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ADAMs and ADAMTSs☆

Carl P Blobel, Hospital for Special Surgery at Weill Medical College of Cornell University, New York, NY, United States
Suneel Apte, Department of Biomedical Engineering (ND20), Cleveland Clinic Lerner Research Institute, Cleveland, OH, United States

ADAMs

Introduction

ADAMs (a disintegrin and metalloprotease) are a family of membrane-anchored glycoproteins that have been implicated in cleaving and releasing proteins from the cell surface. This process, which is referred to as protein ectodomain shedding, affects the function of molecules with key roles in development and disease, including growth factors such as TGFα, HB-EGF, cytokines such as TNFα, and receptors such as the TNFR1. The first recognized ADAMs were the two subunits of a sperm protein termed fertilin, which has a critical role in fertilization. Other ADAMs were subsequently identified based on their sequence homology to fertilin, or based on functional assays, such as their ability to shed the pro-inflammatory cytokine TNFα or process and activate the cell surface receptor Notch.

Structure

The typical domain organization of an ADAM is shown below (Fig. 1). Of over 30 ADAMs that have been identified to date, only about half contain a catalytic site consensus sequence and are therefore predicted to be catalytically active. The remaining ADAMs that are not catalytically active are thought to function mainly in cell-cell or cell-matrix interactions.

Regulation of Production and Activity

All catalytically active ADAMs are synthesized with a pro-domain that helps the metalloprotease domain fold in the ER and keeps it inactive until the pro-domain is cleaved, usually just before reaching the trans-Golgi network. Once the pro-domain is removed, additional mechanisms, including phorbol esters, phosphatase inhibitors, Calcium ionophores and activation of G-protein coupled receptors regulate the catalytic activity of ADAMs. The disintegrin domain and cysteine-rich region of ADAMs are thought to have a role in cell-cell interaction and potentially also in substrate recognition. Finally, the cytoplasmic domain of catalytically active ADAMs usually contains signaling motifs such as potential phosphorylation sites and proline-rich SH3 ligand domains, and several molecules that interact with the cytoplasmic domains of ADAMs and might regulate their maturation and function have been identified.

The catalytic activity and substrate selectivity of ADAMs has been explored using both biochemical and cell biological approaches. One important conclusion from biochemical studies was that individual ADAMs do not have a clear consensus cleavage site in vitro. Since ADAMs and their substrates are both membrane-anchored, cell-based assays are critical tools for understanding the substrate selectivity and regulation of ADAMs in the context of the plasma membrane. Studies using cells from ADAM knockout mice, or cells treated with siRNA against different ADAMs, have revealed that these enzymes display substrate selectivity in cells, although the mechanism underlying this remains to be established. A common feature, however, is that ADAMs frequently cleave their substrates close to the plasma membrane, resulting in release or "ectodomain shedding" of the substrate's soluble ectodomain (see above) (Fig. 2).

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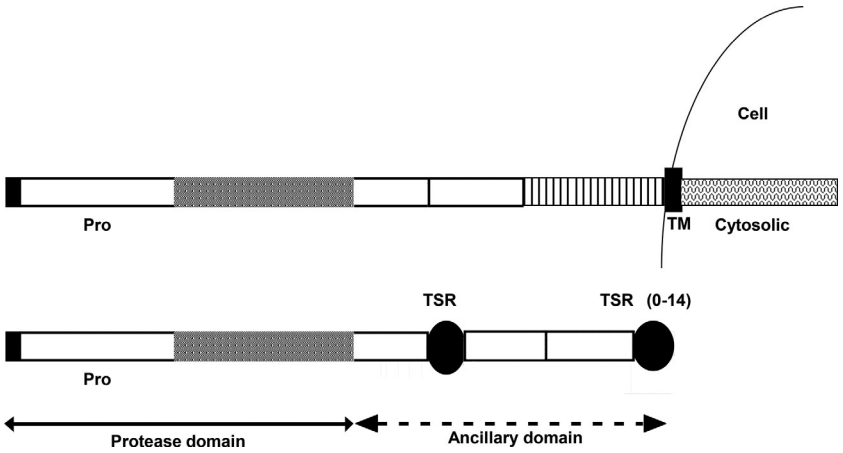

