ADAMTS and Fertility in Females and Males

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The *ADAMTS* (A Disintegrin and Metalloproteinase with Thrombospondin Motifs) family genes code for key metalloproteinases in the remodeling process of different ECM. Several genes of this family encode for proteins with important functions in reproductive processes; in particular, *ADAMTS1*, 4, 5 and 9 are genes that are differentially expressed in cell types and the physiological stages of reproductive tissues. ADAMTS enzymes degrade proteoglycans in the ECM of the follicles so that the oocytes can be released and regulate follicle development during folliculogenesis, favoring the action of essential growth factors, such as FGF-2, FGF-7 and GDF-9. The transcriptional regulation of *ADAMTS1* and 9 in preovulatory follicles occurs because of the gonadotropin surge in preovulatory follicles, via the progesterone/progesterone receptor complex. In addition, in the case of ADAMTS1, pathways involving protein kinase A (PKA), extracellular signal regulated protein kinase (ERK1/2) and the epidermal growth factor receptor (EGFR) might contribute to ECM regulation. Different *Omic* studies indicate the importance of genes of the *ADAMTS* family from a reproductive aspect. *ADAMTS* genes could serve as biomarkers for genetic improvement and contribute to enhance fertility and animal reproduction.

animal reproduction ADAMTS extracellular matrix genetic improvement

1. Introduction

The enormous expansion in the production of food from livestock during the last 70 years has been possible, in great part, through genetic improvement [1]. Reproduction is one of the most relevant aspects in animal production, because of relevancy to productivity and sustainability of the different livestock systems [2]; however, these traits, as well as other economically important traits, are quantitative, multifactorial and have low heritability. The development of molecular and genomic technologies has contributed to the identification of major genes and genetic markers associated with phenotypes, leading to accelerated genetic improvement [3]. Nevertheless, it is important to elucidate how genes that encode for the proteins related to such traits are regulated and how the genetic variants affect their expression [4].

Extracellular matrix (ECM) remodeling is an important physiological process related to reproductive capacity in males and females. This restructuring of the ECM has been associated with the reproductive processes of folliculogenesis, ovulation, implantation and placentation [5][6] in females and in processes that induce correct testicular development, as well as the ongoing production and maturation of millions of spermatozoa in males [6][7]. In addition, the degradation of the ECM in the zona pellucida is an important physiological process for oocyte fertilization [8].

Different matrix metalloproteinases function in the degradation of extracellular matrices [9]. The metalloproteinases superfamily is composed of ADAM proteases (A Disintegrin-like and Metalloproteinase), MMPs (Matrix Metalloproteinases), astacins (BMP/tolloid proteases and meprins in mammals) and ADAMTS (A Disintegrin-like and Metalloproteinase Domain with Thrombospondin type 1 repeat) [10]. Both MMPs and ADAMTS are secretory proteins. ADAMTS are key proteases in the degradation of the ECM, particularly cleaving large proteoglycans, whereas MMPs recognize short peptides as substrates and thus have a wider range of protein targets and a role in many different physiological processes [11][12]. In contrast, the ADAM proteases are integral membrane enzymes that mainly cleave ectodomains of different secretory proteins [13].

In addition to the crucial role of the ADAMTS proteases in the ECM remodeling of the development of reproductive organs and processes, Etacin-related proteins also have an important function, activating growth factors necessary for the assembly of the ECM [14][15][16].

2. Structural Features of ADAMTS Genes

ADAMTS proteinases are multidomain enzymes with highly conserved structures [17]. *ADAMTS1* was the first gene of this family to be described in mice [18], and later, other genes were identified in other species. In mammalian genomes, 19 *ADAMTS* genes have been identified and named *ADAMTS1* to *ADAMTS20*. It was later discovered that *ADAMTS5* and *ADAMTS11* are the same gene, and *ADAMTS11* is no longer used [19][20]. The expansion in the number of *ADAMTS* genes in mammals seems to have occurred due to gene duplication, thus generating sub-functionalization or neo-functionalization regarding the physiological processes in which they participate [13]. Rose et al. [21], in their excellent review, explain that *Gon-1* is the only *ADAMTS* orthologous gene in *Caenorhabditis elegans*, and it has similarity to *ADAMTS9* and *ADAMTS20* in humans. The six ADAMTS proteases in the ascidian *Ciona intestinalis* represent the central evolutionary clades in chordates from which gene expansion into vertebrates occurs [22], along with the evolution of the ECM. Phylogenetic analysis clearly suggests the gene duplication of the *ADAMTS* genes [21].

