**MOLECULAR MECHANISMS OF VASCULAR DYSFUNCTION AND ATHEROSCLEROSIS REGULATED BY HEMODYNAMICS FORCES**

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Atherosclerotic cardiovascular disease remains the leading cause of death and disability worldwide. Normally atherosclerosis tends to occur at predisposed regions exposed to proatherogenic disturbed flow, while steady laminar flow with high fluid shear stress at straight arteries is atheroprotective. We have previously shown that docking protein Grb2-associated binder 1 (Gab1) is a mechano-effector protein in response to laminar flow. The aim of this study was to determine the in vivo role of endothelial Gab1 in flow-mediated vascular remodeling and atherosclerosis and explore the underlying mechanisms. To determine the role of endothelial Gab1 in disturbed flow-induced vascular remodeling in vivo, we performed partial carotid artery ligation in Gab1 endothelium-restricted knockout (Gab1-ecKO) mice and wild-type (WT) littermates, and we observed that Gab1-ecKO mice resulted in increased intima-media thickness. To examine the role of endothelial Gab1 in atherosclerosis, we next crossed Gab1-ecKO mice with ApoE KO mice. After partial ligation, Gab1-ecKO; ApoE KO mice under high fat diet showed increased atherosclerotic lesion size compared to Gab1-WT;ApoE KO mice. Using loss- and gain-of-function studies in cultured human endothelial cells (ECs), we found that Gab1 depletion by siRNA augmented monocyte adhesion to ECs by increasing proatherogenic genes intracellular adhesion molecule-1 (ICAM1) and vascular cell adhesion molecule-1 (VCAM1) expression in response to the proinflammatory cytokine TNFα. Conversely, adenoviral overexpression of Gab1 inhibited TNFα-induced monocyte adhesion to ECs and upregulation of ICAM1 and VCAM1 in ECs. These results demonstrate that endothelial Gab1 represses disturbed flow-induced vascular remodeling and atherogenesis through inhibition of vascular inflammation. Our findings suggest that Gab1 activation might represent novel approaches for the treatment of atherosclerotic cardiovascular disease.