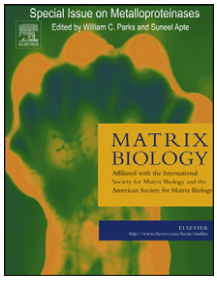
Review



ADAMTS proteases in fertility

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Abstract

The reproductive organs are unique among adult organs in that they must undergo continual tissue remodelling as a key aspect of their normal function. The processes for persistent maturation and release of new gametes, as well as fertilisation, implantation, placentation, gestation and parturition involve cyclic development and regression of tissues that must continually regenerate to support fertility. The ADAMTS family of proteases has been shown to contribute to many aspects of the tissue morphogenesis required for development and function of each of the reproductive organs. Dysregulation or functional changes in ADAMTS family proteases have been associated with reproductive disorders such as polycystic ovarian syndrome (PCOS) and premature ovarian failure (POF). Likewise, proteolytic substrates of ADAMTS enzymes have also been linked to reproductive function. New insight into the roles of ADAMTS proteases has yielded a deeper understanding of the molecular mechanisms behind fertility with clinical potential to generate therapeutic targets to resolve infertility, develop biomarkers that predict dysfunction of the reproductive organs and potentially offer targets for development of non-hormonal male and female contraceptives.

Introduction

Successful development of functional reproductive organs is essential to fertility and thus species propagation. The reproductive organs are exceptional in that they arise from a single bipotential origin and develop differently depending on the sex of the fetus. In both sexes, the function of the adult gonad is dependant on remodelling of the extracellular matrix (ECM) to facilitate the constant (male), or cyclic (female) production of the mature germ cells. Each of the reproductive organs is highly organised, complex structures with multiple cell types acting in coordination to control temporal and spatially restricted cycles of growth and regression. Their remodelling involves tightly controlled activity of a range of specific proteases which target both the ECM to reconfigure structure and also modulate the localisation and activity of a range of signalling ligands and their receptors.

The female reproductive tract provides, perhaps, the best example of adult, post-developmental tissue remodelling. Ovaries remodel daily as around 40 new follicles, each containing a genetically unique oocyte, commence growth and increase in volume by over 100,000-fold over several months [1]. More than 99.9% of these follicles will regress and are resorbed through further tissue remodelling. The other 0.1% of follicles selected to survive will reach full maturity and ovulate their oocyte into the fallopian tube. These follicles then undergo terminal differentiation forming the corpus luteum. This requires one of the most vigorous angiogenesis processes described, to vascularise the previously avascular follicle structure. In the uterus, the endometrial layer regrows and vascularises each month and is then destroyed and sloughed at menstruation in each non-pregnant cycle, while if pregnancy is established it grows even further and forms a syncytium with the placenta. In human males, seminiferous tubules in the testes

cycle through six morphologically distinct stages as they mature and release over 1500 new sperm cells with every heartbeat.

Various members of the ADAMTS protease family have been found to play key functional roles throughout development of the reproductive organs and the adult reproductive lifespan. These physiological roles of the ADAMTS proteases and their association with reproductive dysfunction, fertility disorders and disease are the subject of this review.

