SERPINE1 Regulates Vascular Smooth Muscle Cell Survival: Attenuation of Neointimal Hyperplasia with a Small Molecule Functional Inhibitor That Promotes SERPINE1 Cleavage

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Restenosis is a pathological form of wound healing following endovascular interventions that involves increased vascular smooth muscle cell (VSMC) migration/proliferation combined with reduced apoptosis resulting in luminal narrowing [1,2]. The incidence of restenosis varies (range 20-50%) among the specific procedures used (e.g., stenting vs. balloon angioplasty) and the vessel site. Of the several factors implicated in the vascular response to injury, plasminogen activator inhibitor-1 (PAI-1; SERPINE1), a member of the serine protease inhibitor (SERPIN) superfamily and the major physiologic regulator of the plasmin-based pericellular proteolytic cascade, is perhaps the most prominent. Initially synthesized as an active SERPIN, PAI-1 converts to a latent form (active half-life ~2 h at 37°C, pI7.4) which is unable to inhibit its target proteases uPA or tPA [3,4]. The half-life is increased 2-10 fold, however, upon interaction with the somatomedin B domain of vitronectin which impacts PAI-1 functional activity, integrin-extracellular matrix interactions and downstream signaling [5-8]. A substrate, proteolytically-cleaved form of PAI-1 also exists that is generated without formation of a covalent PAI-1: protease complex [3,9-11]. Since PAI-1 can be both pro- and anti-restenotic depending on the specific wound model, level of PAI-1 induction and the growth factor microenvironment in the vicinity of the injured vessel, the relative abundance of the three different PAI-1 conformations of PAI-1 may determine whether VSMCs migrate or undergo apoptosis in response to injury.

Recently, several low-molecular weight PAI-1 antagonists (e.g., Tiplaxtinin) were developed that have efficacy in models of thrombotic disease, pulmonary remodeling, obesity and tissue fibrosis [12-19]. Tiplaxtinin antagonizes the anti-fibrinolytic activity of PAI-1 [20,21]. While the mechanism is uncertain, tiplaxtinin promotes PAI-1 cleavage and elastase-cleaved PAI-1 (CL-PAI-1) attenuates neointima formation in response to carotid artery ligation while stimulating plasmin-dependent VSMC apoptosis [22]. Elastase levels increase immediately after balloon-angioplasty, peak at one week and then decline [23]. It has been suggested that lowered elastase activity levels, in the latter stages of vessel "repair" may attenuate PAI-1 cleavage at the injury site contributing to reduced apoptosis and increased neointima expansion via both VSMC proliferation and migration. Tiplaxtinin could be a useful therapeutic option in the context of elevated uPA and PAI-1 as it promotes a substrate-like conversion of PAI-1.

PAI-1 also functions as a multifunctional signaling "ligand" where it impacts cellular responses, including the migratory, proliferative and survival programs, at the site of injury [24,25]. The ability of active PAI-1 to inhibit apoptosis, however, is not due to its ability to bind uPA or signal through uPAR. In fact, FL-PAI-1 activates Akt while CL-PAI-1 and a truncated PAI-1 (PAI-1Δ) mutant, deleted in much of the heparin binding-domain and the reactive center loop (RCL), stimulated VSMC and endothelial cell apoptosis, respectively [22,26-30]. It appears that an intact RCL is required for the pro-survival function of PAI-1.

Assessment of the mechanisms underlying the apoptotic response of VSMCs to CL-PAI-1 and Tiplaxtinin implicated the TWEAK/FN14 extrinsic apoptosis signaling pathway [22,31]. TWEAK (TNF-α weak inducer of apoptosis) activates its receptor, FN14, either as a membrane-bound or solubilized ligand. The down-stream signaling and biological repercussions are tissue-type and context-dependent but have been implicated in apoptotic, proliferative and migratory processes [32]. CL-PAI-1, but not the functionally-stable full-length recombinant PAI-1 variant 14-1b (FL-PAI-1), sensitizes VSMCs to TWEAK-induced apoptosis [22]. Collectively, these data are consistent with the hypothesis that PAI-1 regulates VSMC survival. Full-length PAI-1 binds to, and inhibits, uPA attenuating the conversion of plasminogen to plasmin while simultaneously down-regulating surface FN14 receptor expression via LRPs-mediated endocytosis [22]. However, when the conformational pools of PAI-1 shift to increased levels of cleaved PAI-1 (either by Tiplaxtinin or exogenous addition), conversion of plasminogen to plasmin is amplified. Both membrane-bound and soluble TWEAK expressions are potentiated thereby stimulating FN14-TWEAK signaling leading to an apoptotic response. Since Tiplaxtinin and CL-PAI-1 reduced carotid ligation-induced neointima formation [22], therapies directed at manipulation of PAI-1 conformation may have applicability as a treatment option for restenosis.

References


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