The signature domains of the ADAMTS proteins are: a signal peptide, necessary for protein trafficking and secretion, and an inhibitory prodomain that must be cleaved from the ADAMTS zymogens to render them catalytically active. Such cleavage occurs in Golgi, the cell surface or extracellularly. The size of this prodomain comprises about 200 residues in all ADAMTS proteases, with the exception of ADAMTS13, which has a short prodomain that does not need to be removed for the protease to be active [23]. Interestingly, the removal of the ADAMTS9 prodomain reduces the protease catalytic activity upon versican, its substrate; a disintegrin-like domain; a thrombospondin type 1 repeat (TSR-1) motif; and a cysteine-rich domain followed by a spacer region. The TSR-1 domains and the spacer domain appear to be involved in ECM anchoring. The description of the organization of these proteins is based on the structure of ADAMTS4, the other members of the family vary mainly at the C-terminus, with either, more or fewer repeats of the TSR-1 motifs [24]. **Figure 1** illustrates the structure and localization of these proteins.

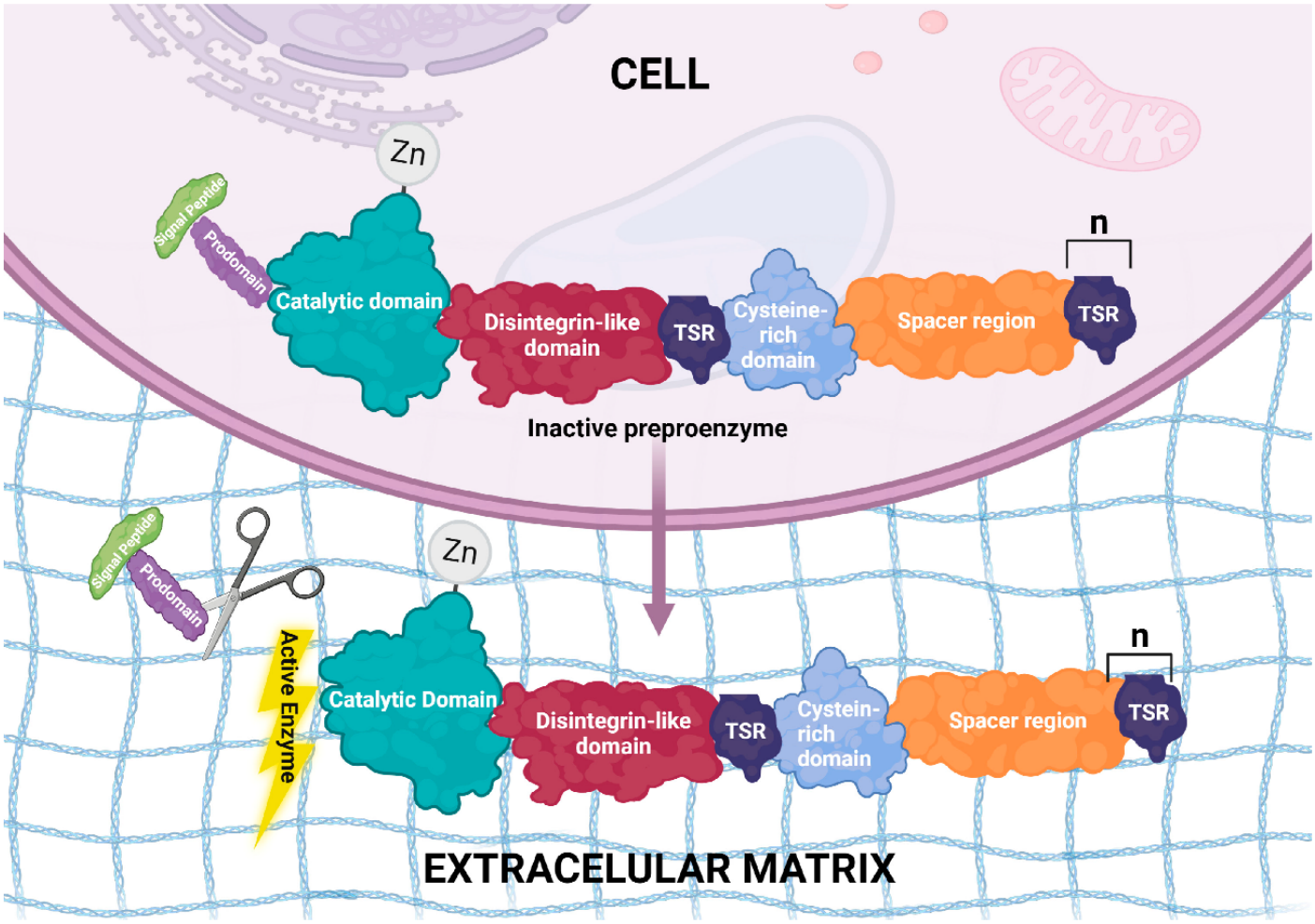

Figure 1. Illustration of ADAMTS protein structure and localization. Cleavage can occur in trans-Golgi, on the cellular surface or extracellularly.

The *ADAMTS* genes are located on different chromosomes that vary depending on the species. These genes code for proteins with a theoretical weight ranging between 70.9 and 225.64 kDa, with 662 amino acid residues in species such as the rooster (*Gallus gallus*) or as many as 2028 in species such as the pig (*Sus scrofa*).

3. ADAMTS and Fertility in Females

3.1. Folliculogenesis

The process of development and maturation of follicles, termed folliculogenesis, is necessary for ovulation to occur [25]. The *ADAMTS* family genes seem to be related to this process, inferred by the relative abundance of mRNA transcripts in the follicles and corpus lutea of several mammalian species. *ADAMTS1* have been reported to be expressed in granulosa cells in cows [26], horses [27] and pigs [28].

According to Brown et al. [29], ADAMTS1 functions are necessary for the structural changes of the ECM to occur during follicular development. The proteoglycans present in the ECM can inhibit the action of certain growth

