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Protein tyrosine phosphatase and redox regulation in vascular neointima formation

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Reactive oxygen species (ROS) represent a class of oxygen-derived molecules that act as physiological or pathophysiological signaling molecules in various vascular functions and diseases. ROS, such as O_2^- and H_2O_2, can be generated through the activation of NADPH oxidase, which is mediated by platelet-derived growth factor (PDGF) stimulation. PDGF and ROS perform crucial functions in the regulation of vascular cell proliferation and migration, resulting in circulatory disorders including atherosclerosis. PDGF stimulates intracellular signal molecules with serine/threonine-specific protein kinases and protein tyrosine phosphatases (PTPs). PTPs regulate signal transduction in receptors containing protein tyrosine kinase and participate in determining the level of tyrosine phosphorylation. Moreover, PTPs are important targets of ROS. Src homology domain 2-containing protein tyrosine phosphatase 2 (SHP2) is one cytoplasmic PTPs expressed in several cell types including vascular smooth muscle cells (VSMC). SHP2 is believed to be a target of protein tyrosine kinases, can bind directly to PDGF-receptors, and is thought to contribute to the proximal signaling events of PDGF-receptors. However, the role of SHP2 and its interaction with ROS in VSMC have not been explored.

PDGF increased SHP2 phosphorylation and activity with a similar pattern without altering SHP2 expression ; this response was similar to the cell migration in response to PDGF. PDGF increased the levels of ROS, O_2^-, and H_2O_2, and treatment of cells with H_2O_2 increased VSMC migration and SHP2 phosphorylation. Both PDGF and H_2O_2 increased the phosphorylation of spleen tyrosine kinase (Syk), p38 mitogen-activated protein kinase (MAPK), and this increase was attenuated by knockdown of SHP2 with small interfering RNA of SHP2 and SHP2 specific inhibitor NSC-87877. SHP2 inhibition also diminished the migration and proliferation in response to PDGF. Treatment with ROS inhibitors suppressed the PDGF-induced stimulation of migration and SHP2 phosphorylation in VSMC. PDGF diminished the phosphoryaltion of C-terminal Src kinase (Csk) and adaptor molecule Csk-binding protein (CBP), and these were recovered by inhibition of SHP2. Oral administration of NSC-87877 significantly suppressed neointima formation and SHP2 phosphorylation in rat carotid artery injury model. SHP2 expression and phosphorylation were observed on the carotid neointima formed by balloon injury and in the medial smooth muscle layer. These results imply that the phosphorylation of SHP2 is controlled by ROS and is positively involved in the regulation of PDGF-induced migration. These results suggest that PTPs and ROS are tightly involved in the regulation of PDGF-induced migration in VSMC and these processes may contribute to the neointima formation during vascular tissue remodeling.