation, gene expressions, and their life cycles.[5] Each tissue constitutes a specific matrix along with its own interstitial elements. Besides the major structural components of ECM, non structural proteins which show up merely in certain periods, and have a fast a cycle, may be found in the matrix. Bornstein (1995) defined these as "Matricellular proteins", which functions in regulation of cellular reactions, cell-to-cell and cell-matrix interactions via providing the interplay among structural macromolecules, growth factors, cytokines, and proteinases.[6]

To date, master defined matricellular proteins include **TSP-1** (Thrombospondin type-1), **TSP-2**, **SPARC** (secreted protein acidic and rich in cysteine= osteonectin), **tenascin-C**, **tenascin-X, OPN** (osteopontin), **CCN family** (cysteine-rich protein 61= Cyr 61), **versican**, and **periostin**.[7]

THROMBOSPONDIN

This is a glycoprotein secreted by platelets in respond to thrombin activity. TSP-1, as one of the five members of thrombospondin family, is the most studied matricellular protein, which acted as pathfinder in obtaining data concerning the matricellular proteins.[8] The effect of the thrombospondin over the cell varies according to the content of the cell: the effect on adhesion, migration and cell growth may both be stimulating or inhibiting. This paradox was explained as cell's expressing receptors, which are inclusive of various signal transduction pathways, in recognizing the thrombospondin-1 protein. Its variable activity facilitated our understanding of the mechanisms and functions of some other matricellular proteins.[9,10]

Expression of thrombospondin-2 is correlated with inhibition of angiogenesis. Despite having a role in cell-to-cell and cell-matrix interactions, the function of thrombospondin-3 and -4 remains cloudy. Thrombospondin-5 is the cartilage oligomeric matrix protein (COMP), AKA a marker of cartilage turnover.[8,10]

SPARC

In human, SPARC (secreted protein acidic and rich in cysteine, osteonectin, basement membrane 40 [BM40]) is encoded by SPARC gene, which does not function as a structural protein, rather regulates the cell-matrix interactions via mineralization of bone and collagen binding. It synthesis by fibroblasts and macrophages in the injured tissue and platelet degranulation suggests a possible role in wound healing. SPARC does not support the intercellular connection, rather, it is anti-adhesive like thrombospondin and tenascin, and plays an inhibitory role in cellular propagation. It supports the proliferation of endothelial cells: its overexpression was shown in mammary, prostate, and colon neoplasms.[7,11]

TENASCINS

These are high molecular weight ECM glycoproteins, which is abundant in embryonic tissues of vertebrates, and also found in human in surroundings of the healing wounds, and in stromal tumors, as well. It functions in tissue regeneration, and in hyperplastic and neoplastic processes. The tenascin gene family has four members: Tenascin-C, R, X, W. Tenascin-C is the most studied one, and has an anti-adhesive feature. It can bind to fibronectin, an ECM glycoprotein, and can block its connection to syndecans, whereby causes the cells to aggregate in tissue culture mediums. Tenascin's presence in tumor stroma is a sign of malignity. Due to its function in migration of vascular endothelial cells, a possible role in angiogenesis was suggested.[12,13]

OSTEOPONTIN

First defined in osteoblasts, osteopontin (OPN) is a phosphorylated glycoprotein found common in tissues, and binds calcium. Its *in vivo* functions remain vague, however, its role in embryogenesis, wound healing and tumor development is known. Normal progress of embryogenesis and fertility in OPN knockout mice were shown. OPN is an integrin binding ligand in endometrium, and is associated endometrial receptivity.[10,14]

CCN FAMILY (CCN1-6)

The nomenclature in this group was set up with the discovery of three members. "CCN family" was announced as the proteins which WNT induced queued up in the family.

