CHARACTERIZATION AND FUNCTIONAL ANALYSIS OF THE P2Y₂R GENE PROMOTER

Nishant Jain

Thesis Advisors: Dr. Cheikh Seye and Dr. Gary A. Weisman

ABSTRACT

Extracellular nucleotides can bind to the P2Y₂R and modulate proliferation and migration of smooth muscle cells, which is known to be involved in intimal hyperplasia that accompanies atherosclerosis and post-angioplasty restenosis. Moreover, the P2Y₂R is up-regulated in vascular smooth muscle cells and endothelial cells in response to tissue injury. These findings suggest that the P2Y₂R is a potential target for the pharmacological control of progression of atherosclerosis and post-angioplasty restenosis. However, the mechanisms governing P2Y₂R up-regulation remain unknown.

In this study, we have cloned a 2071 bp 5’-flanking region of the P2Y₂R gene in a reporter vector and carried out a serial deletion analysis. The deletion of a 175 bp region completely abolished promoter function and results further indicate that the P2Y₂R gene promoter uses an array of positive and negative response elements in the regulation of gene expression. Furthermore, other results show that the cytokine IL-1β may be involved in down-regulation of P2Y₂R activity in human coronary artery endothelial cells. Further studies will potentially lead to the identification of novel pathways involved in the regulation of P2Y₂R gene expression, information that might be useful to suppress neointimal hyperplasia in atherosclerosis and the restenosis of angioplasty.