Gonad development

Invertebrate gonadogenesis

The involvement of ADAMTS enzymes in gonadogenesis and the structural organisation that underpins gonadal function has been reported in many species. The *Caenorhabditis elegans* model has proven an instructive system to interrogate the genetics and biochemistry of ADAMTS–ECM interactions in organ morphogenesis. The hermaphroditic gonad of *C. elegans* forms into an epithelial tube with two U-shaped arms through a guided migration of the gonadal distal tip cells (DTC). The *Gon-1* gene encodes a *C. elegans* ADAMTS family metalloproteinase most closely related to mammalian ADAMTS9/ADAMTS20 proteoglycanases [2]. *Gon-1* is secreted by body wall muscle and DTC cells and is required for the migration of the forming gonad and for appropriate architecture of somatic and germ cells in the gonad [2]. Similarly, the homologous proteoglycanase isoform in Drosophila, *dAdamTS-A*, is also required for normal germ cell development and collective cell migration [3]. *Gon-1* is believed to mediate basement membrane (BM) remodelling required for migratory activity of the gonad cells and achieving a specific organ shape which is crucial to the specification of mitotic stem cells and meiotic gamete cells [4], but *Gon-1* also mediates other morphogenic processes such as patterning of neuronal synapses [5]. There is an antagonistic relationship between *Gon-1* and ECM protein Fibulin-1 suggesting that the contribution of the ADAMTS to ECM structure is a key aspect determining gonad organ shape. Depletion of the gene for *C. elegans* Fibulin-1 (fbl-1) rescues *Gon-1* mutant defects [6] and both regulate collagen IV accumulation in the basement membrane [7]. Interestingly mammalian ADAMTS4 or ADAMTS9 can substitute for *Gon-1* [6], indicating that homologous mammalian family members retain this activity. A second role for *Gon-1* that is shared by ADAMTS9 may be to regulate protein trafficking from the endoplasmic reticulum to golgi [8], though any role for this function in DTC migration or gonad morphogenesis is not determined.

Another ADAMTS member encoded by the mig-17 gene is secreted by body wall muscle cells and localises to basement membrane surrounding and at the leading edge DTC of the gonad [9], through a process that requires activation of the protease through pro-domain excision [10,11]. Directional migration of DTC requires MIG-17 and this involves an interaction with Fibulin and Collagen IV α2 subunit leading to recruitment of Nidogen-1 to the basement membrane [12]. A third ADAMTS member in *C. elegans*, ADT-2, with a sequence equally divergent from all mammalian ADAMTS members appears to contribute to collagen fibril deposition similar to human ADAMTS2/3/14 [13] and modulates TGFβ signalling activity [14].

With only three ADAMTS members and no recognised large aggregating proteoglycans in Drosophila or *C. elegans* these model systems are expected to be simplified compared to mammalian gonadogenesis. It is clear that key roles in morphogenesis and lineage determination in the gonad involving BM remodelling and stability are among the most overt and fundamental roles of the invertebrate ADAMTSs. However the substrates for *C. elegans* ADAMTS proteolytic activity have not been determined, and hence is much of the molecular pathway of action still to be revealed.

Vertebrate gonadogenesis

Divergence of mammalian gonads from the ambiguous genital ridge structure into female and male lineages begins in the 6th week postfertilisation in humans (embryonic day 11.5 in mouse). This is first recognisable morphologically by a change in vasculature in the male presumptive testis as large blood vessels infiltrate the gonadal ridge from the neighbouring mesenephros and seminiferous tubules develop soon after [15]. Differential gene expression can also be observed around the same time with male gonads showing elevated male determining genes *Sry* and *Sox9*, as well as *Cyp17a1* among genes involved in androgen synthesis [16]. The female gonad exhibits elevated *Adamts19* mRNA from day e12.5 in the mouse, and remains higher in the postnatal ovary than testis [17]. This finding has been repeatedly confirmed [18,19], and *Adamts19* is commonly used as an early marker of gonad differentiation and/or sex reversal. There are no reported studies of *Adamts19* knockout mice; however, preliminary reports on a null mouse model recently available from the Sanger Mouse Portal indicate that the null females and males are fertile (http://www.sanger.ac.uk/mouseportal/phenotyping/MGTS/fertility/). Furthermore, a recent novel study using *Adamts19* knockdown through cardiac injection of morpholinos in e11.5 fetuses followed by 48 h culture of the gonads revealed no morphological changes, unaltered somatic to germ cell ratios and no change in male or female specific gene markers in the gonads [20]. The function of ADAMTS19 in the diverging ovary remains unknown; indeed, its protein

