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Review

Three-dimensional domain architecture of the ADAM family proteinases

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ABSTRACT

A disintegrin and metalloproteinase (ADAM) family of proteins constitutes a major class of mammalian membrane-bound sheddases that are responsible for the processing of cell-surface-protein ectodomains, including the latent forms of growth factors, cytokines and their receptors. However, the molecular mechanism by which ADAMs recognize and process their substrates is largely unknown. Recent crystallographic studies on phylogenically related snake venom metalloproteinases (SVMPs) and mammalian ADAM with thrombospondin type-1 motif (ADAMTS) family proteins have shed light on the structure-function properties of ADAMs. This review will highlight these recent structures, particularly the non-catalytic ancillary domains, which might be important for substrate recognition.

Contents

1. Introduction

ADAM family proteins, also called metalloproteinase-disintegrins or metalloproteinase/disintegrin/cysteine-rich (MDC) proteins, are an emerging class of mammalian membrane-bound glycoproteins whose functions have been implicated in cell–cell and cell–matrix adhesion and signaling [1–3]. The best-characterized *in vivo* activity of ADAMs is their ectodomain shedding activity. ADAM17 (TNF-α converting enzyme, or TACE) was initially identified as the physiological convertase for TNF-α [4,5]. ADAMs have also been implicated in mitogenic events associated with EGF receptor transactivation by GPCRs [6,7]. ADAMs appear to play key roles in normal development and morphogenesis through their ability to function as sheddases [8] and are associated with several diseases, including rheumatoid arthritis, Alzheimer's disease, heart disease, and cancer [9–11]. As such, they have also become potential therapeutic targets for various disease conditions. Excluding pseudogenes, human and mouse ADAMs are encoded by 20 and 37 functional genes, respectively. ADAMs are mosaic proteins that generally possess, from N- to C-terminus, pro-peptide (P), metalloproteinase (M), disintegrin-like (D), cysteine-rich (C), epidermal growth factor (EGF), transmembrane (TM) and cytoplasmic (CT) domains, and are unique in that they exhibit both proteolytic and adhesive activities on the cell surface. ADAMs are members of the adamalysin/reprolysin family of the metzincin sub-clan of Zn-dependent metalloproteinases, which also includes the matrixins (matrix metalloproteinases, or MMPs), astacins and serralysins [12,13]. These metalloproteinases share a catalytic site architecture and, in part, an M-domain topology. However, they have distinct C-terminal non-catalytic ancillary

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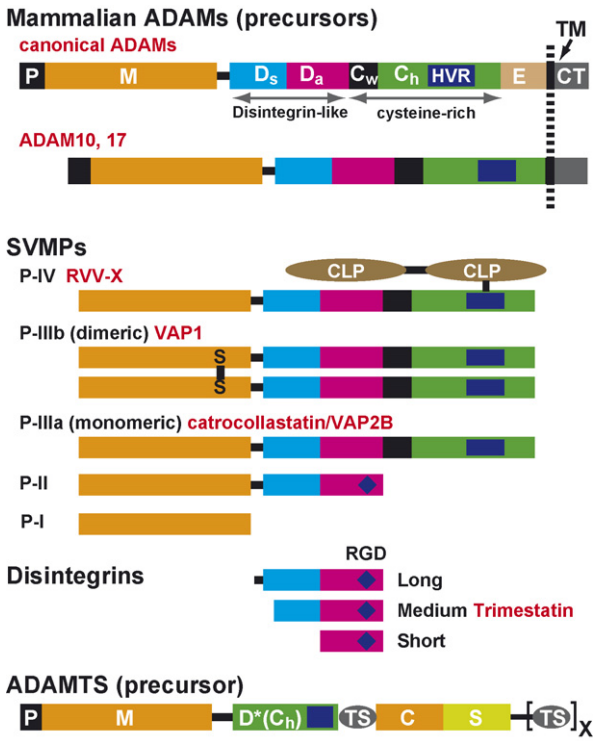

Fig. 1. Schematic representation of the domain structure of ADAM family of proteins. Each domain or segment is represented by a different color.

domains that may contribute to unique regulatory functions for each metalloproteinase. Adamalysin/reprolysin family proteins also include ADAMTS [14,15] family proteins and SVMPs, which constitute two groups of secreted proteinases. In contrast to SVMPs and ADAMTSs, all of which are predicted to be catalytically active enzymes, only ~60% of ADAMs contain a functional catalytic signature sequence (HEXXHXXGXXHD where X denotes any amino acid). The physiological roles of the protease inactive ADAMs remain largely unknown, however, several members of this group play important roles in development [16,17], which suggests that the adhesive activity of these proteins may be relevant to their function. The non-catalytic ancillary domains of ADAMs, particularly the D and C-domains, have been implicated in adhesive activity [18–21] and regulatory activity during proteolysis [22,23]. However, critical questions, such as how metalloproteinase activity is regulated and how substrates are recognized, remain to be answered. Recent crystallographic studies on the high molecular weight SVMPs [24–26] and related mammalian protein structures [27–29] have shown us the MDC domain architecture of ADAMs, as well as potential protein-protein interaction sites that may be important for substrate recognition. This review will summarize our current understanding of the structure of ADAM/adamalysin/reprolysin family proteins and discuss how structure relates to the shedding activity of the ADAM proteins.

