**Endothelial Mechanobiology: May the Flow Be With You**

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**Abstract**

Endothelial cell (EC) dysfunction is the hallmark of cardiovascular diseases and most of them are associated with altered hemodynamics. Our laboratory has been exposing cultured ECs to well-defined fluid mechanical forces and identifying intracellular redox-sensitive signaling pathways that determine cell (dys)function and fate.

Earlier work provided the first evidence that arterial-level steady laminar shear stress (SS) regulates the EC mitochondrial function: SS-induced production of the vasodilator nitric oxide inhibited the electron transport chain complex activities and led to generation of mitochondrial superoxide and other reactive oxygen species (ROS). Mitochondrial ROS upregulated antioxidant genes, thus protecting ECs from oxidative stress. When SS was preceded by simulated ischemia, it resulted in excessive levels of mitochondrial ROS, mitochondrial fragmentation/fission, and EC inflammation/dysfunction.

In more recent work, we determined the role of mitochondria in shaping the SS-induced intracellular Ca$^{2+}$ response: Knockdown of the Mitochondrial Ca$^{2+}$ Uniporter (MCU; channel protein of the MCU complex that mediates mitochondrial Ca$^{2+}$ uptake) inhibited the intracellular Ca$^{2+}$ oscillations in SS-exposed ECs, suggesting that the mitochondrial Ca$^{2+}$ transport is essential for shear-induced Ca$^{2+}$signaling. Our current work focuses on characterizing the effects of atheroprotective vs. atheroprone flows on MCU expression/activity, mitochondrial Ca$^{2+}$/ROS, and EC inflammation/dysfunction, in order to identify new molecular targets for prevention of EC dysfunction, the earliest event in cardiovascular diseases. Additional projects examine the intracellular signaling under more complex mechanical environments and during cell senescence, in order to better understand the EC dysfunction in heart failure with preserved ejection fraction.