localisation or substrate specificity is yet to be determined. Based on its sequence homology *Adamts19* is most closely related to *Adamts17* suggesting that it may participate in extracellular matrix fibrillin microfibril biogenesis [21]. Whether ECM structural differences emerge between diverging male and female gonads at the time when *Adamts19* is sex specifically induced has not been reported. However, interestingly the novel fibrillin isoform, Fibrillin-3, was recently shown to be highly expressed in fetal bovine and human ovaries most strongly in the first trimester [22], though the *Fbn3* gene is inactive in the mouse genome. A polymorphic allele within intron 55 of thein the human Fibrillin-3 gene (FBN3) has been implicated in the aetiology of inheritable forms of polycystic ovarian syndrome (PCOS) [23–27]. *ADAMTS19* polymorphisms are also associated with PCOS [28], and with premature ovarian failure [29–32], reinforcing the hypothesis that ECM changes in early ovarian development may contribute to the PCOS phenotype [33], and other ovarian disorders. Certainly, the function of ADAMTS19 and its impact on ECM fibrillogenesis in early mammalian ovarian development are clear areas in need of further investigation.

Two additional ADAMTS members have been noted in isolated reports of embryonic gonadogenesis. In chickens *ADAMTS12* is elevated in testes but not ovaries around the time of sex determination and was localised in developing testicular chords [34]. Conversely, *ADAMTSL1* is elevated in the developing ovary at the time of gonad differentiation [34]. The functional roles of ADAMTS12 and ADAMTSL1 during gonadogenesis in the chicken, however, have not been determined.

ADAMTS16 was identified in rodent testes and ovaries from embryonic day 13 and in spermatids and follicular granulosa cells of adult males and females respectively [35]. Knockdown of the Wilms tumor-1 gene (Wt1) increased *Adamts16* mRNA in XY but decreased it in XX gonads indicating that its expression is likely to be downstream of Wt1 and has sexually dimorphic expression [35]. A recent report of targeted knockout of *Adamts16* in the rat demonstrates the essential requirement of this isoform for testes development with homozygous males exhibiting cryptorchidism and sterility [36]. In humans mutations in Wt1 are associated with azoospermia and thus infertility in men [37]. This together with the evidence from the knockout rat and that *Adamts16* is coexpressed with Wt1 point toward ADAMTS16 being important for male fertility in humans.

Ovarian function

The mammalian ovary develops into a complex and highly organised structure in adults that undergoes continuous cyclic stages of remodelling throughout reproductive life. Mammalian oocytes mature slowly within follicles which are spherical structures comprising many specialised somatic cell layers which protect and support growth the central oocyte. At birth human ovaries contain a fixed pool of around 1–2 $\times$ 10^5 follicles of around 60 μm diameter each in a quiescent, non-growing state. Throughout reproductive life these follicles sporadically activate growth and reach a size up to 20 mm at the time of ovulation, when the follicle undergoes controlled rupture and release of the mature oocyte. During follicle growth a vital vascular bed is recruited around the structure, but a basement membrane excludes vascularisation of the follicle interior. After ovulation, luteinisation occurs, involving a further doubling in size and rapid vascularization to support extremely high steroidogenesis by the corpus luteum producing progesterone which supports implantation and pregnancy. Most follicles do not achieve full growth to the ovulatory stage and instead regress and are resorbed through a process known as atresia.

Folliculogenesis

A number of ADAMTS family members have been identified in growing follicles, during ovulation and in corpora lutea of several mammalian species. During folliculogenesis a number of ADAMTS members have been shown to be expressed. These include *Adamts1* predominantly expressed by the granulosa cells in rodents [38–40], cows [41], horses [42], pigs [43], monkeys [44] and humans [45]. *Adamts4*, *5*, *9* and *15* are expressed by granulosa cells sand cumulus cells in rodents [46], and/or monkeys [44]. These findings give an impression that members of the proteoglycanase arm of the ADAMTS family are most commonly expressed; however, there has been no complete systematic investigation of all ADAMTS family members during folliculogenesis.

