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The new kids on the block: ADAMTSs, potentially multifunctional metalloproteinases of the ADAM family

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Commentary

Cell-cell and cell-matrix interactions are of vital importance not only for proper cellular homeostasis during embryogenesis and development of an organism, but also in pathological states in diseases ranging from tumor metastasis to AIDS. Tissues owe their dynamic structure both to changes in expression of adhesive proteins and their receptors and to the regulated action of secreted proteinases, particularly members of the metalloproteinase family. Many of these secreted and cell surface proteins and metalloproteinases are found at critical locations that facilitate their involvement in cell-cell and cell-matrix interactions. Metalloproteinases belong to a superfamily of zinc-dependent proteases known as metzincins. Based on sequence and structural similarities, metzincins are grouped in four distinct subfamilies: the astacins, the matrixins (matrix metalloproteinases), the adamalysins (reprolysins, or snake venom metalloproteinases [SVMPs], and ADAMs), and the serralysins (large bacterial proteinases) (1). ADAMs are a family of membrane-associated multidomain zinc-dependent metalloproteinases with high sequence homology and domain organization, similar to the SVMPs of the adamalysin subfamily (2–4). The term “ADAM” stands for a disintegrin and metalloproteinase, which represent the two key structural domains in these molecules. Thus, ADAMs are distinct among cell surface proteins in containing features of both adhesive proteins and proteinases, and their roles in cell-cell interactions have attracted particular interest. In addition, ADAM proteins contain a prodomain, as well as cysteine-rich, EGF-like, transmembrane, and […]

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Cell-cell and cell-matrix interactions are of vital importance not only for proper cellular homeostasis during embryogenesis and development of an organism, but also in pathological states in diseases ranging from tumor metastasis to AIDS. Tissues owe their dynamic structure both to changes in expression of adhesive proteins and their receptors and to the regulated action of secreted proteinases, particularly members of the metalloproteinase family. Many of these secreted and cell surface proteins and metalloproteinases are found at critical locations that facilitate their involvement in cell-cell and cell-matrix interactions.

Metalloproteinases belong to a superfamily of zinc-dependent proteases known as metzincins. Based on sequence and structural similarities, metzincins are grouped in four distinct subfamilies: the astacins, the matrixins (matrix metalloproteinases), the adamalysins (reprolysins, or snake venom metalloproteinases [SVMPs], and ADAMs), and the serralysins (large bacterial proteinases) (1). ADAMs are a family of membrane-associated multidomain zinc-dependent metalloproteinases with high sequence homology and domain organization, similar to the SVMPs of the adamalysin subfamily (2–4). The term "ADAM" stands for *a d*isintegrin *a*nd *m*etalloproteinase, which represent the two key structural domains in these molecules. Thus, ADAMs are distinct among cell surface proteins in containing features of both adhesive proteins and proteinases, and their roles in cell-cell interactions have attracted particular interest. In addition, ADAM proteins contain a prodomain, as well as cysteine-rich, EGF-like, transmembrane, and cytoplasmic tail domains (2–4). These specialized structural domains suggest a possible role for ADAMs in cell-cell and cell-matrix interactions.

At present, more than 25 ADAM family members have been identified from mammalian and nonmammalian sources, including *Xenopus*, *Drosophila*, and *Caenorhabditis elegans* (1, 4). Biological roles are now emerging for some of these proteins. Some ADAM family members perform specialized functions in cell adhesion, fusion processes, and shedding of cell surface proteins (1, 2, 4). For example, ADAM1 (fertilin α) and ADAM2 (fertilin β) participate in sperm-egg fusion (5); ADAM17 (TACE) (6), ADAM9 (MDC9) (7, 8), and ADAM10 (Kuzbanian) (8) mediate the shedding of cell surface proteins and are called sheddases; and ADAM12 (meltrin α) promotes myoblast fusion (9).