- CCN1= CYR61 (cysteine-rich angiogenic protein 61)
- CCN2= CTGF (connective tissue growth factor)
- CCN3= NOV (nephroblastoma overexpressed)
- CCN4= WISP1 (WNT1 inducible signaling pathway protein-1)
- CCN5= WISP2 (WNT1 inducible signaling pathway protein-2)
- CCN6= WISP3 (WNT1 inducible signaling pathway protein-3)

Members of CCN family regulate a number of cellular processes including adhesion, migration, proliferation, differentiation, apoptosis, cellular aging and survival. Moreover, their roles in embryonic development, inflammation, wound healing, angiogenesis, fibrosis, and tumorigenesis were shown, as well. In human, CCN1, -2 and -3 handle a regulatory role trophoblast proliferation and migration. Although little information has been obtained about functions in reproductive system, it is supposed that an imbalance in the expressions is of importance in gynecologic pathologies including endometriosis and preeclampsia.[7,15]

PERIOSTIN

Encoded by unique POSTN gene in human, periostin plays a crucial role in cellular adhesion, bone formation and development. It is known to be expressed in healthy fetal and mature tissues, and was shown to interplay in induction of angiogenesis via increasing a matrix metalloproteinase (MMP-2), and in promoting cellular proliferation

with differentiation, which whereby favors bad prognosis in some tumors including epithelial ovarial cancers.[16,17]

MATRICELLULAR PROTEIN-RELATED MOLECULAR SCISSORS: ADAMTS PROTEINASES

ADAMTS proteins are a group of zinc-dependent metalloproteinases responsible for degradation of ECM structures, which significantly act in many physiologic and pathologic processes. ADAMTS proteins comprise of collective molecular structures with MMP and ADAM (a disintegrin and metalloproteinase) proteins, though they differ by direct secretion trait to the ECM and having thrombospondin type-1 repeats.[18] It was no earlier than Kuno et al. first defined the first member of the family in 1997, ADAMTS-1, the scrutinizing studies started up panning out 19 various ADAMTSs and seven ADAMTS-like protein subtypes.[19,20] ADAMTSs are synthesized as inactive pre/proprotein like other proteins, which have *N*- and *C*-terminals. Starting from the *N*-terminal, all members of the family comprise of a signal peptid, a pro-peptid (pro-) domain, a zinc-dependent catalytic domain, a disintegrin-like domain, thrombospondin (type-1) motif repeats, a cysteine-rich domain, a linkage domain, and a varying region at the *C*-terminal.[18,20] Figure 1 shows the domain organization of ADAMTSs. Pro- domain maintains the structural integrity of the functional molecule barriering to the catalytic processes in the ECM. For the action, the signal and the propeptide region should be cleaved. The peptidase/catalytic domain is the zinc-dependent region responsible for the catalysis of target ECM proteins. The disintegrin-like domain was designated due to the similarity with a disintegrin module of ADAM family members binding to integrin receptors, yet, no ADAMTS member was shown to bind to an integrin receptor via this domain.[20,21] The motif is suggested to function in connection to a cell or ECM components. The thrombospondin type-1 domain is associated with binding of the molecule to glycosaminoglycans and CD36 receptors. Notwithstanding the exact role of this motif, too, remains uncovered, a possible role in connection to other ADAMTSs and protein trafficking in ECM of various tissues was suggested. The cystein-rich and connection regions act in recognition of the substrate and true localization in ECM.[18,20-22]

Previously defined functions of ADAMTSs include procollagen's maturation to collagen, degradation of matrix proteoglycans like aggrecan, versican and brevican, inhibition of angiogenesis, and cleavage of von Willebrand factor (vWF) in regulation of coagulation. Some other roles in processes including inflammation, organogenesis, fertility, tumorigenesis, and atherosclerosis are also known.[18,20,23] Basic approaches in the topic enclose ADAMTS knock-out mice studies, mutation and polymorphism studies in ADAMTS genes, variations of expression of the family in healthy and pathologic tissues.[23]

Recent classification of the ADAMTSs is as follows (Figure 1):[24]