Follicle stimulating hormone (FSH), the pituitary hormone which promotes follicle growth and survival, induces expression of *Adamts1*, *4* [40,45], and *16* [47], suggesting that these enzymes are linked to follicle growth. Investigation of the protein localisation during folliculogenesis has only been performed with ADAMTS1 in mice, which showed the mature (pro-domain removed) protein in the basement membrane surrounding growing follicles [48]. Versican, the best characterised substrate for ADAMTS1 is also located in the follicular basement membrane from the earliest discernible stages of follicle growth in rats, mice and cows [49,50] and it is suggested that ADAMTS1 cleavage of versican may contribute to structural remodelling at the follicle-stromal boundary as follicles grow. Indeed, *Adamts1* knockout mice revealed a requirement for ADAMTS1 in basement membrane remodelling similar to Gon1 and Mig17 in *C. elegans* gonads. Some growing follicles in Adamts1 null ovaries lose structural

integrity, granulosa cells are progressively lost and follicles deteriorate while the oocytes persist and accumulate with age in the ovarian stroma [51,52].

Ovulation

The ADAMTS family has been known to be involved with ovulation since the earliest days after its discovery. *Adamts1* was identified in a survey for genes upregulated in ovulating rat follicles using differential display PCR [38]. This induction was shown to be dependent on the expression of the progesterone receptor (*Pgr*) in granulosa cells. *Pgr* knockout mice are completely infertile due to a failure to ovulate any oocytes and their failure to up-regulate Adamts1 in the periovulatory phase strongly suggested that ADAMTS1 is a protease that mediates follicular rupture [39]. PGR has now also been shown to mediate ADAMTS1 induction in rats [38], cows [53], pig [43], horse [42] and primates [44]. Subsequent knockout of *Adamts1* in mice confirmed a key role for this protease as a downstream effector of PGR function in ovulation. *Adamts1*$^{-/-}$ females are subfertile, producing litters with 4- to 5-fold fewer pups born compared to control littermates and large follicles that failed to rupture were present in the ovaries [54]. The less severe infertility compared to *Pgr*$^{-/-}$ mice, which have no litters indicates that other progesterone receptor regulated genes also contribute to the ovulatory mechanism, possibly including the Cathepsin serine protease family [39], but the other important PGR regulated genes remain to be definitively identified. The ADAMTS1 protein is present in its pro-form in mural granulosa cells of periovulatory follicles, which is also the site of PGR action. However, the mature ADAMTS1 is secreted and the vast majority of it is found in cumulus ECM surrounding the oocyte where *Pgr* and *Adamts1* are not expressed [55]. A very similar spatiotemporal pattern of expression and dynamic protein trafficking of the large aggregating proteoglycan versican also occurs [49]. Also, the ADAMTS1 accumulating in the cumulus oocyte complex (COC) has been shown to be necessary to cleave versican, with the majority of cleavage occurring right around the time oocyte release from the follicle occurs [55]. How this contributes mechanistically to ovulation remains unclear, but COCs exhibit extremely dynamic changes in adhesion properties in the same time frame [56] and it is proposed that the ADAMTS1/versican interaction may modulate this adhesion.

Further investigation of the ovaries in *Adamts1*$^{-/-}$ mice revealed that this gene contributes to a number of facets of ovarian development. In addition to follicular basement membrane remodelling and ovulation, vascular defects have also been identified, which is consistent with the many studies in other systems demonstrating that ADAMTS1 regulates development of vascular networks. Originally, this was described as extra capillary layers around growing follicles and fewer large ovarian medullary vessels staining for CD31 marker in *Adamts1*$^{-/-}$ ovaries [51]. Later, the ovarian lymphatic vasculature was characterised for the first time and a defect in development of lymphatic vessels and their recruitment around growing follicles was demonstrated [52,57]. It was demonstrated that lymphatic vessels staining for the lymphatic-specific vascular marker, Lyve-1, are not present in normal mouse ovaries at birth. These vessels first infiltrate the ovary from via the ovarian stalk around postnatal day 10 [52]. This infiltration is ADAMTS1 dependent as *Adamts1*$^{-/-}$ ovaries are devoid of lymphatic vessels, yet liver and skin lymphatics develop normally [52]. The ovarian lymphatic defect could be partially restored by exogenous stimulation of the ovary with the FSH analogue eCG [57] which possibly induced expression of a related ADAMTS member(s) to rescue the loss of ADAMTS1 activity. Despite the recognised importance of the lymphatic vasculature in several ovarian disorders [58] there has been little further investigation of how ADAMTS1 participates in the secondary lymphangiogenesis occurring in the ovary.

