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ADAMs family and relatives in cardiovascular physiology and pathology

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ABSTRACT

A disintegrin and metalloproteinases (ADAMs) are a family of membrane-bound proteases. ADAM-TSs (ADAMs with thrombospondin domains) are a close relative of ADAMs that are present in soluble form in the extracellular space. Dysregulated production or function of these enzymes has been associated with pathologies such as cancer, asthma, Alzheimer's and cardiovascular diseases. ADAMs contribute to angiogenesis, hypertrophy and apoptosis in a stimulus- and cell type-dependent manner. Among the ADAMs identified so far (34 in mouse, 21 in human), ADAMs 8, 9, 10, 12, 17 and 19 have been shown to be involved in cardiovascular development or cardiomyopathies; and among the 19 ADAM-TSs, ADAM-TS1, 5, 7 and 9 are important in development of the cardiovascular system, while ADAM-TS13 can contribute to vascular disorders. Meanwhile, there remain a number of ADAMs and ADAM-TSs whose function in the cardiovascular system has not been yet explored. The current knowledge about the role of ADAMs and ADAM-TSs in the cardiovascular pathologies is still quite limited. The most detailed studies have been performed in other cell types (e.g. cancer cells) and organs (nervous system) which can provide valuable insight into the potential functions of ADAMs and ADAM-TSs, their mechanism of action and therapeutic potentials in cardiomyopathies. Here, we review what is currently known about the structure and function of ADAMs and ADAM-TSs, and their roles in development, physiology and pathology of the cardiovascular system.

Contents

Abbreviations: ADAM, A disintegrin and metalloproteinase; ADAM-TS, ADAM with thrombospondin domains; APP, amyloid precursor protein; APPsα, α-secretase-released N-terminal APP domain; C-domain, cysteine-rich domain; COMP, cartilage oligomeric matrix protein; DCM, dilated cardiomyopathy; D-domain, disintegrin domain; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transformation; ERK, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; GPCR, G protein coupled receptor; HB-EGF, heparin-binding EGF-like growth factor; HVR, hyper-variable region; ICAM-1, intercellular adhesion molecule 1; LVAD, left ventricular assist device; MDC, metalloproteinase disintegrin cysteine-rich; M-domain, metalloproteinase domain; MI, myocardial infarction; MMP, matrix metalloproteinase; PDK1, phosphatidyl inositol-dependent kinase-1; PI3K, phosphatidylinositol 3-kinase; PMA, phorbol 12-myristate 13-acetate; PPC, furin-like pro-protein convertase; RECK, reversion-inducing cysteine-rich protein with Kazal motifs; RIP, regulated intramembrane proteolysis; SH3, Src homology region-3; SNP, single nucleotide polymorphism; SVMP, snake venom metalloproteinase; TACE, TNF-alpha converting enzyme; TIMP, tissue inhibitor of metalloproteinase; TSP1, thrombospondin-1; TSR, thrombospondin type 1 sequence repeat; TTP, thrombotic thrombocytopenic purpura; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; vWF, von-Willebrand factor.

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1. Introduction

Diseases of the cardiovascular system remain one of the primary causes of death worldwide. The cardiomyocytes, fibroblasts and coronaries within the myocardium are interconnected through a network structure, the extracellular matrix (ECM) [1,2]. A number of growth factors and cytokines are present in the myocardium in a membrane- or ECM-bound form, where they remain inactive until released in response to a cue and through the action of different proteases [1]. One family of enzymes that mediate ectodomain shedding of these molecules is A disintegrin and metalloproteinases (ADAMs). ADAMs and ADAM-TSs (ADAMs with thrombospondin domains) belong to the adamalysin protein family and are closely related to other metalloenzymes such as matrix metalloproteinases (MMPs). The disintegrin domain in ADAMs can bind to integrins, while its metalloproteinase domain mediates shedding of membrane-bound growth factors, cytokines and receptors. Therefore, ADAMs are unique cell surface proteins as they display both proteolytic and adhesive activities. While ADAMs and ADAM-TSs possess similar molecular structures, ADAM-TSs are secreted enzymes lacking integrin binding domains, whereas ADAMs are membrane-bound. Although a number of ADAMs are restricted to the reproductive system, ADAMs 9, 10, 12, 15, 17 and 19 exhibit a broader somatic expression distribution and some have been shown to be involved in cardiovascular development [3]. ADAM-TSs 1, 5 and 9 have been found to contribute to cardiovascular development and pathologies as further discussed in this review.

