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Metalloproteinases in atherosclerosis

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ABSTRACT

Atherosclerosis underlies most cardiovascular diseases, and is accepted as a primary cause of mortality worldwide. Proteases have been implicated in the development and progression of atherosclerosis, due to their ability to provoke focal destruction of the vascular extracellular matrix. Members of the metalloproteinase family, especially matrix metalloproteinases (MMPs), and their endogenous tissue inhibitors (TIMPs) have been suggested to perform complex dual roles during late-stage progression and rupture of atherosclerotic plaques. Proposed favourable actions of metalloproteinases include the promotion of vascular smooth muscle growth and survival which stabilises plaques, while conversely extracellular matrix destruction alongside interminable monocyte/macrophage accumulation can encourage plaque rupture. This review provides a summary of the cogent evidence connecting the contribution of individual metalloproteinases to atherosclerotic plaque development, progression, and instability. Topics discussed include structural, functional and cell-specific diversity of MMP members; evidence from animal models of atherosclerosis and comparisons with findings in humans; the dual role of MMPs and the requirement to selectively target individual MMPs; and the need for efficient surrogate markers of MMP inhibition. Accordingly, as our knowledge of the complex roles individual MMPs play especially during the progression and rupture of atherosclerotic plaques expands, new impetus is required for clinical trials evaluating the therapeutic potential of selective MMP inhibition, which could limit cardiovascular morbidity and mortality worldwide.

1. Introduction

The destruction and loss of collagen, elastin, and other extracellular matrix proteins from the fibrous cap and adjacent shoulder regions overlying the necrotic core of atherosclerotic plaques, is considered to precipitate plaque rupture and consequent clinical sequelae such as myocardial infarction and stroke. Accordingly, researchers have examined the production of extracellular proteases from vascular cells resident within the blood vessel wall and atherosclerotic plaque, especially foam cell macrophages as they are an abundant source of proteases and accumulate in advanced unstable plaques (Johnson and Newby, 2009). Cysteine proteases (including cathepsins), serine proteases (for example the plasminogen activator-plasmin system, and mast cell related proteases including chymase and tryptase), and metalloproteinases (including the MMP family) all exist within human plaques. These differing but complimentary protease families use different modes of substrate hydrolysis (for example, cysteine, serine, metalloproteases) and harbour the potential to moderate essentially all aspects of atherosclerosis, from lesion formation, development and subsequent progression to plaque instability and thrombosis, predominantly through secondary effects on extracellular matrix proteolysis alongside modulating vascular cell proliferation, migration, and apoptosis. Indeed, a host of biochemical and histological studies have defined a prominent role for proteases in atherosclerotic plaque progression and vulnerability, alongside delineating the cellular sources of potential culprit proteases. However, to determine causality over guilt by association, researchers have turned to animal models to elucidate the contribution of select proteases in atherogenesis, the formation of advanced plaques, and the progression to unstable and rupture-prone lesions. Most of the published studies have focussed on members of the metalloproteinase family, and as such, this group of proteases will form the focus of this review.

2. Metalloproteinases

The metalloproteinase family of proteases (also termed metzincins) consist of ADAMs (a disintegrin and metalloproteinase family), ADAMTSs (ADAM with thrombospondin motifs), and MMPs (matrix metalloproteinase), as they all contain a zinc atom and a conserved methionine in the catalytic domain (Murphy, 2010). The roles of these three related families will be discussed separately, with particular focus on MMPs, as they have been extensively researched in the

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Table 1
Results of in vivo animal studies evaluating the effects of modulating ADAMs and ADAMTS on atherosclerotic plaque size and cellular composition.

ADAM/ADAMTS	Modulation	Site	Effect on plaque size and composition	Reference
ADAM				
ADAM10	Knockout	Aorta	Size (↔), VSMCs (↔), Mø (↔)	Van der Vorst et al, 2012
ADAM15	Knockout	Aorta	Size (↓), VSMCs (↓), Mø (↓)	Sun et al, 2012
	Over-expression	Aorta/carotid	Size (↔/↓), VSMCs (ND/ND), Mø (ND/↓)	Bültmann et al, 2011
ADAM17	Knockdown	Carotid	Size (↑), VSMCs (↑), Mø (↑)	Nicolaou et al, 2016
ADAMTS				
ADAMTS7	Knockout	Aorta/BCA	Size (↓/ND), VSMCs (↔/↔), Mø (↔/↔)	Bauer et al, 2015
ADAMTS13	Knockout	Aorta	Size (↑), VSMCs (ND), Mø (↑)	Jin et al, 2012

Abbreviations: VSMCs, vascular smooth-muscle cells; Mø, macrophages; BCA, brachiocephalic artery; ND, not determined; ↓, decreased; ↑, increased; ↔, no change. In separate studies where different vascular sites have been assessed and discrepancies in effects are observed, red, green and blue text colour are used to define the different sites.

atherosclerosis arena.