Recently, new members of the ADAM family, known as ADAMTSs (*a d*isintegrin *a*nd *m*etalloproteinase with *th*rombo*s*pondin motifs), have been cloned and studied (10–12). These proteins, which are not counted among the 25 known ADAMs, are novel in that they contain unique thrombospondin type I motifs in addition to some of the structurally conserved domains of other ADAM family members (Figure 1). The ADAMTSs are also distinguished from the ADAMs by their lack of cysteine-rich, EGF-like, transmembrane, and cytoplasmic domains (10). Kuno et al. first cloned and identified ADAMTS-1, a tumor-selective gene expressed in colon tumor cells (13). ADAMTSs 2–11 have now also been cloned, and the proteolytic activity and biological functions of some of them have been demonstrated. For example, ADAMTS-2 has been implicated in the normal development of the skin. This enzyme was long known as procollagen N-proteinase (14), a proteinase that proteolytically removes amino peptides in the processing of type I and type II procollagens to collagens, and it was shown to be deficient in the skin of individuals with the inherited connective tissue disorder type VIIC Ehlers-Danros syndrome and in cows and sheep with a

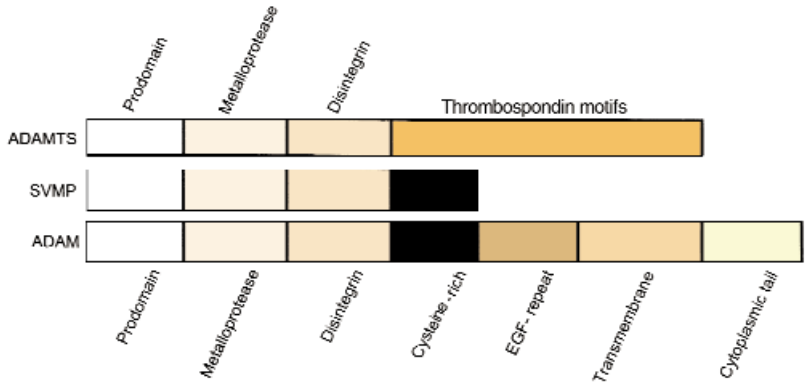

Figure 1
Comparison of domain structures of ADAMTSs, ADAMs and SVMPs. The first three boxes of each bar represent, respectively, the common prodomain and the metalloprotease and disintegrin domains present in all of the members of adamalysin family. ADAMTSs also possess a thrombospondin domain but lack the cysteine-rich, EGF-like, transmembrane, and cytoplasmic domains found in ADAMs. SVMPs and ADAMTSs do not contain transmembrane domains and are therefore secreted, whereas ADAMs are transmembrane proteins that localize to the cell surface.

similar condition, dermatosparaxis. With the recent cloning of procollagen N-proteinase (15) came its recognition as a member of the ADAMTS family, ADAMTS-2. ADAMTS-4 and ADAMTS-11 are known as aggrecanase-1 and -2 because of their ability to cleave specific sites in aggrecan, a proteoglycan that maintains the mechanical properties of cartilage (12, 16, 17). Progressive degradation and depletion of aggrecan has been implicated in degenerative joint diseases such as osteoarthritis and inflammatory joint diseases such as rheumatoid arthritis. A human orthologue of ADAMTS-1, known as METH-1, and the related protein METH-2 have been recently shown to have antiangiogenic activity (18), and these or other ADAMTS family members may play important roles in regulating vascular development.

Impaired organogenesis in *ADAMTS-1*$^{-/-}$ mice

The report of Shindo et al. in this issue of the *JCI* provides valuable clues to the biological role of ADAMTS-1 (19). The phenotype of *ADAMTS-1*$^{-/-}$ mice revealed marked reduction in size, with body weights about 70% of their wild-type or heterozygous littermates. Pathological features of these knockout animals include remarkable changes in kidney structure, particularly an obstructive fibrosis extending from the ureteropelvic junction into the ureter. The calyceal space was also significantly enlarged and contained hypoplastic or atrophic papillae. In addition, capillary networks within the adrenal glands were disrupted, and numerous cavities formed in the adrenal medulla. In *ADAMTS-1*$^{-/-}$ females, other phenotypic abnormalities were found in the uterus and ovaries, and fertilization was impaired.