In summary, *Adamts1*$^{-/-}$ mice have revealed roles for this enzyme in ovarian folliculogenesis, lymphangiogenesis and ovulation. A semi-penetrant developmental defect in extracellular matrix of the kidney with a fibrosis like appearance has led to the suggestion that ADAMTS1 has a primary, non-redundant role in development and function of the urogenital tissues [54,59].

While no overt roles for the other members of the ADAMTS family have been identified in the ovary, a number of members with redundant activity have been shown to be expressed and regulated in periovulatory follicles. In mice *Adamts4* mRNA is induced within 2 h after exogenous induction of the ovulation process and the 58 kDa processed form of the protein is elevated after 8 h and ADAMTS5 is abundant in granulosa cells, but unregulated [46]. In primate ovaries *ADAMTS1* is present, but *ADAMTS4*, *9* and *15* show the highest levels of induction during the periovulatory interval [44]. It is likely that varying degrees of redundant activity exist among the members of this proteoglycanase subgroup of the ADAMTS family and also that different members play the major roles each species. ADAMTS1 has been identified in human granulosa cells [45] and cumulus cells [60,61] collected shortly before ovulation as a part of assisted reproductive procedures. A unique study of human ovaries collected in the preovulatory period or early or late stages of ovulation showed that *ADAMTS1* and *ADAMTS9* gene expression were induced 30- or 40-fold respectively in granulosa cells but unchanged in theca. Furthermore, abundant protein for ADAMTS1 and 9 was also seen in the

human granulosa layers of ovulating follicles [62]. Additionally *ADAMTS1* and *ADAMTS9* have both been reported to be higher in cells isolated from around oocytes with superior developmental competence compared to those that arrested without completing meiosis, or arrested in early embryo development [61,63]. The expression of the ADAMTS1 substrate versican in cumulus cells has also been associated with higher competence of oocytes to achieve a pregnancy [64,65].

Ovarian disease and dysfunction

The demonstration that ADAMTSs, particularly those of the proteoglycanase subgroup, play important roles in mammalian ovarian development and function suggests that their dysregulation may also contribute to the aetiology of ovarian disease. Indeed, a number of findings do indicate that ADAMTSs contribute to disease pathogenesis of the ovary. Polycystic ovarian syndrome (PCOS) is a highly prevalent condition suffered by around 10–20% of women in developed countries. This disease is defined by the accumulation of unusually high numbers of antral follicles, identified by their cystic appearance on ultrasound, and also associated with hyperandrogenism, hirsutism and importantly insulin resistance and potentially type 2 diabetes [66]. The accumulation of follicles is due to arrested growth and ovarian *ADAMTS1* expression has been associated with this phenotype. An early microarray analysis identified *ADAMTS1* as one of the most highly downregulated genes in PCOS ovaries (4.5-fold) as well as long-term androgen treated female to male transsexual ovaries (3-fold) [67], suggesting that high androgen may mediate the reduced expression in both scenarios. This was supported in a more recent study of 40 PCOS patients and controls which showed lower *ADAMTS1* mRNA and protein in granulosa cells of the PCOS cohort and lower *ADAMTS1* was also associated with lower oocyte recovery in assisted reproductive cycles, poor oocyte maturation rate and poor fertilisation rate [68]. Lower expression of *ADAMTS9* in cumulus cells physically associated with oocytes that failed to progress through meiosis from PCOS patients has also been reported [63]. Premature ovarian failure occurs through an insufficiency of oocytes that results in a premature loss of follicles necessary to maintain normal endocrine secretion patterns and early menopause ensues. Intriguingly, single nucleotide polymorphisms (SNP) in an intron of the *ADAMTS19* gene have also been reproducibly associated with premature ovarian failure [29,31,32]. Each of these studies is based on only small patient numbers and requires further verification, and the impact of these intronic SNP on ADAMTS19 protein function has not been investigated. However, these reports combined with the fact that *Adamts19* is enriched in the early developing ovary (see above) suggest that ADAMTS19 and or related genes may play an important role in determining the numbers of oocytes sequestered into follicles which sustain the fertile lifespan.

