Flow-mediated Endothelial Mechanotransduction and Atherosclerosis

Jeng-Jiann Chiu, PhD.

Abstract

Vascular endothelial cells (ECs) are exposed to hemodynamic forces, which modulate EC functions and vascular biology/pathobiology in health and disease. The flow patterns and hemodynamic forces are not uniform in the vascular system. In straight parts of the arterial tree, blood flow is generally laminar and wall shear stress is high and directed; in branches and curvatures, blood flow is disturbed with nonuniform and irregular distribution of low wall shear stress. Sustained laminar flow with high shear stress upregulates expressions of EC genes and proteins that are protective against atherosclerosis, whereas disturbed flow with associated reciprocating, low shear stress generally upregulates the EC genes and proteins that promote atherogenesis. These findings have led to the concept that the disturbed flow pattern in branch points and curvatures causes the preferential localization of atherosclerotic lesions. Understanding of the effects of disturbed flow on ECs can provide mechanistic insights into the role of complex flow patterns in pathogenesis of vascular diseases and can help to elucidate the phenotypic and functional differences between quiescent (nonatherogenic/nonthrombogenic) and activated (atherogenic/thrombogenic) ECs. Our previous studies demonstrated that “small mothers against decapentaplegic homolog 1/5” (Smad1/5) is a convergent signaling molecule for chemical (e.g., bone morphogenetic proteins [BMPs]) and mechanical (e.g., disturbed flow) stimulations, and hence may serve as a promising hemodynamic-based target for anti-atherosclerosis drug development. Our recent studies have developed a novel drug screening platform to demonstrate that KU-55933 and its combination with Apicidin inhibited Smad1/5 activation induced by disturbed flow and BMPs in vascular ECs, as well as their proliferation and inflammation, thereby inhibiting atherosclerosis development. These findings indicate that KU-55933 and its combination with Apicidin are promising therapeutic compounds for atherosclerosis. In addition, in the combination of porcine models, large-scale phosphoproteomics, transgenic mice, and human specimens, we

have recently demonstrated that disturbed flow induces vinculin phosphorylation at S721 (VCL^{S721p}) in vascular endothelium to enhance endothelial permeability and atherosclerosis. VCL^{S721p} abundance was found to be positively correlated with atherosclerotic stages in clinical biopsies and sera from patients with coronary artery disease, suggesting that VCL^{S721p} abundance can be used as a seromarker to guide medication selection. Thus, endothelial VCL^{S721p} is a promising target for clinical assessment and treatment of atherosclerosis. Our findings contribute to our understanding of the etiology of lesion development in vascular niches with disturbed flow and help to generate new approaches for therapeutic interventions.