Fig. 1 All ADAMs are membrane anchored glycoproteins that are characterized by a conserved domain structure: an amino-terminal signal sequence followed by pro-, metalloprotease and disintegrin domains, a cysteine-rich region, usually containing an EGF-repeat, and finally a transmembrane domain and cytoplasmic tail. Only about half of the known ADAMs have a catalytic site consensus sequence, and are therefore predicted to be catalytically active. The disintegrin domain was first identified in snake venom toxins that bind to platelet integrins and function as anticoagulants, but is now known to be a characteristic feature of all ADAMs and ADAMTS proteins. ADAMTS proteins are similar to ADAMs in the pro-metalloprotease domain, but unlike ADAMs, all ADAMTS are catalytically active. ADAMTS have a functionally critical ancillary domain containing specific modules not found in ADAMs (see text for details). A critical difference between these protease families, as shown in the figure, is the absence of an integral membrane segment in ADAMTS proteases.

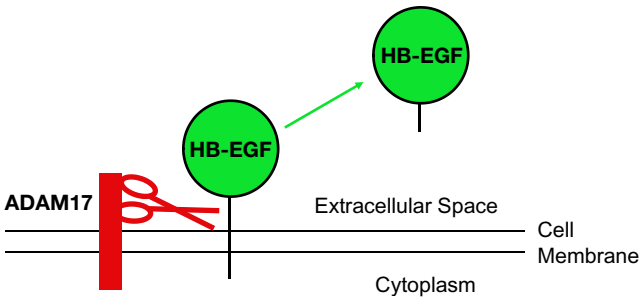

Fig. 2 Proteolytic processing of heparin binding EGF-like growth factor (HB-EGF) by ADAM17 releases this growth factor from its membrane tether. The ADAM17-dependent ectodomain shedding of HB-EGF is thought to be critical for the function of this growth factor during lung and heart development.

Biological Function

As noted above, ADAM-dependent ectodomain shedding can profoundly affect the function of the released substrate protein. Ectodomain shedding can enable the released molecule to act at a distance from the cell that it was shed from, which is referred to as paracrine signaling. For example, processing of the EGF-receptor ligands TGFα and HB-EGF by ADAM17 is critical for activation of the EGFR during development, and therefore mice lacking ADAM17 resemble mice lacking TGFα or HB-EGF or the EGF-receptor. Ectodomain shedding is also a key mediator of the role of TNFα in autoimmune diseases such as rheumatoid arthritis. Interestingly, receptors can be either inactivated by ectodomain shedding, such as the TNFR1, or activated, such as Notch. Recent studies have shown that ADAM17, which is crucial for EGFR and TNFα signaling, is regulated by partner proteins called iRhoms 1 and 2 (inactive Rhomboid proteins). These are seven-membrane spanning molecules that are essential for the maturation and activity of ADAM17. The related ADAM10, which is essential for Notch signaling, is regulated by different partner proteins called C-8 tetraspanins, which have four transmembrane domains. There are six C-8 tetraspanins that can interact with ADAM10, leading to the hypothesis that these different tetraspanins can differentially regulate the function and substrate selectivity of ADAM10, similar to what has been shown for the iRhom1/2 ADAM17 complexes.

Function of ADAMs in Lung Development and in Respiratory Diseases

Currently, ADAM17 is the only ADAM with a clearly established role in lung development. Mice lacking ADAM17 are born with respiratory distress, presumably caused by abnormal alveoli with septation defects and thickened mesenchyme as well as impaired branching morphogenesis and delayed vasculogenesis, and thus reduced surface for gas exchange. Since similar defects are observed in mice lacking HB-EGF or the EGFR, the abnormal lung development in *Adam17*$^{-/-}$ mice are most likely explained by a lack of HB-EGF shedding. With respect to respiratory diseases, smoking has been implicated in the activation of ADAMs and the resulting

