The Role of Cyclin-Dependent Kinase 8 in Vascular Disease

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Abstract:

In response to injury, mature vascular smooth muscle cells (SMCs) undergo dedifferentiation, also known as phenotype modulation or switch. This process is characterized by a downregulation or loss of expression of contractile genes and coincidence with increased cell proliferation, migration, and extracellular matrix production, thereby leading to vascular lesion formation. However, the underlying molecular mechanism is not fully understood. The objective of my study was to determine whether cyclin-dependent kinase 8 (CDK8), a transcription-regulating kinase, plays a mediator role in vascular SMC dedifferentiation and lesion formation. Our results from immunochemical staining and western blot revealed that CDK8 expression was upregulated in vascular SMCs in mouse injured arteries and human arteries with atherosclerosis. In cultured rat aortic SMCs (RASMCs), the dedifferentiated phenotype exhibiting the downregulation of SMC contractile genes such as smooth muscle 22 alpha (SM22α), calponin-1 (CNN1), and alpha smooth muscle actin (αSMA) as well as increased proliferation, migration, and cytokine production was dramatically suppressed and reversed into a more differentiated state by CDK8 inactivation via highly selective CDK8 inhibitor, Senexin A, and shRNA knockdown approaches. Peri-vascular delivery of CDK8 inhibitor, Senexin A attenuated ligation-induced neointima (NI) formation in mouse carotid arteries. At the molecular level, we uncovered that CDK8 facilitated the activation of AKT to inhibit GSK3β which phosphorylates c-MYC for degradation by

proteasomes, thereby promoting vascular SMC dedifferentiation. In addition, activated CDK8 formed signaling complex with AKT thereby activating AKT in vascular SMCs. In conclusion, our results demonstrate that CDK8 is a critical mediator of vascular SMC dedifferentiation at least partly by facilitating the AKT-mediated inhibition of GSK3β to stabilize c-MYC, thereby contributing to NI formation. Targeting CDK8 may be a novel therapeutic approach for the treatment of occlusive vascular disease due to the abnormal growth of vascular SMCs.