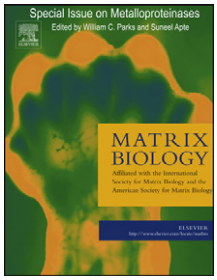
Review



ADAMTS proteases in vascular biology

Juan Carlos Rodríguez-Manzaneque [1], Rubén Fernández-Rodríguez [1], Francisco Javier Rodríguez-Baena [1] and M. Luisa Iruela-Arispe [2]

1 - GENYO, *Centre for Genomics and Oncological Research, Pfizer, Universidad de Granada, Junta de Andalucía, 18016 Granada, Spain*
2 - Department of Molecular, *Cell, and Developmental Biology, Molecular Biology Institute, University of California, Los Angeles, Los Angeles, CA 90095, USA*

Correspondence to Juan Carlos Rodríguez-Manzaneque and M. Luisa Iruela-Arispe: *J.C Rodríguez-Manzaneque is to be contacted at: GENYO, 15 PTS Granada - Avda. de la Ilustración 114, Granada 18016, Spain; M.L. Iruela-Arispe, Department of Molecular, Cell and Developmental Biology, UCLA, 615 Charles Young Drive East, Los Angeles, CA 90095, USA. juancarlos.rodriguez@genyo.es; arispe@mcdb.ucla.edu*
http://dx.doi.org/10.1016/j.matbio.2015.02.004
Edited by W.C. Parks and S. Apte

Abstract

ADAMTS (*a disintegrin and metalloprotease with thrombospondin motifs*) proteases comprise the most recently discovered branch of the extracellular metalloenzymes. Research during the last 15 years, uncovered their association with a variety of physiological and pathological processes including blood coagulation, tissue repair, fertility, arthritis and cancer. Importantly, a frequent feature of ADAMTS enzymes relates to their effects on vascular-related phenomena, including angiogenesis. Their specific roles in vascular biology have been clarified by information on their expression profiles and substrate specificity. Through their catalytic activity, ADAMTS proteases modify rather than degrade extracellular proteins. They predominantly target proteoglycans and glycoproteins abundant in the basement membrane, therefore their broad contributions to the vasculature should not come as a surprise. Furthermore, in addition to their proteolytic functions, non-enzymatic roles for ADAMTS have also been identified expanding our understanding on the multiple activities of these enzymes in vascular-related processes.

Introduction

Our understanding of the mechanisms that regulate vascular growth has expanded significantly in the last three decades. The morphological and rather rudimentary knowledge of the vasculature in mid-1980s has been quickly filled with information on specific genes, signaling pathways and heterotypic cellular interactions that trigger growth, pattern, and provide differentiation cues to distinct segments of the vascular tree regulating the emergence of arteries, veins and capillaries. It is in this context that we review the function of ADAMTS proteases. Our goal is to provide a cohesive summary of how these extracellular enzymes contribute to the morphogenesis and maintenance of blood vessels and participate in the promotion or resolution of vascular pathology.

Extracellular proteases, particularly members of the MMP family are essential to the process of angiogenesis [1]. They participate in the initial degradation of the basement membrane facilitating sprout formation and promoting invasion of connective tissue through restricted degradation of extracellular matrix (ECM) proteins [2]. In addition, bioactive fragments resulting from processing of ECM proteins have uncovered important layers of regulatory control, both inhibitory and stimulatory in nature [3]. In this manner, posttranslational modifications of the extracellular milieu have emerged as a basic mechanism for regulation of vessel repair, promotion of atherosclerosis, as well as, stimulation and inhibition of angiogenesis. In this context, much of our recent understanding on the specific molecular landscape of substrates and proteases has

benefited from technological advancements that enabled a detailed profile of the repertoire of proteolytic events in the extracellular milieu, as per initiatives such as the *Degradome Project* [4].