2. General architecture of ADAM family proteinases

The mammalian ADAMs are most closely related to the P-III class of SVMPs. The SVMPs are classified into four groups (P-I to P-IV) according to their domain organization [30] (Fig. 1). The mature P-III SVMPs contain M, D and C domains. Vascular apoptosis-inducing protein-1 (VAP1) was the first P-III SVMP structure to be resolved by X-ray crystallography [24,31]. The structures of VAP1 revealed an MDC domain architecture, which is shared by mammalian membrane-bound ADAMs. A comparison of the six catrocollastatin/VAP2B crystal structures and the structures of VAP1 revealed a dynamic property of the MDC domains that may be important for the function of ADAM family proteins [25].

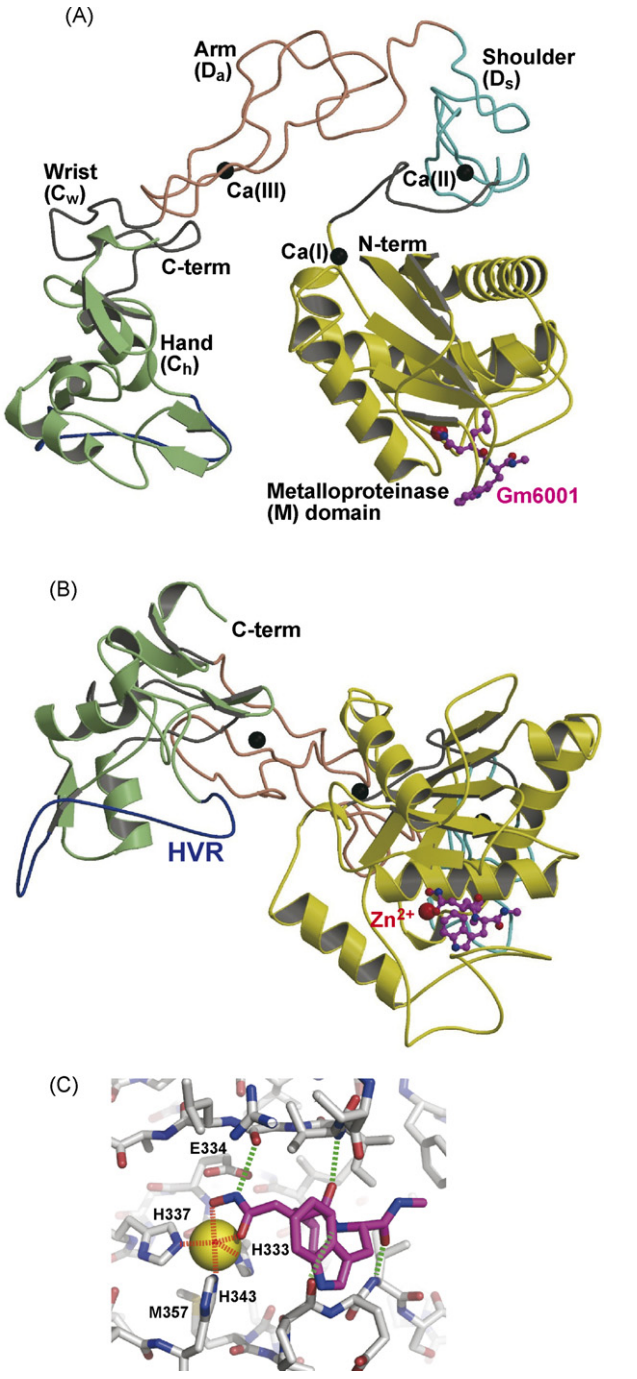

Fig. 2. ADAMs MDC domain architecture. (A and B) Two orthogonal views of the MDC domain of catrocollastatin/VAP2B. The M-domain, linker, D_s, D_a, C_w and C_h segments and the HVR are shown in yellow, gray, cyan, pink, gray, light green and blue, respectively. Zinc and calcium ions are represented as red and black spheres, respectively. The hydroxamic inhibitor GM6001 bound to the protein molecule is shown in ball-and-stick representation. (C) Close up view of the catalytic site of catrocollastatin/VAP2B. The residues involved in the coordination of the zinc ion, the catalytic base, and the Met-turn are indicated.

Fig. 2 depicts the MDC domain architecture of catrocollastatin/VAP2B, a monomeric P-III SVMP that is the structural prototype of mammalian ADAMs [25]. The globular M-domain