- Aggrecanases: ADAMTS 1, 4, 5, 8, 9, 15, 16, 18
- Anti-angiogenic ADAMTSs: ADAMTS 1, 8, 9
- COMP (Cartilage oligomeric matrix protein) ADAMTSs : ADAMTS 7,12
- GON (Gonadal) ADAMTSs: ADAMTS 9, 20
- Procollagen ADAMTSs: ADAMTS 2, 3, 14
- von Willebrand factor ADAMTS: ADAMTS 13
- Orphan ADAMTSs: 6,10,17,19

MATRICELLULAR PROTEINS AND ROLE OF ADAMTS PROTEINASES IN INFERTILITY

Matricellular proteins modulate the ECM and cellular functions interacting with surface receptors. Isoforms produced by degradation of matricellular proteins by ADAMTS proteases crucially figure in this modulation.[25] By means of their integrated catalytic domains, ADAMTS proteases cleaves specific substrates in ECM and on the surface of the cells, whereby the ECM protein turnover is handled and cellular actions take part.[26] ADAMTS-4 and -5, have been shown to degrade members of the lectican family of proteoglycans. Matricellular proteins constitute an interface favoring the interaction of other matricellular proteins and ECM proteins (Figure 2).[27] Outcomes of numerous studies in

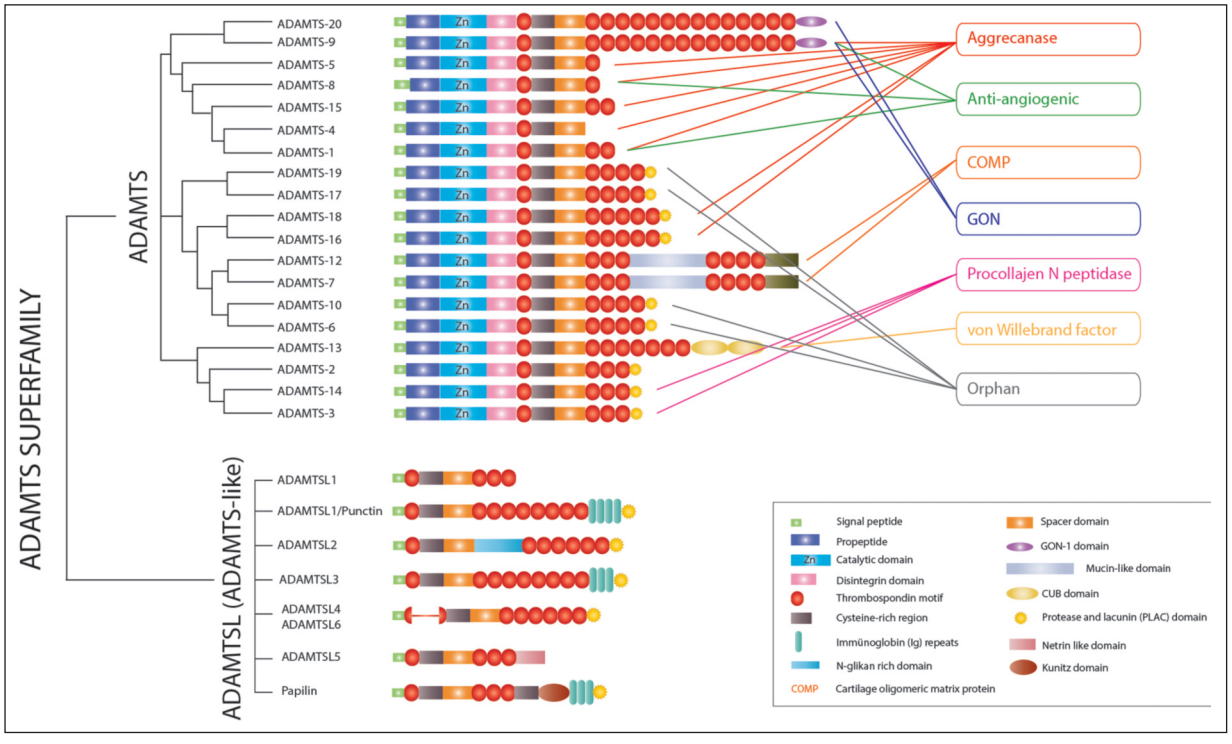

FIGURE 1: ADAMTS Family, domain organization and tissue functions.