The first link between ADAMTS proteases and angiogenesis emerged early on during the cloning of the first human members of the family [5]. The original strategy was to identify proteins that harbored "anti-angiogenic domains" first identified in thrombospondin-1, i.e., the thrombospondin type I repeats (TSR) [6]. This effort resulted in the cloning of ADAMTS1 and 8 (originally named METH-1 and METH-2, respectively, to refer to a chimeric protein that contained both metalloprotease (ME) and thrombospondin (TH) domains). Experiments using in vivo and in vitro assays, confirmed that the TSR domains in ADAMTS1 and 8 harbored anti-angiogenic function [5]. Additional members of this family were subsequently discovered and associated with multiple biological functions; however, their potential contribution to neovascularization was not always evaluated. The presence of TSR motifs within the structure of ADAMTS reiterates the possibility for a latent function in the regulation of vascular growth. Subsequently, it also became clear that in addition to the TSR motifs, the catalytic function of ADAMTS proteases could also suppress vascular growth, as it will be discussed.

To date the field has identified 19 members with similar overall domain structure, but with relatively unique properties and functions [7–10]. The earlier identification of ADAMTS1 and ADAMTS8 as endogenous angiogenic inhibitors was followed by reports implicating the potential contribution of other members, such as ADAMTS2, 3, 4, 5, 9, 12, 13, 15 and 18. Moreover, some reports also reported pro-angiogenic activities for a number of ADAMTS proteases, as it would be reviewed here. This highlights the delicate equilibrium and spatiotemporal complexity required to form and preserve the vasculature.

Multi-domain structure of ADAMTS: a range of multi-functional possibilities

As other matrix metalloenzymes, ADAMTS proteases exhibit a common multi-domain structure (Fig. 1A). The backbone organization consists of a prodomain, a catalytic motif and a disintegrin-like module, linked to an additional C-terminal sequence, referred to as ancillary domain. This region includes at least one TSR, a cysteine-rich domain, and a spacer fragment, that may or may not be followed by a variable number of additional TSR domains and other motifs (Cub, Gon1-like, mucin-like, lacunin). The composition of this C-terminal region offers a distinctive feature to each individual member of the family and provides cues as to their potential functional abilities, binding and anchoring properties, substrate recognition, half-life, and evolutionary trajectory, as reviewed previously [8]. Conversion of the zymogen form into an active ADAMTS protease is facilitated by proprotein convertases that activate the enzymes by removing the prodomain [11]. Furthermore, most ADAMTS are modified by proteolysis at their C-terminal region, with consequences to their respective affinities to ECM and cell surface proteins [11]. This additional modification offers expansion of functional properties, as it might alter binding and recognition of alternative partners. Besides, some of the released C-terminal fragments might exhibit autonomous biological activities, although their identification in vivo has not been widely determined.

To date several studies have addressed the contribution of both the catalytic domain, as well as the C-terminal ancillary regions in the modulation of angiogenesis. Here, we review the non-catalytic and subsequently the catalytic functions of ADAMTS proteases in vascular function.

Effects of ADAMTS in the vasculature

Non-enzymatic functions of ADAMTS in angiogenesis/vascular function

As mentioned previously, the approach used to clone human ADAMTS1 and ADAMTS8 genes was based on a search for TSR-containing modules [5], as this single TSR motif by itself exhibits antiangiogenic properties [6,12]. Since all ADAMTS members contain at least one TSR (1 to 15), multiple reports in the literature have hone on exploring their relevance to vascular sprouting. Following this rationale, it would be expected that all ADAMTS members display some degree of anti-angiogenic activity. However, to date this type of inhibitory properties has been attributed to the TSR motifs present in ADAMTS1, 2, 4, 5, 8, 12 and 13, although other domains were also implicated in these properties, as discussed below.

In several cases, the anti-angiogenic activity of the TSR domains of distinct ADAMTS proteases was determined as isolated fragments; that is in the contextual absence of the catalytic regions (Fig. 1B). While these experiments are of importance, the determination as to whether these domains exist independently is of relevance. Alternatively, evaluation of these domains in the context of a catalytically active or inactive full-length protein would offer additional validation and important biological relevance. For example, a recent report communicated both anti-tumorigenic and anti-angiogenic activity of the C-term ancillary region of ADAMTS4 in a mouse melanoma model. This was in contrast to the full length protease that was found to be pro-tumorigenic [13]. The findings with the C-fragment validated