factors, such as FGF-2, FGF-7 and GDF-9 [30], which are essential for various exquisite reproductive processes to occur. For example, FGF-2 stimulates angiogenesis and granulosa cell proliferation and function in cattle [31] and buffalo [32]. FGF-2 also stimulates the initiation and development of follicular growth in sheep and goats [33][34].

Thus, the functions of ADAMTS1 and 4 are thought to enhance these processes by controlling the amount and location of various proteoglycans [35]. Shozu et al. [36] inactivated the *ADAMTS1* gene and reported that the absence of ADAMTS1 led to follicular atresia. Versican is an abundant ECM proteoglycan that is hormonally regulated by the ovary. Versican abundance varies throughout the several stages of follicular growth but particularly during ovulation in rodents [37]. The presence of versican in bovine and porcine follicular basement membrane [38][39], suggests that ADAMTS1 may also regulate the development of follicles during folliculogenesis.

3.2. Ovulation

The preovulatory surge of gonadotropins induces a series of biochemical processes within the dominant follicle that culminate in ovulation and, subsequently, in the formation of the corpus luteum. Ovulation is associated with the degradation of the follicular basement membrane and the fragmentation of the ECM at the apex of the follicle wall, resulting in the release of the oocyte [40]. Metalloproteinases enzymes are responsible for the degradation of the follicular ECM during ovulation [9]. ADAMTS1 degrades versican, aggrecan and brevican, proteoglycans present in the ECM of the follicle. Such degradation of the follicular wall allows oocyte release [41][42]. Indeed, ADAMTS1 was reported to have a fundamental function in ovulation, as reported by Mittaz et al. [43], based on results from a study with female mice lacking the ADAMTS1. In this study, exon 2 was deleted to disrupt the *ADAMTS1* gene and a selectable marker gene was inserted in intron 1. The modified *ADAMTS1* allele was functionally null. The authors reported that these females were subfertile due to impaired ovulation, resulting in the mature oocytes not being released from the follicles, as would typically occur during ovulation. Likewise, Brown et al. [44] reported that the ovulation rate was 77% less in female mice lacking the ADAMTS1 enzyme, compared to the wild-type animals. The finding was explained by the lack of versican degradation during the matrix expansion of the cumulus–oocyte complex.