19 ADAMTSs and 7 ADAMTS-like proteinase members are accepted as ADAMTS superfamily. Figure 1 gives a brief and recent classification of ADAMTSs in terms of philogeny, domain organizations and tissue functions.

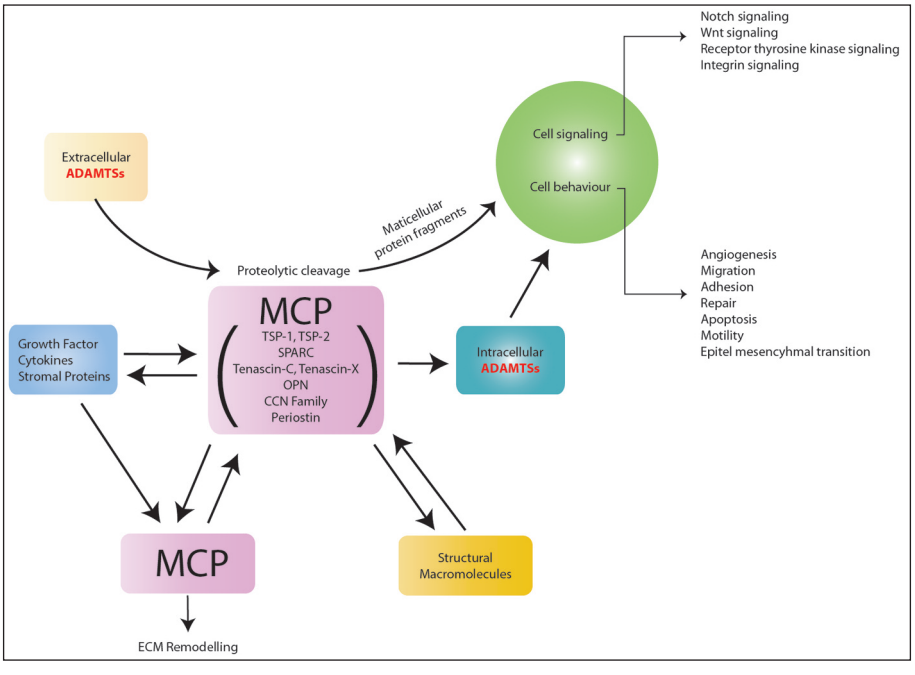

FIGURE 2: Matricellular proteins and ADAMTSs in Extracellular matrix (ECM).

Figure 2 summarizes collective function of ADAMTSs and matricellular proteins (MCP), which are members of ECM proteins, in reorganization of ECM, cell-matrix signaling and cellular behavior.

functions of matricellular proteins, ADAMTSs and ECM mesh in infertility are classified according to fertilization stages as follows.