release of EGFR-ligands such as amphiregulin. The resulting activation of the EGFR can presumably contribute to the pathogenesis of lung cancer by stimulating cell proliferation and DNA replication at the same time that mutagens are delivered in smoke. Moreover, gram-positive bacteria stimulate the G-protein coupled platelet activating receptor (PAR) in patients with cystic fibrosis, which in turn activates ADAM dependent release of HB-EGF, and thus mucin production. Therefore, inhibitors of ADAMs, such as hydroxamic acid type metalloprotease inhibitors, might be useful in the treatment of cystic fibrosis and lung cancer. Finally, mutations in the ADAM33 gene have been linked to asthma susceptibility, although the mechanism underlying the role of ADAM33 in asthma remains to be determined. In light of the key roles of ADAMs in regulating signaling via the EGF-receptor and other cell surface signaling pathways, and the critical roles for ADAMs in lung development and in asthma, cystic fibrosis and coronavirus infection, it appears likely that further studies of the role of this protein family in respiratory disease will uncover novel functions, thus hopefully also providing new targets for drug design.

ADAMTSs

Introduction

ADAMTS (A disintegrin-like and metalloprotease domain [reprolysin type] with thrombospondin type 1 motifs) comprises a family of 19 secreted metalloproteases. The founding member of this family, ADAMTS1, was so named because it resembled the ADAMs in the sequence of the metalloprotease domain and was initially thought to be a variant ADAM. Soon afterward, it became clear that all 19 ADAMTS proteases shared common structural features and constituted a separate protease family from ADAMs. The consistent points of distinction from ADAMs, apart from the absence of a transmembrane segment, are the presence of modules resembling thrombospondin type 1 repeats (TSRs), and their characteristic arrangement within a distinct C-terminal ancillary domain (Fig. 1).

Structure

A typical ADAMTS consists of pro-metalloprotease and ancillary domains. The pro-metalloprotease domain active site sequence, like ADAMs is of the reprolysin (snake venom) type. Basic amino acid-rich sequences providing cleavage sites for subtilisin-like proprotein convertases (SPCs) such as furin are present within the propeptide and at its junction with the protease domain, which on the basis of experimentally determined 3-dimensional structures, also includes the disintegrin-like module. The ancillary domain (from N to C-terminus) consists of a central TSR, a cysteine-rich module, a cysteine-free spacer, and a variable number of additional TSRs, ranging from 0 (ADAMTS4) to 14 (ADAMTS9 and 20) (see figure). Indeed, a family of ADAMTS-like (ADAMTSL) proteins exists, which have a domain structure similar to the ADAMTS ancillary domain, but lack a catalytic domain and hence are not proteases, but secreted proteins resident in the ECM. An interesting feature of ADAMTS proteases and ADAMTSLs is their clear grouping into distinct subfamilies of 2–3 members each, although ADAMTS13 is a solitary standout. Proteases within ADAMTS subfamilies have an identical modular organization, gene structure, and similar active site sequences, suggesting evolution by gene duplication from a common precursor (Fig. 1). For example, ADAMTS7 and ADAMTS12 constituting one such subfamily, each have a mucin-like module and glycosaminoglycan attachment sites rendering them the only known proteases that are also proteoglycans. ADAMTS9 and ADAMTS20 constitute a subfamily with the most TSRs and a C-terminal Gon-1 domain found nowhere else in mammalian proteomes.