Hu et al. [45] reported that SNP-type polymorphisms in *ADAMTS1* are related to litter size in goats; therefore, they could be used as molecular markers for the selection of litter size. *ADAMTS1*, 4 and 9 are considered to be of great importance for animal production, where reproductive prolificacy is a determinant for sustainability. **Figure 2** depicts the possible functions of ADAMTS proteins in folliculogenesis and ovulation in livestock.

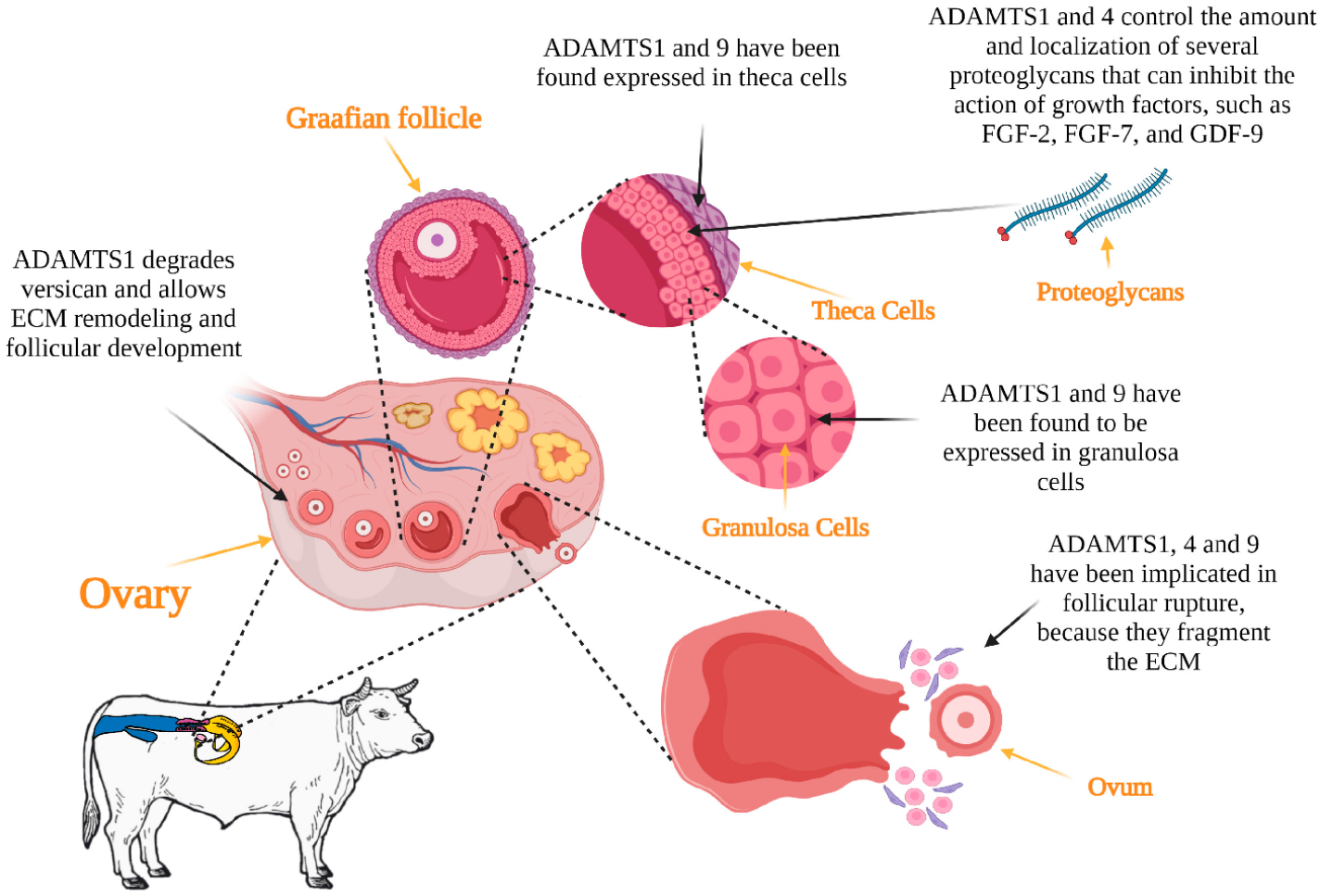

Figure 2. ADAMTS genes are involved in folliculogenesis and ovulation. The specific gene, site of expression and function is shown.

