Expression of the TGF-β1/p53 Target SERPINE1 Gene in Alzheimer’s Dementia: Molecular Mechanisms and Therapeutic Opportunities

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INTRODUCTION

Cardiovascular, thrombotic and neurodegenerative diseases significantly increase with age. These disorders are likely the result of ageing-related pathophysiologic changes in the vascular, hemostatic and central nervous systems (CNS) reflecting the development of coagulation anomalies, advanced sclerotic changes and deficiencies in protein degradation and clearance. Accumulation of neuronal tangles and amyloid peptides (Aβ) is a major cause of age-onset dementia and a hallmark neuropathologic feature of Alzheimer’s disease (AD) for which there is currently no effective treatment. The plasmin-generating cascade, involving urokinase (uPA) and tissue-type (tPA) plasminogen activators, convert plasminogen to the broad-spectrum protease plasmin. Plasmin provides an Aβ-clearing function in the brain degrading Aβ and catalyzing amyloid precursor protein (APP) α-site APP proteolysis producing nontoxic peptides. Plasmin activation, in turn, is negatively regulated by the clade E, member 1, serine protease inhibitor PAI-1 (plasminogen activator inhibitor type-1; SERPINE1) resulting in Aβ accumulation. PAI-1 and its major physiological inducer transforming growth factor-β1 (TGF-β1), moreover, are both increased in animal models of Alzheimer's disease (AD) for which there is currently no effective treatment. The plasmin-generating cascade, involving urokinase (uPA) and tissue-type (tPA) plasminogen activators, convert plasminogen to the broad-spectrum protease plasmin. Plasmin provides an Aβ-clearing function in the brain degrading Aβ and catalyzing amyloid precursor protein (APP) α-site APP proteolysis producing nontoxic peptides. Plasmin activation, in turn, is negatively regulated by the clade E, member 1, serine protease inhibitor PAI-1 (plasminogen activator inhibitor type-1; SERPINE1) resulting in Aβ accumulation. PAI-1 and its major physiological inducer transforming growth factor-β1 (TGF-β1), moreover, are both increased in animal models of Alzheimer’s disease (AD) for which there is currently no effective treatment. The plasmin-generating cascade, involving urokinase (uPA) and tissue-type (tPA) plasminogen activators, convert plasminogen to the broad-spectrum protease plasmin. Plasmin provides an Aβ-clearing function in the brain degrading Aβ and catalyzing amyloid precursor protein (APP) α-site APP proteolysis producing nontoxic peptides. Plasmin activation, in turn, is negatively regulated by the clade E, member 1, serine protease inhibitor PAI-1 (plasminogen activator inhibitor type-1; SERPINE1) resulting in Aβ accumulation. PAI-1 and its major physiological inducer transforming growth factor-β1 (TGF-β1), moreover, are both increased in animal models of Alzheimer’s disease (AD) for which there is currently no effective treatment.
appears to have multifunctional roles in the CNS where it maintains neuronal cellular structure and initiates signaling through mitogen-activated protein kinases [12]. Recent findings, moreover, suggest a more global impact on intracellular networks as PAI-1 also activates the Jak/Stat and Akt pathways by binding to the low-density lipoprotein receptor-related protein-1 (LRP-1), a member of the low density lipoprotein (LDL) receptor gene family [Czekay, Archambeault and Higgins, unpublished data]. Whether these varied effects are dependent on the anti-proteolytic function of PAI-1 is not clear but significantly increased PAI-1 immunoreactivity in the CNS of AD patients is associated with development of senile plaques and ghost tangle structures [13], consistent with the colocalization of plasminogen activators and PAI-1 in plaque structures [14] which are sites of sustained inflammation [15]. Tg2576 and TgCRN8 transgenic mice, that are genetically-engineered to express the brain-targeted Swedish and the double Swedish/V717F Aβ mutants, respectively, exhibit age-dependent Aβ plaque development as well as cognitive deficiencies [16]. Importantly, tPA activity in these mice was specifically decreased significantly in the hippocampus and amygdala which correlated corelating with regional increases in PAI-1 expression [17]. Since direct Aβ peptide injection increased PAI-1 expression and whereas Aβ hippocampal clearance required both tPA and plasminogen, a functional tPA-plasmin axis appears necessary for Aβ removal [17]. While PAI-1 may be neuroprotective in specific settings (e.g., tPA-triggered neuronal apoptosis) [18,19] and is a CNS injury-response gene [20], chronically elevated PAI-1 levels nevertheless promote Aβ accumulation by inhibiting plasmin-dependent degradation. Genetic evidence clearly indicates that brain PAI-1 expression is increased in Aβ precursor protein presenilin 1 (APP/PS1) transgenic mice as well as in AD patients [21] while PAI-1-deficiency in an APP/PS1 background reduces amyloid accumulation likely by increasing IPA and plasmin activities [22]. Indeed, a diet containing the phenolic anti-oxidant tert-butylhydroquione reduced brain Aβ load in APP/PS1 transgenics and inhibited PAI-1 expression [22]. The translational impact of this study is highlighted by the realization that TGF-β1-induced PAI-1 gene expression is dependent on the generation of reactive oxygen species by p22(Phox)-containing NADP(H) oxidases [23,24].

**THERAPEUTIC OPPORTUNITIES**

The development of pharmacologic approaches to inhibit the function of a key contributor (PAI-1) to disease progression has significant translational relevance. AD patients have elevated neuronal levels of tPA, uPA, PAI-1 and α2-antiplasmin where they associate with Aβ plaques; their offsetting activities may blunt plasmin generation and inhibit Aβ clearance [25]. Importantly, a small molecule inhibitor of PAI-1 activity (PAZ-417) partially blocks amyloid deposition in a mouse AD model. PAI-1 inhibition stimulates tPA/plasmin activity, decreasing CNS Aβ levels and reverses cognitive deficits [26] suggesting that such targeting may have clinical utility. In addition, histone deacetylase inhibitors (HDACi) are emerging as a promising therapy for neurodegenerative disease [27]. Sodium butyrate (NaB), a broad-spectrum HDACi, improved learning and memory in rats subjected to the standard Morris water maze challenge [28]. Butyrate localizes to the cerebral cortex in KCl-induced spreading cortical depression [29]. NaB (as well as TSA) are neuroprotective in the context of ischemic brain injury [30] and effectively reduced TGF-β1-induced PAI-1 expression [19]. Brain TGF-β1 levels increase during the onset and progression of Parkinson’s disease, AD, and stroke [reviewed in 19]. Elevated TGF-β1 expression correlates with Aβ angiopathy and transgenic mice that overexpress TGF-β in astrocytes exhibit early onset Aβ deposition [31]. TGF-β1, moreover, induces astrocyte APP expression while Aβ production was enhanced by TGF-β1 signaling [32]. The coordinate overexpression of PAI-1 and increased Aβ generation in response to elevated TGF-β1 in AD patients may dispose to disease progression [33]. Collectively, these findings raise the possibility that targeting specific TGF-β1-inducible genes (e.g., PAI-1, APP) may have therapeutic benefit in the setting of AD. HDACi coupled with a small molecule central nervous system-accessible PAI-1 functional inhibitor may have efficacy as an approach to reverse the ongoing accumulation of amyloid deposits even after disease development.

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