FOLLICULOGENESIS, OOCYTE MATURATION, OVULATION AND FERTILIZATION

The whole reproductive system is under control of complex regulatory local, genetic, hormonal and environmental factors, failure of which drive the system down to infertility.[28] Ovarian folliculogenesis, cumulus-oocyte complex (COC) formation and ovulation, all are extremely complex processes regulated by gonadotropins and receptors. Remodeling of ovarian follicular matrix is required for ovulation and vascularization of corpus luteum. Genetic auditing and proteins responding to hormonal impulses are of importance in these interactions. Ovulation in the mammalian ovary occurs in response to the luteinizing hormone (LH) outpour that activates several ECM remodeling processes. Dissolution of the connective mesh and cellular layers at the follicular apex and ovarian surface are required for release of the oocyte. Based on the anovulatory phenotypes of mice with null mutations of cyclooxygenase-2 (COX-2), prostaglandin E2 receptor, and bikunin, it is becoming evident that expansion of the matrix surrounding the cumulus cells and oocyte is essential for ovulation.[29-31] The formation of this specialized matrix is also required for successful passage of the COC into the oviductal lumen, transport through the oviduct, and subsequent interaction with sperm during fertilization.[32] The principle component and obligatory backbone of the expanded COC matrix are large hyaluronan (HA) molecules produced through cumulus cell expression of hyaluronan synthase-2 and activated in response to LH and intrafollicular growth factors.[33] Versican is a member of the lectican/hyalectan family including aggrecan, brevican and neurocan, all of which possess large glycosaminoglycan attachment domains substituted with chondroitin sulfate or keratan sulfate. Versican is a large ECM proteoglycan (chondroitin sulfate) present in numerous tissue, and is often considered an anti-adhesion molecule.[34] Expressed by granulosa cells, versican binds the HA-rich matrix surrounding expanded COC through a HA-binding link module in the *N*-terminal globular domain. The *C*-terminal globular domain seems to interact with sulfated cell surface glycolipids, and ECM glycoproteins such as tenascin-R.[33,35]

It is well known that proform ADAMTS-1, of which its synthesis is induced by the effects of LH through a progesterone receptor-dependent mechanism, and of progesterone in pre-ovulatory phase, is secreted by mural granulosa cells, then locates in matrix of COC, and subsequently degrades versican in the ovulatory phase (Figure 3).[36] Recent re-

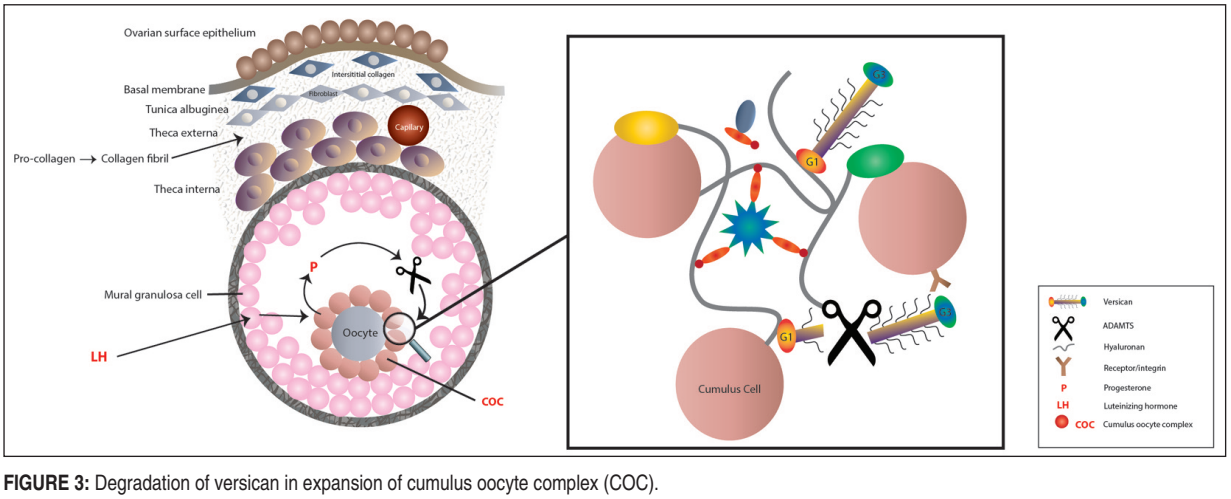

FIGURE 3: Degradation of versican in expansion of cumulus oocyte complex (COC).