3.3. Implantation, Placentation and Parturition

Similar to the constant remodeling of the ECM required for the cyclical transformations of the ovary, the uterus also undergoes the cyclic development and remodeling of the endometrial tissue matrix. This remodeling is necessary for implantation and placentation [46]. Implantation is a critical process for the establishment of pregnancy and begins with essential signaling from the blastocyst to the endometrium, which must be prepared to respond [47][48]. The attachment of the blastocyst to the uterus and subsequent trophoblast cell invasion occurs through ECM remodeling [49]. Uterine tissue remodeling is also required for placental cotyledon formation and angiogenesis near trophoblast tissue in sheep, as well as a decrease in endometrial thickness during implantation [50][51].

Another member of this family of metalloproteinases, ADAMTS9, has been reported to contribute to remodeling in the uterus at the time of parturition. The extracellular matrix undergoes remodeling during late gestation to allow smooth muscle cells to connect to each other and effect uterine contractions at the time of parturition [52]. ADAMTS9 is present in all reproductive states and contributes to uterine tissue remodeling. The accumulation of versican from the extracellular matrix in the uterus leads to abnormal contractions. Mead et al. [53] reported that there are abnormally large concentrations of versican in mice that do not produce ADAMTS9, leading to abnormal

parturition processes. This abnormality was due to a reduction in focal adhesions between cells that interact with one another to generate uterine contractions. Thus, ADAMTS9 contributes to the remodeling of the uterine extracellular matrix through the degradation of versican, and its null or poor functionality disrupts parturition processes. The possible functions of the ADAMTS proteases in implantation, placentation and parturition in livestock is illustrated in **Figure 3**.