2.1. ADAMs

ADAM proteases cleave numerous cell-surface molecules including receptors for cytokines, chemokines, and growth factors, alongside a range of adhesion molecules, and as such their role in cardiovascular diseases is now gaining interest (van der Vorst et al., 2012). ADAM9, ADAM10, ADAM15, ADAM17, and ADAM33 have all been shown to be present within human atherosclerotic plaques and at increased levels compared to healthy vessels (Satoh et al., 2008; Oksala et al., 2009; Donners et al., 2010; Holloway et al., 2010). While ADAM9, 15 and 17 expression is localised to macrophage-rich regions (Oksala et al., 2009), and ADAM10 within neovascular endothelial cells and macrophages (Donners et al., 2010), ADAM33 was preferentially present within plaque smooth muscle cells (Holloway et al., 2010). Genetic studies have also provided associative evidence for ADAM8 (Levula et al., 2009), ADAM17 (Holdt et al., 2008) and ADAM33 (Holloway et al., 2010) expression in atherosclerosis. Animal studies have been recently undertaken in an attempt to demonstrate causality over association alone (see Table 1). Myeloid-specific deletion of ADAM10 in Ldlr KO mice did not affect plaque size, but favourably altered composition through increased collagen content and decreased macrophage accumulation in advanced atherosclerotic lesions (van der Vorst et al., 2015), supporting a pro-atherosclerotic role for ADAM10. Genetic ablation of ADAM15 in Apoe KO mice limited plaque development, attributable to ADAM15 promoting endothelial cell dysfunction and monocyte transmigration (Sun et al., 2012). In direct contrast gain- and loss-of-function studies in athero-susceptible rabbits demonstrated that ADAM15 activity exerts protective effects on plaque progression, potentially through ADAM15-mediated cleavage of endothelial adhesion molecules which act to facilitate monocyte recruitment (Bültmann et al., 2011). These discordant findings may highlight the importance of determining the temporal and spatial expression of ADAM15 during atherogenesis. Plaque size was increased and composition adversely altered in ADAM17 hypomorphic mice (used as ADAM17 global KO mice are not viable) ascribed to over-activation of TNFR2 signalling, and therefore implying an atheroprotective role of ADAM17 (Nicolaou et al., 2017). The aforementioned ADAMs have been shown to have many substrates, a number of which may underlie their effects on atherosclerosis. In particular, ADAMs can influence the recruitment and differentiation of inflammatory cells through the release of chemokines (CX3CL1 and CXCL16), adhesion molecule modulation (ICAM-1 and VCAM-1), and generation of active pro-inflammatory mediators (TNFα) (Dreymueller et al., 2012; van der Vorst et al., 2012). Evidently further research is required to clarify the contribution of individual ADAMs to atherosclerotic plaque progression and instability, particularly if these proteases are to be pursued as therapeutic targets.

2.2. ADAMTSs

ADAMTS proteases have been implicated in cardiovascular diseases, especially atherosclerosis due to their ability to cleave proteoglycans (Salter et al., 2010), which populate pre-atherosclerotic adaptive intimal thickenings and early lesions, and contribute to the retention of lipids alongside adhesion and recruitment of monocyte/macrophages (Nakashima et al., 2007; Otsuka et al., 2015). Within human atherosclerotic lesions, ADAMTS1 is expressed by smooth muscle cells (Jönsson-Rylander et al., 2005), and can stimulate migration of vascular smooth muscle cells in culture (Jönsson-Rylander et al., 2005), and therefore ADAMTS1 may favour plaque stability. Conversely, ADAMTS4 and ADAMTS8 are prominent in the macrophage-rich regions and their expression increases during lesion progression (Wågsäter et al., 2008). Moreover, elevated circulating levels of ADAMTS4 have been reported in patients with coronary artery disease and acute coronary syndromes (Zha et al., 2010). Concurring, loss of ADAMTS4 reduced atherosclerosis and enhanced plaque stability in Apoe KO mice (Kumar et al., 2016). A protective role in atherosclerosis has been ascribed to ADAMTS5 as its expression is depleted in atherosclerotic aortas, leading to the accumulation of proteoglycans such as versican and biglycan, which may favour lipid retention and macrophage accumulation (Didangelos et al., 2012).

Genome-wide association studies have identified single-nucleotide polymorphisms within the genomic region of ADAMTS7 which associate with coronary artery disease (Reilly et al., 2011) (Patel and Ye, 2013). However, there is controversy over the contributory role of ADAMTS7 to atherogenesis and disease progression. Histological studies have demonstrated vascular smooth muscle cells (VSMCs) express abundant ADAMTS7 within carotid and coronary atherosclerotic plaques (Reilly et al., 2011; Pu et al., 2013). In association, ADAMTS7 has been shown to play a functional role in promoting VSMC migration and neointima formation (Wang et al., 2009; Pu et al., 2013; Bauer et al., 2015), in part through cleavage of its primary substrate cartilage oligomeric protein (COMP), which normally exerts an inhibitory effect on VSMC motility (Hanby and Zheng, 2013; Pu et al., 2013). Further mechanistic studies highlighted that VSMCs with an ADAMTS7 SNP

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