ROLE OF $P2Y_2$ NUCLEOTIDE RECEPTORS IN REACTIVE ASTROGLIOSIS

Min Wang

Dr. Gary A. Weisman, Thesis Supervisor

ABSTRACT

Astrocytes become activated in response to brain injury characterized by increased expression of GFAP and increased rates of cell migration and proliferation. Damage to brain cells causes the release of cytoplasmic nucleotides, such as ATP and UTP, ligands for P2 nucleotide receptors. Results in this study with primary rat astrocytes indicate that activation of a G protein-coupled $P2Y_2$ receptor for ATP and UTP increases GFAP expression and both chemotactic and chemokinetic cell migration. UTP-induced astrocyte migration was inhibited by silencing of $P2Y_2R$ expression with $P2Y_2R$ siRNA. UTP also increased the expression in astrocytes of $\alpha_V\beta_{3/5}$ integrins that are known to interact directly with the $P2Y_2R$ to modulate its function. Anti-α_V integrin antibodies prevented UTP-stimulated astrocyte migration, suggesting that $P2Y_2R/\alpha_V$ interaction mediates the activation of astrocytes by UTP. $P2Y_2R$-mediated astrocyte migration required the activation of the PI3-K/Akt and MEK/ERK signaling pathways, responses that also were inhibited by anti-α_V integrin antibody. These results suggest that $P2Y_2Rs$ and their associated signaling pathways may be important factors regulating astrogliosis in brain disorders.