Regulation of Production and Activity

Transcriptional regulation appears to be very important, since many ADAMTS mRNAs are highly regulated during embryogenesis or induced in specific circumstances such as inflammation, e.g., ADAMTS1. ADAMTS proteases are synthesized as zymogens and undergo removal of their propeptides by SPCs either within the secretory pathway or at the cell surface. Subsequent to SPC processing, proteolysis within the ancillary domain, occurring by autocatalysis in several instances, also appears to be an important post-translational regulator of activity, since it may alter the substrate specificity by modifying the ancillary domain. Several ADAMTS proteases bind to the cell surface through mechanisms that are not fully understood, but may involve cell-surface glycosaminoglycan interactions, and suggest that like ADAMS, they may act as operational cell surface proteases. An important distinction in mode of action from ADAMs, which cleave generically at the cell-surface in a “lawn-mower” effect, is that ADAMTSs work in diverse settings, such as at the cell-surface or distal extracellular matrix, and ADAMTS9 is internalized and relocated to the base of the primary cilium. They attack specific cleavage sites in their substrates, but these cannot be predicted in silico from a single consensus sequence. ADAMTS4 and ADAMTS5 appear to work as glutamyl endopeptidases that process Glu-Xaa bonds in many proteoglycan core proteins, whereas ADAMTS13 specifically cleaves von Willebrand factor (vWF) at the Tyr1605-Met1606 peptide bond, but only when VWF is partially unfolded by physical forces in vivo. An important concept in the ADAMTS family is that their catalytic domains alone appear not to possess activity towards natural substrates. Instead, the ancillary domain is critical for the recognition and binding of substrates, which may require specific post-translational modifications (such as glycosylation of proteoglycans, triple-helicity of procollagens or physical unfolding of vWF by fluid shear force). In addition, the substrate binding regions of ADAMTS proteases appear to be longer and more complex than matrix metalloproteinases and hence few synthetic peptide substrates are known. This makes the development of ADAMTS activity assays quite problematic. In addition to these challenges, full-length ADAMTSs are difficult to obtain as purified preparations, either from native sources or as recombinant

proteins, and therefore, like ADAMs, their activity is frequently elicited using cell-based assays. The inherent caveat of cell-based assays is that the observed cleavages could result from ADAMTS proteolytic activation of another protease. The only known ADAMTS inhibitors are TIMP-3 and α2-macroglobulin.

Biological Function

Unexpectedly diverse functions for ADAMTS proteases have been identified from mutations discovered in human genetic disorders and by analysis of transgenic animals. These findings have revealed definitive roles for nearly every ADAMTS protease and/or ADAMTS subfamily. The various morphogenetic roles of ADAMTS proteases are too numerous to describe here in detail, but include remodeling of versican-rich provisional extracellular matrix (ECM) during palate closure, interdigital web regression and cardiac development, roles in other aspects of cardiac morphogenesis, development of the eye, reproductive tract and skeleton, modulation of fibrillin microfibril composition, prevention of tendon ossification, and regulation of ciliogenesis.

All human and animal ADAMTS genetic disorders are recessive, which is typical of enzyme deficiencies. Ehlers-Danlos syndrome VIIC (or the dermatosparactic type) is a consequence of *ADAMTS2* mutations. In this disorder, tissue (especially skin) fragility results from incomplete procollagen processing and reduction of structurally competent collagen fibrils. ADAMTS1 is needed for mouse urinary tract development and female fertility, and inhibits angiogenesis in vitro and in vivo by binding to VEGF. *Adamts4* and *Adamts5* null mice are developmentally normal, but *Adamts5* mice are resistant to both mechanically induced and immune arthritis, supporting work in humans identifying ADAMTS5 as a major cartilage-degrading enzyme in osteoarthritis. ADAMTS variants, which are function-reducing, were strongly associated with alteration of the QRS interval in electrocardiograms. *ADAMTS9* mutations were recently identified in human ciliopathies (Joubert syndrome and nephronopthisis). *ADAMTS10* and *ADAMTS17* mutations cause Weill-Marchesani syndrome (WMS) spectrum, comprising short stature, brachydactyly, cardiovascular defects and ectopia lentis. Intriguingly, several aspects of WMS (other than ectopia lentis, which is shared) are the opposite of those seen in Marfan syndrome, a fairly common inherited connective tissue disorder, where an emphysema-like phenotype in mice and rupture of lung bullae in humans has been described. *ADAMTS13* mutations lead to inherited thrombocytopenic purpura, a hemostatic disorder characterized by retention of unusually large polymers of VWF owing to failure to process these into forms that are optimal for hemostasis. Acquired TP may result from circulating anti-ADAMTS13 auto-antibodies. *ADAMTS18* and *ADAMTSL4* mutations give rise to eye genetic disorders, the latter resulting in non-syndromic ectopia lentis, mimicking an ocular manifestation of Marfan syndrome. ADAMTS20 mediates melanoblast migration from the neural crest and is deficient in a natural mouse mutant named *Belted* because of the belt of white fur across the torso. Together with ADAMTS9, this protease regulates morphogenetic signaling via a role in formation of the primary cilium.