Uterine function

Like the ovary, the mammalian uterus is challenged by repeated cycles of growth and development followed by regression and remodelling. The mRNA and protein products of *Adamts1* are expressed in mouse uterine luminal and glandular epithelium and regulated, the mRNA being highest at estrus and protein abundance peaking slightly later at metestrous [69]. This is consistent with a possible regulation by PGR in these cells as in the ovary [39]. Indeed progesterone (P4) induces and mifepristone (RU486) blocks *ADAMTS1* expression [70], as well as *ADAMTS5*, *8* and *9* [71] in cultured human endometrial stromal cells. This is also supported by the finding that *Adamts1* expression is acutely regulated and PGR dependent in the oviduct [72]. In the earliest studies with *Adamts1* knockout mice uterine defects were described including an abnormal uterine lumen and cystic-like glandular structures [59]. Subsequent studies of another *Adamts1*$^{-/-}$ line, however, did not reproduce the uterine defects [54]. Some histological differences in *Adamts1*$^{-/-}$ uteri may simply be the result of altered ovarian steroidogenesis secondary to the altered ovarian folliculogenesis already described.

Implantation

In pregnancy *ADAMTS1* was found to be highest in the pregnant uterus around the time of implantation and spatially highest at the site of implantation [69]. However study of functional implantation and decidualisation of the *Adamts1*$^{-/-}$ mouse uterus demonstrated these processes to be normal [54]. Likewise, none of the other *Adamts* null mouse models have demonstrated a uterine or implantation defect. In human decidualised stromal cells ADAMTS1 and ADAMTS5 proteins have been identified and their mRNA expression found to be regulated by interleukin 1β (IL1β) and transforming growth factor β (TGFβ) [73,74]. Similarly, in bovine uteri *Adamts1* mRNA is present in luminal epithelial and stromal cells and regulated by progesterone in cultured stromal cells [75]. Thus redundancy or species differences may have prevented the identification of a requirement for ADAMTS function during implantation in the individual null mouse models.

Placentation

Several members of the ADAMTS family have been reported in the placenta. In bovine preimplantation embryos *ADAMTS1* mRNA is present in the

trophoblast cells which will subsequently invade the uterine endometrium and implant to form the placenta [75]. In mice *Adamts1* is also present in the placenta [76] and surveys of human tissues have identified *ADAMTS14* [77] and *ADAMTS9* [78] and *ADAMTS1* was shown to be present and regulated by the PKA pathway activating hormone polyadenylate cyclase activating polypeptide (PACAP) in human extravillous cytotrophoblast cells. *ADAMTS1*, *4*, *5* and *14* were all expressed in regulated patterns throughout gestation in human placentas, with *ADAMTS4* and *5* most highly expressed in the first trimester when placental invasion is most pronounced. Furthermore, a small increase in *ADAMTS1* and larger increases in *ADAMTS4* and *5* were associated with placental carcinoma or precancerous disease conditions [79]. It is believed that the cancerous conditions of the placenta arise from dysregulation of normal trophoblast implantation mechanism [80]. A relationship between connective tissue abnormalities and placental dysfunction has been under recent investigation [81] and newer studies build a case for ECM remodelling involving ADAMTSs in placental membrane function and diseases that can lead to preterm birth. Upregulation of *ADAMTS9*, among several ECM genes in the placenta of smokers, implicates it in the placental abnormalities that lead to small birth size for gestational age and preterm delivery [78]. An SNP in the *ADAMTS9* gene is strongly associated with increased type 2 diabetes risk [82] and *Adamts9* expression is reduced in high fat diet fed mice that develop insulin resistance [83], prompting the hypothesis that ADAMTS members may also contribute to gestational diabetes [84]. In vitro studies with first trimester human placental explants indicate that placental cell adhesion to ECM substrata and invasion requires ADAMTS12 interaction with αvβ3 integrin and is not dependent on the protease function [80]. Together the existing data indicate that the role for ADAMTS9 and other proteoglycanases in effective placental invasion and function warrants further investigation.

