

Public Abstract

First Name:Zhongji

Middle Name:

Last Name:Liao

Adviser's First Name:Gary

Adviser's Last Name:Weisman

Co-Adviser's First Name:Laurie

Co-Adviser's Last Name:Erb

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Title:THE ROLE OF THE P2Y2 NUCLEOTIDE RECEPTOR IN INFLAMMATION: THE MECHANISMS OF P2Y2 RECEPTOR-MEDIATED ACTIVATION OF G PROTEINS

The extracellular ATP/UTP receptor, i.e., the P2Y2 receptor, mediates pro-inflammatory responses in the vasculature, including the endothelium-dependent infiltration of monocytes and their transendothelial migration into sites of infection, injury, or stress. This dissertation concerns the mechanisms whereby the P2Y2R mediates chemotaxis as well as the modulation of endothelial intercellular junctions. Specifically, this dissertation focuses on the mechanisms underlying the P2Y2R-mediated activation of G proteins, such as heterotrimeric G₁₂ and G_{i/o} and the monomeric Rho family of GTPases that are responsible for regulating chemotaxis, endothelial permeability and leukocyte transendothelial migration. The P2Y2R is a G protein-coupled receptor with an extracellular integrin binding domain (RGD) that enables this receptor to directly interact with $\alpha_v\beta_3/\beta_5$ integrins. The integrin binding domain is required for P2Y2R-mediated activation of G₁₂, G_o and G₁₂, G_o-mediated events, including RhoA and Rac activation, stress fiber formation and chemotaxis towards UTP. In human coronary artery endothelial cells (HCAEC), UTP causes a rapid and transient association of the P2Y2R and the vascular endothelial growth factor receptor-2 (VEGFR-2) with VE-cadherin, a transmembrane component of endothelial adherens junctions. Inhibition of VEGFR-2 kinase activity, or siRNA-mediated down-regulation of VE-cadherin, inhibits Rac activation induced by UTP. This dissertation provides novel findings indicating that to be fully functional, the P2Y2Rs must couple to a large complex containing multiple receptor and signaling proteins, such as α_v integrin, growth factor receptors and VE-cadherin, each of which could be a potential target for the prevention and treatment of inflammatory diseases.