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Vascular proteoglycans and atherosclerosis: Not over yet

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The role of proteoglycans in atherosclerosis has been under increasing study lately. Proteoglycans are a family of molecules composed of a core protein with attached glycosaminoglycan chains. As a class they are ubiquitous, although different proteoglycan species have different tissue distributions and expression patterns. In the vasculature, extracellular matrix proteoglycans, especially those in the small leucine rich repeat class, have several putative roles in atherosclerosis. Proteoglycans are thought to have a role in collagen fibrillogenesis and the organization and structure of the extracellular matrix. As such, changes in the proteoglycan composition of the matrix can affect matrix stability, elasticity, tensile strength, and other functions[1]. In addition to their roles in extracellular matrix organization, a number of proteoglycans have been shown to have a role in the regulation of cytokines and growth factors including TGF-β[2]. Thus, changes in the proteoglycan composition of the vasculature may alter the bioavailability of signaling molecules that can have pathogenic consequences. As an example, overexpression of decorin via an adenoviral vector in apoE−/− mice was shown to decrease the progression of atherosclerosis, and the authors suggested that this may be due to the reduction in circulating free TGF-β observed[3]. Recently, additional studies have described a role for soluble proteoglycans in the regulation of inflammation. For example biglycan, primarily in its soluble form released from matrix during tissue injury, has been shown to interact with a number of molecules including bone morphogenic proteins (BMP)-2,4,6, TGF-β, TNF-α, VEGF, and is a ligand for a number of receptors including the toll-like receptors (TLR)-2 and 4 (for review see [4]). Other putative roles for proteoglycans in the vasculature include the regulation of vascular smooth muscle proliferation and migration[5,6]. Furthermore, as outlined in the “response to retention hypothesis” proteoglycan-mediated lipid retention is thought to be one of the initiating steps in atherosclerosis development[7]. Positively charged motifs on apolipoproteins B and E can ionically interact with negatively charged sulfate and carboxylic acid groups on glycosaminoglycans, leading to prolonged retention of atherogenic lipoproteins in the subendothelial space. Co-localization studies have suggested that in humans biglycan is a key proteoglycan mediating lipid retention[8,9], whereas in mice both biglycan and perlecan co-localize with apolipoproteins[10,11]. However, the role of

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biglycan in atherosclerosis development is unclear: we recently demonstrated that overexpression of biglycan increased atherosclerosis, but biglycan deficiency was not protective[12,13]. In these studies we demonstrated increased vascular perlecan content in biglycan deficient mice suggesting a compensatory response of the vasculature for the biglycan deficiency[12]. However, the role of perlecan in atherosclerosis is also unclear: decreased vascular perlecan content (using a heterozygous model as the perlecan deficient mouse is not viable) was shown to have decreased early atherosclerosis, but not later atherosclerosis in the apoE−/− model, and no effect in the LDL receptor deficient model[14]. Thus, various proteoglycans appear to play a variety of roles in atherosclerosis development, but their effects vary and definitive proof of a critical role for proteoglycans remains elusive.

Osteoglycin (also known as mimecan) is another member of the small leucine rich proteoglycan family. It was initially thought to be a bone proteoglycan, but subsequently was found in vascular extracellular matrix. Animal studies demonstrate up-regulation of osteoglycin mRNA expression in vascular smooth muscle cells (VSMC) after balloon catheterization and endothelial injury with maximal increase after VSMC proliferation had ceased. Examination of post-natal aortic development suggested that osteoglycin is not required for the proliferative phase of vascular development but may have a role in the development and maintenance of the mature matrix[15]. This is further supported by the demonstration of normal fertility and viability of osteoglycin deficient mice[16]. In atherosclerotic lesions of rabbits osteoglycin was up regulated in activated endothelial cells in the neointima and in the front edge of migrating vascular smooth muscle cells[17]. Thus, like other small leucine rich proteoglycans, osteoglycin may have a role in atherosclerosis development. In this issue, Moncayo-Arlandi et al used the osteoglycin deficient mouse to determine if osteoglycin had a role in the development of murine atherosclerosis. Osteoglycin deficient mice were crossed with the hyperlipidemic apolipoprotein E (apoE) deficient atherosclerosis model; this model develops atherosclerosis spontaneously over its lifespan thus avoiding the requirement for any pro-atherogenic interventions. They found no differences in atherosclerotic lesion area between osteoglycin-deficient or osteoglycin-wildtype apoE−/− mice at 18 or 22 weeks of age. Histological analyses of lesions found no differences between the genotypes in glycosaminoglycan content, collagen content, or cellular composition at 18 and 22 weeks of age, or calcium deposition at 22, 34 or 52 weeks of age. Thus, they conclude that osteoglycin is not required for atherosclerosis development or progression, and its deficiency is not protective[18]. This study is not definitive: for example, atherosclerosis was only examined at relatively early stages, no pro-atherogenic or ostoglycin-up-regulating stimuli were examined, and only one murine model was studied. However, the data adds to the literature suggesting that no single proteoglycan may be key for atherosclerosis. The question of whether osteoglycin has any role in atherosclerosis remains; it is possible that similar to the biglycan knockout model, the osteoglycin knockout model may have compensatory up-regulation of another proteoglycan. Moncaya-Arlandi et al did not specifically examine if other proteoglycans were up-regulated in the osteoglycin deficient model; they only used Masson trichrome or alcian blue staining, which is a crude measure at best. Thus, although osteoglycin-deficiency does not appear to affect atherosclerosis development, this is not a nail in the coffin of proteoglycans in atherosclerosis, but rather, an indication of the complexity of proteoglycan biology.

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