Receptors

Although some ADAMTS proteases can bind to the cell surface, a specific receptor, syndecan-1, has been identified only for ADAMTS4. Nevertheless, because of the affinity of many ADAMTS for heparin and chondroitin sulfate, cell surface proteoglycans may constitute a broad category of receptors for this family. Low-density lipoprotein-1 related receptor protein 1 (LRP1) is a scavenger receptor for numerous secreted molecules, including ADAMTS proteases such as ADAMTS5 and ADAMTS9.

ADAMTS Proteases in Respiratory and Airway Diseases

ADAMTS proteases and ADAMTS-like proteins have a role in diverse airway and lung disorders. Pneumothorax has occasionally been reported in EDS-VIIC patients and *Adamts2* null mice have widening of their distal air spaces, attributed to pulmonary hypoplasia. These mice show deficiency of procollagen I and procollagen III processing. Both collagens are major structural components of the lung. Genome-wide analysis of airway obstructive disease in the Norwich terrier breed identified a missense variant in TSR3 of ADAMTS3 affecting a conserved arginine residue, which may impair folding and function of this protease. Histology of the airway from affected animals showed tissue swelling. Since *ADAMTS3* mutations in humans lead to deficient lymphangiogenesis (Hennekam lymphangiectasia lymphedema syndrome 3), it is possible that the swelling results from abnormal lymphatic development and poor airway tissue drainage with resulting edema.

ADAMTS5 protects against experimental influenza infection in mice, since *Adamts5*$^{-/-}$ mice had delayed viral clearing, compromised T-cell migration and immunity, possibly mediated through pulmonary accumulation of the ADAMTS5 substrate versican. *ADAMTS8* mRNA was found to be upregulated in pulmonary artery smooth muscle cells from patients with pulmonary artery hypertension (PAH). Vascular smooth muscle-specific *Adamts8* deletion in mice attenuated the development of hypoxia-induced PAH. Furthermore, the same study demonstrated that cardiomyocyte-specific *Adamts8* knockout suppressed right heart failure in response to hypoxia-induced PAH, enhanced cardiac ventricular angiogenesis and reduced right ventricular fibrosis and ischemia. *Adamts9* mRNA is strongly expressed in the lung mesenchyme and vasculature, and since it is required (together with *Adamts20*) for ciliogenesis, likely has a significant role in regulating hedgehog-related pulmonary morphogenetic processes. *Adamts10* mutant mice, in contrast to mouse models of Marfan syndrome, appear to have more advanced pulmonary septation. Analysis of *Adamts12* mutant mice challenged with allergens showed exacerbated eosinophilic bronchial infiltration, more mast cells and higher interleukin-33 levels. Thus, ADAMTS12 protects against bronchial inflammation and hyperresponsiveness to allergens, and indeed, the *ADAMTS12* locus was found to show a strong association with asthma susceptibility in a genome-wide analysis. Since ITP (loss

of ADAMTS13 function) is a systemic coagulation disorder, patients can develop microthrombi in their lungs and have sometimes manifested with acute respiratory distress syndrome. Analysis of *Adamts18* null mice has shown increased proximity of branched airways, suggesting more acute angles of separation between branched bronchi, as well as increased bronchial lumen dimensions and thinner bronchial walls.

Humans with geleophysic dysplasia, which can be caused by *ADAMTSL2* mutations, are reported to have obstructive airway disease affecting proximal airways that may require tracheostomy, whereas *Adamtsl2* null mice die at birth with a severe bronchial dysplasia in which there is engorgement of epithelial cells with carbohydrate-filled vesicles that obstruct airflow. Structurally, the bronchi show higher staining intensity of fibrillin-2, which is an ADAMTSL2 ligand.

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