Because many steps in morphogenesis require cell adhesion, migration, differentiation, and polarization, these developmental abnormalities may be explained by changes in extracellular matrix (ECM) remodeling, cell adhesion, or growth factor signaling in the absence of ADAMTS-1 (20, 21). Indeed, many extracellularly expressed proteinases that process secreted proteins, adhesive molecules, or their receptors play important roles in embryogenesis and morphogenesis. With its various specialized domains, ADAMTS-1 may act as a proteinase or may mediate changes in cell adhesion through its disintegrin or thrombospondin domains. Future studies will no doubt clarify the molecular interactions that account for the organogenesis defects in *ADAMTS-1*$^{-/-}$ mice.

Given the intriguing domain structure of ADAMTS-1, the pleiotropic developmental defects in these mice suggest several fruitful lines of investigation. First, since ADAMTS-1 is secreted (22), contains metalloprotease catalytic site consensus sequence HEXXH, and has been shown to have protease activity (23), the identities of its physiological substrates at the cell surface are of great interest. To date, ADAMTS-1 has not been shown to act on proteins of the ECM. Second, because ADAMTS-1 is synthesized as an inactive proform, a conserved cysteine residue in its prodomain is predicted to be proteolytically processed during its maturation to an active enzyme; other metalloproteinases, including matrixins and adamalysins, are maintained in the latent state by such prodomains. It will be of considerable interest to identify proteinases or possibly cascades of proteinases that activate ADAMTS-1 in response to physiological cues. Meprin A (24), one of the major ECM-degrading enzymes in the kidney, may be a candidate for such a role because of its localization at the cell surface. Third, like other members of the ADAM family, ADAMTS-1 contains a conserved disintegrin domain that may act as a ligand for integrins (2). The role of the disintegrin domain of sperm surface glycoprotein, ADAM1 (fertilin β), has been extensively studied in binding and fusion to egg plasma membranes (25, 4). If the disintegrin domain of ADAMTS-1 is found to participate in cell-cell interactions, future studies should focus on the residues in the disintegrin loop of ADAMTS-1 that mediate specific binding, as well as the identity of its cognate integrins. Fourth, the signature COOH-terminal thrombospondin motif that distinguishes ADAMTS-1 and other ADAMTSs from the ADAMs has been shown to bind sulfated glycosaminoglycans (22). Whether the ADAMTS-1 metalloproteinase activity and its putative adhesive interactions are mutually exclusive is not known, but it will be of interest to learn what potential substrates colocalize with ECM-bound ADAMTS-1. Finally, one of the prominent phenotypic abnormalities observed in the kidney, the substantial reduction in corticomedullary tissue, may be attributed to interstitial fibrosis in the kidney consequent to the obstruction of the ureter. However, this interstitial fibrosis in the kidney, which is an integral part of all progressive kidney diseases, clearly requires a mechanistic explanation. It is conceivable that proteolytically active ADAMTS-1 participates in normal ECM turnover and that its absence contributes to the fibrosis seen in the mutant mice.

While the knockout mice provide important information on development of organs, they do not suggest potential roles for ADAMTS in pathological states. In vitro studies demonstrated that ADAMTS-1, like other matrix-degrading metalloproteinases, is induced by IL-1, indicating that inflammation can induce its expression (13). Indeed, ADAMTS-1 is weakly expressed in the normal mouse kidney and heart, but it is specifically induced at the mRNA level in these two tissues by administration of lipopolysaccharide. Study of the knockout model in pathological states such as inflammation should provide important additional clues to ADAMTS-1's biological functions.

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