Latent proform ADAMTS-1, the synthesis of which is induced by luteinizing hormone (LH) and progesterone in the preovulatory period, and its substrate versican are secreted by mural granulosa cells, then takes place in COC matrix; ADAMSs degrade versican during ovulation, thus the COC matrix expands.

search showed that, COC matrix is driven to approximately 20-fold enlargement, and degradation of vesican is crucial in this process. To date, the most investigated ADAMTS functioning in fertility is ADAMTS-1. Studies conducted in mice with ADAMTS-1 null mutation prove that, the ovulation decreases to an extent of 70-90%, and the offsprings are 75% smaller than normal. Moreover, these mice show an evident lag in phases of folliculogenesis.[37] LH increases the synthesis of progesterone and receptors, which, in turn, causes the synthesis of ADAMTS-1 synthesis from granulosa cells.[38] Progesteron receptor gene knockout mice lack ovulation, and their ADAMTS-1 protein levels and mRNA expressions are reported to be prominently lower than in normal.[39] The observations suggest that one function of ADAMTS-1 in ovulation is to cleave versican in the expanded COC matrix, and that the anovulatory phenotype of progesterone receptor gene knockout mice is at least partially due to loss of this function.[40]

To date, most of the studies under this topic were carried out investigating the mechanism of ADAMTS-1 action, however, seven different ADAMTS (ADAMTS-1, -4, -5, -9, -16, -19 and -20) expressions were detected in the ovary of mammals.[41] Various roles of ADAMTS-4 and ADAMTS-5 proteins were defined in mice ovarian cells and in phases of folliculogenesis. Besides ADAMTS-1, ADAMTS-4, too, is highly expressed in development, stabilization and functioning of the matrix surrounding the oocytes in COC in pre- and postovulatory phases.[41] ADAMTS-16 was shown to be expressed in granulosa cells via effect of follicular stimulating hormone (FSH), presence of α-2 macroglobulin, a substrate of ADAMTS-16, in follicular fluid was also proven.[42]

Expression of ADAMTS-1 is lower in granulosa cells in patients with polycystic ovary syndrome (PCOS) than in normoovulatory healthy individuals, and this decrease is strictly associated with obtained number and maturity of oocytes, and fertilization ratios. Expressions of some of the genes in PCOS are proven o be increased, whereas, near 30 genes besides ADAMTS-1 are decreased; moreover, changes in ECM architecture induces the ovarian capsule thickening, and causes anovulatory phenotype.[43]

In three studies by Pyun et al., ADAMTS-19 and ACVR2B (activin-A receptor type II) polymorphisms were investigated in Korean patient with premature ovarian failure (POF). The epitasis in these genes and synergistic interaction between ADAMTS-16 and thyroglobulin gene polymorphisms was shown to be increased.[44-46] There is an established balance between the anti-angiogenic effect of thrombospondin like motif type-1 (TSP-1) and pro-angiogenic effect of vascular endothelial growth factor (VEGF) in ovaries. Overexpression of TSP-1 inhibits angiogenesis and consequently the folliculogenesis, driving the follicle to atresia.[47]

Tenascin functions in ECM as an anti-adhesive, whereas fibronectin counteracts. Tenascin is expressed along with fibronectin in the tissues, in addition to whose its function requires, too, the presence of fibronectin. In the process of folliculogenesis, tenascin is detected only in the external theca in developing follicles, and both in the external theca and basal membrane in atretic follicles. It was shown in much lower levels in young luteal cells, whereas older ones contain way too higher concentrations. With these data, it was concluded that tenascin induces degenerative changes in mouse ovary.[48] Tenascin-C and type-1 collagen were shown to play a role in ovarian follicle morphogenesis, and formation and regression of corpus luteum in a gonadotropin-dependent manner.[49]

In mouse, SPARC protein was shown in ovarian thecal storma, corpus luteum, testes, and adrenal glands, all of which are classified in steroidogenic tissues. Its expression in the granulosa cells increases after human chorionic gonadotropin (hCG) administration in preovulatory phase.[50] In SPARC null mice, an increase in number of adipocytes due to lowered collagen accumulation was shown, whereas specific ovarian abnormalities were followed in the same animals.[51]

CCN-1 expression is triggered by corpus luteum, and consequently angiogenesis is induced. CCN-2 is thought to be expressed in theca interna and granulosa cells, and its estrogen induced secre-

tion is shown in follicular growth, which is suggestive of a potential role in follicular development, ovulation and regression of corpus luteum. Similar research concerning a possible role of CCN-5 in oogenesis is carried out.[52] The combined endocrine and paracrine signaling in the follicle renders coordination of oocyte maturation and ovulation with maternal receptivity.