ADAMs and ADAM-TSs have been extensively explored in cancer and in embryonic development, and have been implicated in diseases of respiratory system, central nervous system, liver, kidneys, muscles, and joints. However, the function of these multifunctional enzymes in heart disease has started to be investigated in recent years, and their importance as potential therapeutic targets in cardiovascular diseases is beginning to become evident. Studies so far reveal differential upregulation of ADAMs 10, 12, 15 and 17 in patients with dilated cardiomyopathy and hypertrophic cardiomyopathy [4], and ADAMs 10 and 15 in patients with atrial fibrillation [5]. ADAM-TS7 has been linked to severity of LV dysfunction and dilation [6], and ADAM-TS13 to thrombotic thrombocytopenic purpura (TTP) and end-organ damage [7]. Absence of reports on the contribution of other ADAMs and ADAM-TSs merely indicates lack of investigation of their function in the cardiovascular field. Given the diverse functions of ADAMs and ADAM-TSs in different organs and pathologies, it is important to determine the mechanism of their action in specific cardiomyopathies towards developing therapeutic intervention strategies for heart diseases.

2. A Disintegrin and Metalloproteinases (ADAMs)

ADAMs, originally named the metalloproteinase disintegrin cysteine-rich (MDC) [8], are Zn^{2+}-dependent, transmembrane proteins that belong to the adamalysin protein family. Disintegrins are small proteins isolated from snake venom, typically with an Arg-Gly-Asp (RGD) recognition sequence, that inhibit platelet aggregation via integrin binding. ADAMs are the only family of cell surface proteins to possess a disintegrin domain (D-domain) and therefore, integrins have been suggested to be common receptors for ADAMs [9]. However, the RGD sequence in the disintegrin loop of ADAMs is usually replaced by XXCD, and therefore, its adhesive potential has been controversial [9]. Like all other metalloenzymes, ADAMs contain a metalloprotease domain which confers them the ability to proteolytically process the ectodomain (extracellular domain) of diverse cell surface ligands, receptors and signaling molecules. As such, ADAMs are important mediators of cell signaling that determine cell fate, differentiation, proliferation and growth [10,11]. To date, 37 ADAMs have been identified in rat, 34 in mouse, and 21 in human genome among which only 13 are proteolytically active [11]. ADAMs 1, 7, 22, 23, 29, 31, and 32 lose their metalloenzyme domain during intracellular maturation while other ADAMs (ADAM2, 11, 18) lack the necessary Zn^{2+}-binding sequence (HEXXHXXGXXH) in their metalloproteinase domain, and therefore are proteolytic inactive [3]. These catalytically inactive ADAMs may be involved in protein folding and protein-protein interactions through their adhesive properties. Based on a phylogenetic tree, mammalian ADAMs are divided into two major groups: those predominantly expressed in testes and associated structures that are involved in spermatogenesis and/or fertilization (ADAM2, -7, -18, -20, -21, -29, -30); and those expressed broadly in somatic tissues (-8, -9, -10, -11, -12, -15, -17, -19,-22, -23, -28 and -33) [12]. In this review, the focus will be on the second group.

2.1. Structure

ADAMs, ADAM-TSs, MMPs, and snake venom metalloproteinases (SVMPs) share similarities in their structure with key distinct features (Fig. 1). For instance, they all possess a signal sequence at their N-terminus which directs the enzyme to the secretory pathway. Next to the signal sequence is the pro-domain which ensures correct protein folding and maintains enzyme latency via a “cysteine-switch” mechanism for the majority of ADAMs [13]. In the “cysteine-switch” mechanism, a conserved cysteine residue in the prodomain forms a complex with catalytic zinc, thereby blocking the active site. The pro-domain of ADAMs has multiple functions including maintaining latency and stability, and ensuring proper folding and entry into the secretory pathway. Metalloprotease domain is adjacent to the prodomain and possesses

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