Public Abstract
First Name:Ningpu
Middle Name:
Last Name:Yu
Adviser's First Name:Gary
Adviser's Last Name:Weisman
Co-Adviser's First Name:Cheikh
Co-Adviser's Last Name:Seye
Graduation Term:FS 2007
Department:Biochemistry
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Title:The Role of P2Y2 Nucleotide Receptors in Vascular Inflammation

Extracellular nucleotides act on P2 receptors to regulate vascular tone. Large amount of extracellular nucleotides are released at the site of tissue injury and may play an important role in the vascular inflammation. In vascular injury models, P2Y2 mRNA was significantly up-regulated. Activation of up-regulated P2Y2 receptors in the injured artery increased monocyte/macrophage infiltration and intimal hyperplasia. In this dissertation, we showed that activation of the P2Y2 receptor modulates the expression of VCAM-1 in vascular endothelial cells that is important for monocyte recruitment. Suppression of P2Y2 receptor expression by P2Y2 anti-sense oligonucleotide inhibited UTP-induced VCAM-1 expression. Expression of VCAM-1 in HCAEC increased the adherence of monocytic U937 cells to HCAEC monolayers. We also report here that P2Y2 receptor-induced VCAM-1 expression is mediated by rapid tyrosine phosphorylation of VEGFR-2 in HCAEC. RNA interference (RNAi) targeting of VEGFR-2 expression or inhibition of VEGFR-2 tyrosine kinase activity abolished P2Y2 receptor-mediated VCAM-1 expression. We also discovered that the P2Y2 receptor is linked to the cytoskeleton through direct interaction with the actin-binding protein filamin A (FLNa), which is a large protein of 280 kD and serves as a cross-linker of actin polymers and as a scaffolding protein for various signaling molecules. This interaction was mapped to the C-terminal tail of the P2Y2 receptor (amino acids 322 to 333) and is required for FLNa phosphorylation, spreading and migration of smooth muscle cells induced by extracellular nucleotides. These results encourage drug design targeting the P2Y2 receptor as a means to prevent and/or treat arterial disease.