UTERINE RECEPTIVITY, DECIDUALIZATION, IMPLANTATION AND PLACENTAL FORMATION

Synchronization of embryonic development and endometrial reconstitution along with receptive medium is essential in an accomplished pregnancy. Reconstruction of ECM under regulation of gonadal steroids is the sign of steroid-mediated morphologic and functional maturation of endometrium.

Expression of ADAMTS-1 in menstrual cycle and pregnancy in certain localizations of human endometrium, which, *in vivo*, is associated with the beginning and maintenance of decidaulization, was shown.[53,54] What is known today is gonadal steroids regulate expression of ADAMTS-1, -5, -8 and -9 in a time and concentration-dependent manner in human stromal cell culture; these enzymes play a critical role in endometrial decidualization, and a defect in their synthesis results in infertility.[55] In ADAMTS-1 null mice, implantation collapses in conjunction with ovulation.[56] The presence of ECM proteins including syndecan and perlecan that are the substrates of ADAMTS-1 in the period of implantation suggests a role in implantation.[57] ADAMTS gene family mediate the mechanism in terminal differentiation of cytotrophoblast and development of invasive type. The presence of ADAMTS-1, -2, -4, -5, -6, -7, -9 and -12 in placenta in the first trimester was shown, and ADAMTS-12 expression is regulated by trophoblasts, suggesting a role in epithelial invasion.[58] In addition, ADAMTS-1 action is required for revascularization in feeding of placental tissues.[59]

TSP-1 was defined as an angiogenesis inhibitor, and known to be under control of tumor supressor genes. Despite the fact that the interaction of TSP-1 with various extracellular molecules and growth factors has a striking importance in this process, the mechanism remains hazy. A second ambiguity arises for the function of TSP-1 in endometrium where it is expressed.[60]

SPARC protein was shown in mouse uterine stroma in normal reproductive cycle, in decidua in the first days of implantation, and in luminal epithelium.[61] In terms of eutopic and ectopic gene expression, regulation of SPARC gene expression is distorted in the endometrium in cases of endometriosis, whereby the mechanism may mediate the pathology of endometriosis.[62]

The expression of tenascin in endometrium shows alteration through out the menstrual cycle with the effects of ovarian steroids. Notwithstanding the function of tenascin is obscure in endometium, it is well known that it functions in the implantation via interplaying in th endometrial regeneration and cellular adhesion. Studies depicted that tenascin expression shows cyclic changes in eutopic and ectopic endometriosis tissues.[63] It might quite possibly contribute via ECM degradation expressing temporarily and invading the peritoneal surfaces in ectopic endometrium.

Osteopontin is an integrin binding ligand in the endometrium. Its transient increase in the implantation window brought about to be seen as a receptivity marker. Osteopontin levels increase along with in this period, as well. However, both cytokines show a decrease in adenomyotic uterus in the priod of implantation. The role for ostepontin in paracrine signaling pathways in angiogenic formation involved for implantion in the decidua is delineated. Its expression is increased in the patients with endometriosis, elongating the invsion strength, prolifaretion, and cellular life-time.[64]

CCN-1 acts as a pro-angiogenic factor in the endometrium, and its release in proliferative and premenstrual phases is incremented by estrogen and low oxygenation, and decreased by progesterone. It is increased in the endometriosis tissue, and overexpressed in PCOS. CCN-2 is expressed through out the cycle, ad function in stromal remodeling and neovascularization. The expression of both CCN-1 and -2 increase in the implantation period in the endometrial epithelium, whereas knock-out mice showed no deterioration in the im-

plantation. Like CCN-2, CCN-5 is expressed through out the cycle in the endometrium, yet, the function is not known.[65,66]

