The Prolyl Peptidyl Isomerase Pin1 as a Potential Therapeutic Target in Atherosclerosis

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Atherosclerosis is the major underlying pathology of cardiovascular disease which is in turn the largest cause of premature mortality in developed countries [1]. Rising obesity and diabetes rates are associated with factors that greatly accelerate the development of coronary artery and other macrovascular diseases. The major areas of investigation of atherosclerosis are focused on the initial pre-inflammatory stage in which atherogenic lipoproteins are trapped in the vessel wall by modified proteoglycans, the inflammatory stage in which immune cells penetrate the vessel wall accumulate cholesterol debris and generate atherosclerotic plaques and the final stage in which plaques rupture precipitating the lethal clinical event [2,3]. The initial stage depends upon the action of growth factors to stimulate hyperelongation of chondroitin sulfate/dermatan sulfate glycosaminoglycan (GAG) chains on the small lipid binding proteoglycan biglycan [4]. This is associated in vivo with the elevated expression of GAG synthesizing enzymes in mouse models of atherosclerosis [5]. Transforming Growth Factor (TGF)-β is closely associated with the development of atherosclerosis and it is an important modifer of GAG structure [6,7]. TGF-β signals via serine/threonine phosphorylation of Smad transcription factors [8,9]. This pathway is involved in proteoglycan synthesis in vascular smooth muscle cells [10] and also induces growth in fibroblasts [11]. Phosphorylation of Smad2/3 can occur directly in the carboxy terminus and indirectly in its linker region [12]. These phosphorylation sites in the linker region of Smad2/3 provide potential sites for the action of the prolyl peptidyl isomerase, Pin-1. Pin-1 is being investigated for its potential as a therapeutic target in cancer [13] but it might also in this context be a therapeutic target in cardiovascular disease.

Pin1, a member of the parvulin family of peptidyl prolyl isomerases, has a unique preference for binding via its N-terminal WW domain to phosphorylated-serine/proline or -threonine/proline sequences in proteins. The unique Pin1 C-terminal catalytic domain subsequently catalyses a cis or trans isomerisation of the bound protein. The prolyl isomerisation is a rate-limiting step in protein folding and induces conformational changes, leading to distinct effects in different target proteins, including increased stability or turnover, changes in sensitivity to phosphatases, altered enzymatic activity or subcellular localization, and enabling different ligand protein interactions. Over 30 Pin1 targets have been identified [5,14,15]. Pin1 is overexpressed in many cancers and is associated with transformation and uncontrolled cell growth, Alzheimer’s disease and asthma [14,15]. Pin1 is a significant component of TGF-β signalling, TGF-β signals can regulate cell proliferation, differentiation, migration and apoptosis all known to be important processes in the pathogenesis of atherosclerosis. A role for TGF-β in neointimal hyperplasia of early atherosclerosis is well established [16]. Receptor Smad transcription factors Smad2 and Smad3 are critical signalling components of the TGF-β signal cascade that result in regulation of Smad transcription. A Pin1 binding motif in the linker region of Smad3 at threonine residue 179 is phosphorylated by kinases CDK8/9 in response to TGF-β [17] and binds the WW domain of Pin1 to generate maximum transcriptional activity of genes involved in promoting TGF-β mediated migration and invasion [18]. Pin1 is also involved in intimal hyperplasia via regulation of the antioxidant enzyme hemeoxygenase-1 and in vascular smooth muscle proliferation [19]. Overexpression of Pin1 in vascular smooth muscle cells reduces nuclear levels of nuclear factor E2-related factor-2 via induction of ubiquitinylation and thereby decreases the levels of hemeoxygenase-1 and subsequent neointimal formation [19].

Recently it has been shown that Pin1 catalyses protein isomerisation of activated Protein Kinase C (PKC) [11,20]. The pro-atherogenic effects of activated PKC in vascular smooth cells and endothelial cells are well-known. A number of critical cell surface receptor signalling pathways activate PKC including the receptor for endothelin, a G protein coupled receptor and the receptor for PDGF a protein tyrosine kinase receptor. Both receptor signalling cascades lead to atherogenic changes in the extracellular matrix of the blood vessel wall particularly changes to the lipid binding glycosaminoglycan chains of proteoglycans [21,20]. Other important atherogenic vascular changes induced by agonist induced PKC activation include increases in contractility [22], extracellular matrix deposition [23] and cellular hypertrophy and proliferation. Pin1 binding and isomerisation to the trans configuration of activated conventional PKC isoforms results in down-regulation of their PKC expression and activity as a result of ubiquitinylination and degradation. Pin1 acts as a molecular timer to determine the cellular lifetime of the active conventional isoforms, in contrast the novel PKCisozymes are already in the trans configuration and are bypassed by Pin1 [11]. The length of time active PKCisozymes are able to signal will have significant impact on subsequent signalling outputs thereby influencing atherogenic changes in susceptible cells. Pin1 catalysed isomerisation of PKC thus adds an additional post-translation protein modification that significantly impacts on its downstream signalling pathways in concert with the more well-known and fully described phosphorylation and dephosphorylation events. Cis-trans isomerase Pin1 is increasingly being recognised as a key component of growth factor signalling pathways. Pin1 causes important changes in a number of crucial signalling elements and warrants detailed studies of its actions and roles in vascular biology and particularly in the development of atherosclerosis. Its relevance as a potential target in the prevention of the development of atherosclerosis needs to be fully explored.

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