Parturition

At gestational term ADAMTS family members are also involved in remodelling of the uterus and cervix to enable parturition. The cervix is a rigid tissue during pregnancy with a collagen rich matrix, but this remodels during parturition with increased hyaluronan (HA) and decreased collagen allowing a more flexible matrix. In mice the HA-binding proteoglycan and ADAMTS substrate versican is also highly abundant in cervical stromal matrix and ADAMTS1 protein becomes detectable acutely from around 1 day before through in the hours immediately postpartum, leading to the suggestion that it contributes the cervical ripening and birth [85]. While no defect in this process is reported in *Adamts1*$^{-/-}$ mice, redundancy is again likely to mask effects of individual genes. Indeed *Adamts9* was found to be increased in the myometrium of women with arrested dilatation during labour [86] adding to the evidence that ADAMTS9 is particularly important in uterine remodelling of implantation, placentation and parturition. Homozygous *Adamts9* null mice are embryonic lethal meaning that the full importance of the gene in pregnancy has not been determined by this approach.

Testicular and sperm function

Testis morphogenesis and function

Like the female reproductive tissues, testes are organs that undergo consistent cycles of remodelling in order to constantly mature and release thousands of new sperm cells every second and a range of evidence indicates that ADAMTS enzymes are important at various stages in testicular development sperm production and function. Null mutation of *Adamts2* in mice causes progressive dysgenesis of collagen fibrils in skin, but also causes male infertility through reduced mature sperm present in seminiferous tubules and in semen [87]. *Adamts20* is highly expressed in testis [88] and detectable from late prenatal developmental stages. In bovine *ADAMTSL3* is more highly expressed in adult testis than other tissues [89]. As already described above *Adamts16* appears to be differentially regulated in early developing mouse testis and ovary [35], and *Adamts16* null mutant rats generated by ZFN technology are infertile with cryptorchidism and azoospermia, resulting from a loss of sperm progenitor cells [36]. The female mutants are apparently normal, except that males and females exhibit morphological kidney defects, consistent with a role for the ADAMTS family in urogenital development and function.

Sperm function

While the ADAM family is best known for its role in sperm–egg interactions at fertilisation, a novel sperm ADAMTS-like protein has been reported in sea urchin (*Strongylocentrotus franciscanus* and *Strongylocentrotus purpuratus*). Termed egg receptor for binding (ERB1), it shares homology with both the N-terminus, as well as thrombospondin type-1 domains, and is proposed to mediate species-specific sperm adhesion [90].

Mammalian sperm incorporate ADAMTS10, which is secreted by testis, into the acrosomal domain at the apex of the sperm head and appears to participate in the acrosome's role in adhesion between the sperm and egg zona pellucida [91]. Antibodies against

ADAMTS10 reduced sperm–zona pellucida adhesion, and so does the metalloproteinase inhibitor galardin (or GM6001), indicating that this adhesion function is dependent on the protease activity of ADAMTS10 [91]. Additionally, as eluded to above, in humans undergoing *in vitro* fertilisation (IVF), *ADAMTS1* expression in the cumulus cells was correlated with higher fertilisation capacity [61]. The evidence together indicates that ADAMTS as well as ADAM proteins participate in sperm–egg adhesion events in a number of species. Mutations in the human ADAMTS10 gene are widely recorded and known to cause a connective tissue disorder, Weill–Marchesani syndrome, characterised by abnormalities of the lens, shorter stature and digits, and joint stiffness [92]. This is thought to arise through altered microfibril biogenesis [21], but fertility has not been shown to be affected or unaffected.