Periostin is a fetal and adult human protein playing a crucial role in cellular adhesion, bone formation and development, also functioning in the early embryogenesis. In the endometrium, periostin is expressed in the stromal and epithelial cells, which overexpresses in pregnancy and early secretory phase.[67] The overexpression is thought to activate differentiation of endometrium thru implantation via integrins. Serum levels and endometrial expression studies revealed that it may reflect the endometrial receptivity, the quality of embryo, and predict the success of pregnancy. Low levels of serum, endometrium and fetal expression may imply poor implantation, as a hypothesis. Thus, studies on periostin in repeated and unaccomplished implantations continue.[68]

TUBAL AND CERVICAL TRANSPORT

In a study on fallopian tubes, some of the ECM molecules including ADAMTS-1 and ADAMTS-13 showed various expression patterns throughout the cycle in the tubal tissues, and the expressions were under control of steroid hormones.[69] Like all other reproductive tissues, ADAMTS proteases seem to be responsible for reorganization of the tubes in the luteal phase.[56] Any defect in the reconstruction would give rise to some reasons of infertility including tubal transport dysfunction, hydrosalphinx, and ectopic pregnancy. Another reason for infertility due to tubal dysfunction is the case of salpingitis induced by sexual contagious pathogens, which, also, is associated with ADAMTS-1 via inflammatory process.[54]

In fertilization, the sperm quality requires storage of sperms in endocervical crypts and sperm-mucus interaction in transport thru cervix. Cervix provides a functional and anatomic barrier for endometrial cavity against infectious agents.[70] Due to the collagen-rich chemical structure, a defect in expressions of ADAMTS-2, -3, and -14, AKA procollagen N-proteinases, may give rise to infertility via cellular changes including changing the structure of cervical mucus, or deformations at organ level including cervical stenosis and failure.[71]

MALE INFERTILITY

Studies in males concerning ADAMTSs and matricellular proteins for the infertility in the literature is insufficient to figure out the frame. Only a few ADAMTS proteins and osteopontin were associated with the sperm biology. ADAMTS-2 null male mice were diagnosed infertile due to a defect in spermatogenesis.[72] In mice, ADAMTS-10 is expressed in acrosomal domain of spermatid developing in the late phase of spermatogenesis, and function in adhesion of the spermium to zona pellucida.[73] In a study on osteopontin detection in seminal plasma, a positive correlation with abnormal forms of spermatozoon, and a negative correlation with number and motility.[74] Likewise, a correlation between osteopontin and fertility was proven in a study in camels, and its likelihood as a marker for fertility in sperm was discussed.[75]

OTHER CONDITIONS

Endometriosis, peritoneal adhesions and pelvic infections are significant cause of infertility, of which the pathology involves deterioration in fibrinolytic activity, apoptosis, production of cytokines, angiogenesis and turnover of ECM.[18,20,53,63] Future research is prone to enlightening the roles of members of matricellular proteins and ADAMTS family in reorganization of reproductive tissues.

CONCLUSION

Reproductive process is too complex with a variety of components. Although the colossal development in in vitro fertilization methods and genomic technology untangled our understanding to an extent, genetic heterogeneity, various localizations and multifunctionality of proteins requires a broad approach in future studies. As the ADAMTS proteases unraveled a path in cancer treatment, the matricellular proteins regulating the ECM and recognition of the multifaceted ADAMTS gene family, along with functionality and structural association, will probably provide new frontiers in pathogenesis and treatment of infertility.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Idea/Concept: *Müberra Namlı Kalem*

Design: *Ziya Kalem*

Control/Supervision: *Kadir Demircan*

Data Collection and/or Processing: *Ayla Eser Açar*

Analysis and/or Interpretation: *Ziya Kalem*

Literature Review: *Ziya Kalem, Ayla Eser Açar*

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