Vascular Smooth Muscle Cell Plasticity and Signaling Networks in Small Vessel Disease: Role of Oxidative Stress, Noxs and Notch3

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Vascular smooth muscle cells (VSMCs) exhibit remarkable plasticity and are multifunctional. The primary physiological role of VSMCs is contraction/dilation to maintain vascular tone. Mature VSMCs exhibit a contractile phenotype. In pathological conditions or in response to injury, contractile VSMCs undergo dedifferentiation characterized by proliferation, migration, inflammation and extracellular matrix synthesis, with decreased expression of contractile proteins. VSMC transition between differentiated and dedifferentiation phenotypes is reversible and important in vascular development and repair. However, perturbed phenotype switching leading to a primarily dedifferentiated state contributes to altered vascular function, important in cardiovascular diseases. Molecular mechanisms driving VSMC plasticity, heterogeneity and differentiation in pathological conditions are complex and involve multiple interacting signaling pathways and networks. VSMC contraction is typically triggered by an increase in intracellular free calcium concentration ($[Ca^{2+}]_i$), promoting actin-myosin cross-bridge formation. Growing evidence indicates that contraction is also regulated by calcium-independent mechanisms involving RhoA-Rho kinase and signal transduction typically associated with cell growth (ERK, p38MAPK, Src). On the other hand, proliferation and inflammation involve $[Ca^{2+}]_i$ and pro-contractile signaling and activation of immune/inflammatory pathways and noncoding RNAs, indicating the multifunctionality of signaling molecules. Common to many of these processes is oxidative stress, which regulates transcription factors and redox-sensitive proteins through post-translational oxidation and changes in the redox milieu. Subcellular compartmentalization of ROS and proximity to target signaling molecules likely impact the VSMC phenotype in health and disease. Here we will focus on VSMC signaling networks and the role of Nox5 as a point of cross-talk between Ca^{2+} and redox signal

transduction and will provide new insights on Notch3. We will highlight how perturbations of these systems contribute to VSMC phenotypic switching to a proliferative and proinflammatory phenotype, processes that underlie vascular dysfunction and remodeling in hypertension and small vessel disease, including CADASIL.