Conclusion

The ADAMTS protease family plays multifaceted roles in male and female fertility (Fig. 1). Invertebrate ADAMTS members are required for normal gonadal morphogenesis and function. Among the mammalian family of 19 members, 13 have been demonstrated to participate in one of the many essential processes in male or female reproduction, spanning most of the functionally different ADAMTS subgroups. These contribute to processes including the divergent development of male and female gonads, through aspects of male and female gametogenesis, sperm–egg fusion and implantation of the conceptus. The most common features of these processes are being requirements for cell–ECM interaction and tissue remodelling and regeneration. These insights into the roles of ADAMTS proteases offer clinical potential to generate therapeutic targets to resolve infertility, develop biomarkers that predict dysfunction of the reproductive organs and potentially offer targets for development of non-hormonal male and female contraceptives.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. The authors have nothing to disclose.

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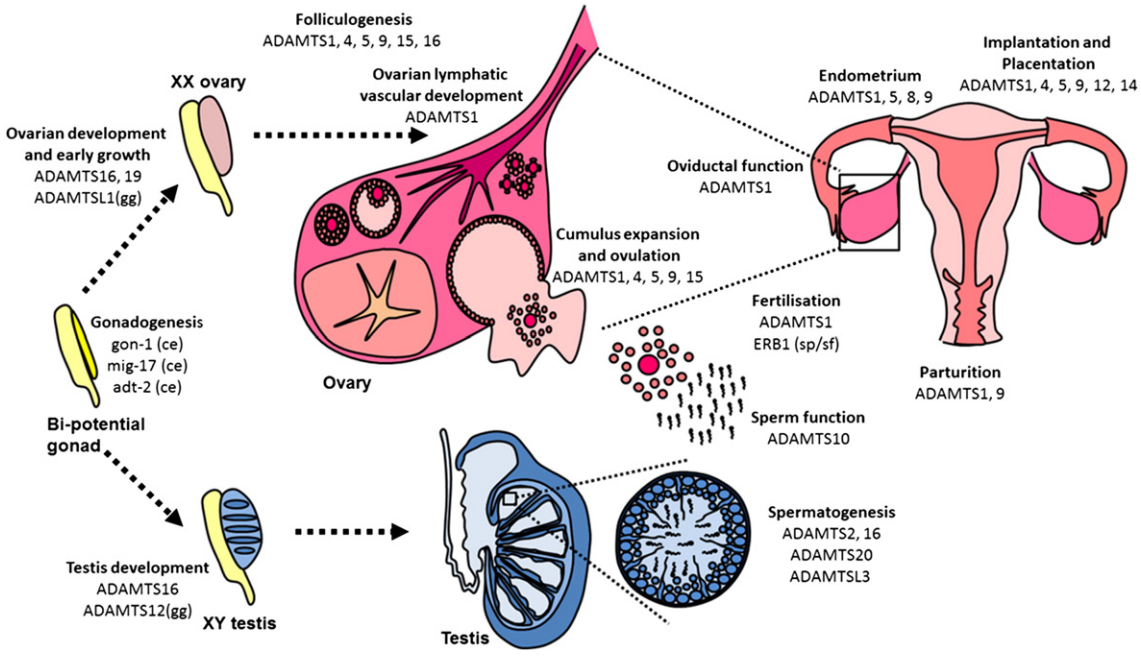

Fig. 1. The multiple sites of expression the ADAMTS family of proteases in male and female reproductive tissues or processes in different species. Schematic representation of the ADAMTS family members in male and female fertility. Mammalian gene and or protein involvement represented by ADAMTSX. Non-mammalian gene or protein involvement as follows: gg—Gallus gallus (chicken); ce—*Caenorhabditis elegans* (worm); sp/sf—*Strongylocentrotus franciscanus* and *S. purpuratus* (sea urchin).

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