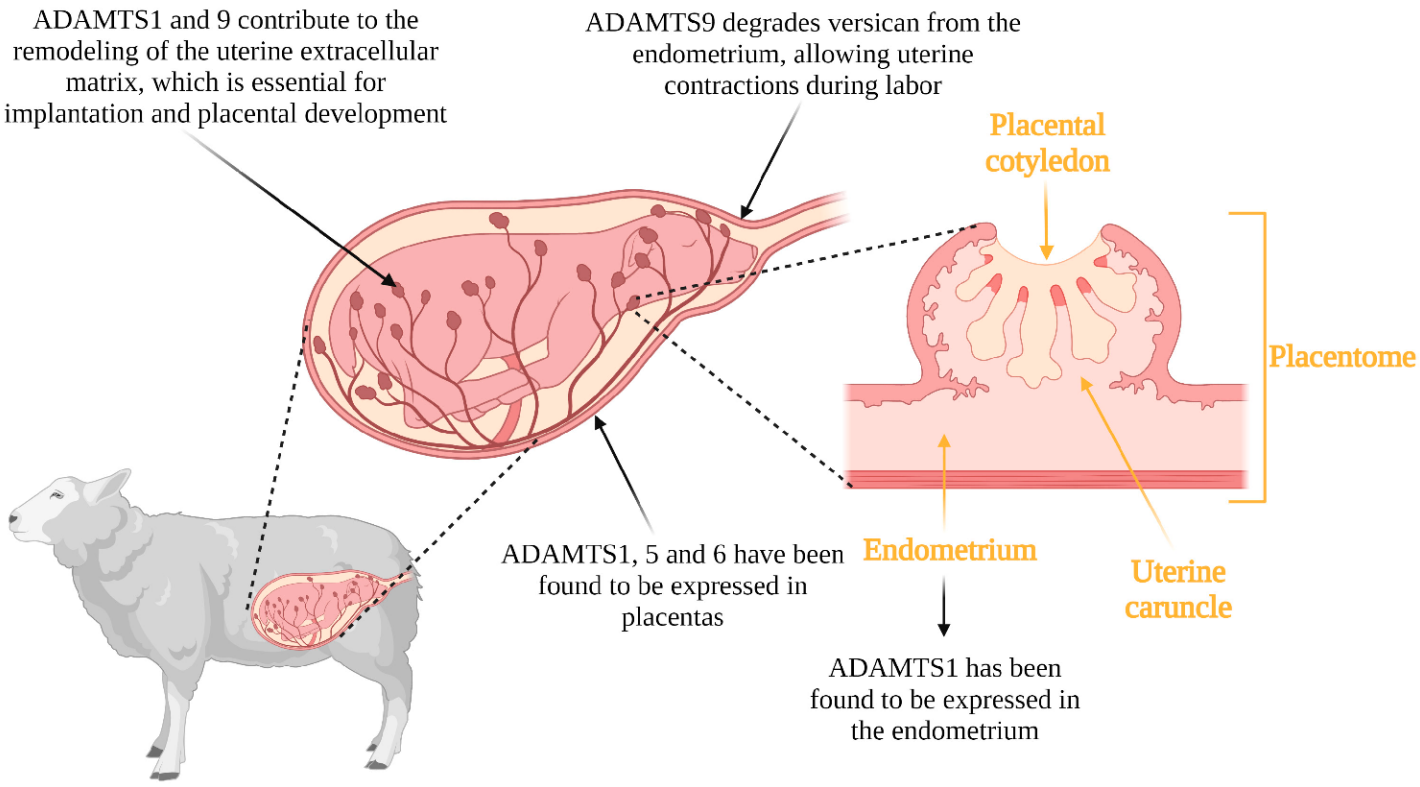

Figure 3. ADAMTS genes are involved in implantation, placentation and parturition. The specific gene and its site of expression and function is shown.

4. ADAMTS and Fertility in Males

4.1. Testicular Development

The expression of *ADAMTS* family genes, in addition to being related to fertility in females, has also been linked to reproductive capacity in males, specifically to testicular development [54]. The testicles develop in the abdomen during the embryonic and fetal stages. Subsequently, the testes pass through the inguinal canal into the scrotum [7], with this process requiring the tissue remodeling of the ECM [6]; however, regarding this process, the literature is limited to only a few studies of rodents. Jacobi et al. [55] reported there was expression of *ADAMTS16* in the testes of mouse embryos. Likewise, alterations in *ADAMTS16* led to cryptorchidism and infertility in male rats [54][56].

4.2. Spermatogenesis

Spermatogenesis is the process through which germ cells multiply and differentiate to produce sperm in the seminiferous tubules [57]. The presence of *ADAMTS10* expression in the testis, epididymis and ejaculated spermatozoa of Asian buffalo (*Bubalus bubalis*) [58] suggests a possible function in the sperm maturation process [59]. ADAMTS2 has also been linked to sperm maturation in mice, as shown by Li et al. [60]. In transgenic mice homozygous for the inactive alleles of *ADAMTS2*, there was less sperm maturation and activity compared to those in the control group; however, more research is needed to determine the functions of these proteins in sperm maturation.

In bulls with besnoitiosis compared to healthy bulls, *ADAMTS1* mRNA abundance is lower in scrotal skin, the pampiniform plexus and testicular parenchyma [61]. This disease causes the fibrosis and thickening of the skin of the scrotum, which leads to failure in thermoregulation and to the inhibition of spermatogenesis, ultimately causing infertility [62].

Wu et al. [63] performed a transcriptomic analysis of yak and cattleyak testes to investigate the genetic causes of hybrid animal sterility, and several *ADAMTS* genes were differentially expressed. *ADAMTS1*, 10, 12, 3, 5 and 14 were upregulated, whereas *ADAMTS16*, 20, 6 and 18 were downregulated; thus, these proteins could be involved in cattleyak sterility. However, how these proteins are associated with hybrid animal sterility is still unclear.

4.3. Fertilization

ADAMTS is apparently involved in sperm and egg fertilization processes. In a study conducted by Dun et al. [8] in mice, *ADAMTS10* was expressed during the late stages of spermatogenesis, and the protein was incorporated into the acrosome of developing spermatids. ADAMTS10 presence in the acrosome is thought to function by inducing sperm adhesion to the zona pellucida. The zona pellucida is an ECM that surrounds the oocytes and must be crossed by spermatozoa to penetrate the oocyte and carry out fertilization. ADAMTS10 has important functions in this process by acting in the degradation of the zona pellucida [64]; however, further research in farm animals is needed to understand the role of ADAMTS10 in fertilization.

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