THE ROLE OF $P2Y_2$ NUCLEOTIDE RECEPTORS IN VASCULAR INFLAMMATION

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ABSTRACT

Extracellular nucleotides act on P2 receptors to regulate vascular tone. Large amounts of extracellular nucleotides are released at the sites of tissue injury and may play an important role in the vascular inflammation. In vascular injury models, $P2Y_2$ mRNA was significantly up-regulated. Activation of up-regulated $P2Y_2$ receptors in the injured artery increased monocyte/macrophage infiltration and intimal hyperplasia. In this dissertation, we showed that activation of the $P2Y_2$ receptor modulates the expression of VCAM-1 in vascular endothelial cells that is important for monocyte recruitment. We report here that $P2Y_2$ 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 $P2Y_2$ receptor-mediated VCAM-1 expression. We also discovered that the $P2Y_2$ 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 $P2Y_2$ 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 $P2Y_2$ receptor as a means to prevent and/or treat arterial disease.