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NFATs and Their Potential Role in Vascular Wall Remodeling

Vascular smooth muscle cell growth and migration play a pivotal role in vascular wall remodeling. Since nuclear factors of activated T cells (NFATs) have been shown to be involved in the regulation cytokine genes, we asked the question whether these transcriptional factors have any role in vascular wall remodeling. To address this, we have examined their role in the regulation of vascular smooth muscle cell (VSMC) growth and migration by platelet-derived growth factor-BB (PDGF-BB) and thrombin, the receptor tyrosine kinase (RTK) and G protein-coupled receptor (GPCR) agonists, respectively. NFATc1 but not NFATc2 or NFATc3 was translocated from the cytoplasm to the nucleus upon treatment of VSMC with PDGF-BB or thrombin. Translocation of NFATc1 was followed by an increase in NFAT-DNA binding activity and NFAT-dependent reporter gene expression. Cyclosporin A (CsA), a potent and specific inhibitor of calcineurin, a calcium/calmodulin-dependent serine phosphatase involved in the dephosphorylation and activation of NFATs, blocked NFAT-DNA binding activity and NFAT-dependent reporter gene expression induced by PDGF-BB and thrombin. CsA also completely inhibited PDGF-BB and thrombin-induced VSMC growth and motility. In addition, forced expression of VIVIT, a NFAT competing peptide, significantly attenuated both VSMC growth and motility induced by PDGF-BB and thrombin. In addition, we found that NFATs mediate PDGF-BB and thrombin-induced VSMC motility via enhancing the expression of IL-6. To extend the role of NFATs in the regulation of VSMC growth and migration in vitro to in vivo, we used a rat carotid artery balloon injury (BI) model. The levels of NFATc1 increased in balloon-injured arteries compared to uninjured arteries. Furthermore, intra-peritoneal injection of CsA suppressed balloon injury-induced neointima formation by 40%. Similarly, adenoviral-mediated expression of VIVIT in injured arteries also reduced neointima formation by about 40%.

Towards understanding the mechanisms by which NFATs regulate VSMC growth, we identified cyclin D1 and cyclin A2 as target genes of these transcriptional factors. PDGF-BB induced cyclins D1 and A expression and CDK4 and CDK2 activities in VSMC. Interference with NFAT activation signaling by CsA and VIVIT completely suppressed PDGF-BB-induced cyclins D1 and A expression and CDK4 and CDK2 activities, resulting in blockade of VSMC in G1 phase. Bioinformatic analysis of cyclins D1 and A promoters revealed the presence of NFAT binding elements, and PDGF-BB induced the binding of NFATs to these elements in CsA and VIVIT-sensitive manner. Consistent with NFAT binding to their promoter elements, blockade of NFAT activation signaling by CsA and VIVIT suppressed PDGF-BB-induced cyclins D1 and A mRNA levels. ChIP analysis showed that NFATc1 binds to both cyclins D1 and A promoters in vivo in response to PDGF-BB treatment in VIVIT-sensitive manner. BI induced cyclins D1 and A expression and CDK4 and CDK2 activities in rat carotid arteries and these responses were completely blocked by adenovirus-mediated transducion of VIVIT. Adenovirus-mediated expression of VIVIT in the arteries also attenuated BI-Induced SMC proliferation as measured by a decrease in PCNA staining resulting in reduced neointima formation. Together, these findings demonstrate that NFATs play a crucial role in the regulation of genes that are involved in the propagation of inflammation and cell cycle regulation and thereby in injury-induced vascular wall remodeling. Based on these observations, NFATs may be used as potential target transcriptional factors for the development of drugs against proliferative cardiovascular diseases such as atherosclerosis and restenosis.

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8th Floor Neuroscience Center Conference Room,
LSU Lion's Building, 2020 Gravier Street New Orleans