

Role of p38 MAPK in IL-4-Induced IL-6 Expression in Vascular Endothelium

Cardiovascular disease caused by atherosclerosis is the leading cause of illness and death in the United States. A number of previous studies have demonstrated that the pro-oxidative and pro-inflammatory pathways within vascular endothelium play an important role in the initiation and progression of atherosclerosis. For example, the recruitment of inflammatory cells such as monocytes/macrophages, and their migration throughout the vascular endothelium are thought to be critical early pathological events in atherogenesis. Recently, we have discovered new evidence to strongly indicate that interleukin-4 (IL-4) can induce pro-inflammatory vascular environments *via* oxidative stress-mediated up-regulation of inflammatory mediators, such as cytokine, chemokine, and adhesion molecules. Indeed, our most recent finding, showing that IL-4 significantly induced the mRNA and protein expression of pro-inflammatory cytokine interleukin-6 (IL-6) in human vascular endothelial cells, appears to be the first to document the stimulatory effect of IL-4 on IL-6 expression in vascular endothelium. The detailed molecular signaling mechanisms responsible for IL-6 overexpression by IL-4, and the potential involvement of antioxidant-sensitive mechanisms underlying this process, however, remain to be further investigated. Therefore, we hypothesize that IL-4 may induce inflammatory pathways in vascular endothelium through the p38 MAPK-mediated up-regulation of IL-6 expression.

To test this hypothesis we will pursue the following three specific aims:

- (1) To examine whether IL-4 induces IL-6 expression and inflammatory environment through antioxidant-sensitive mechanisms in vascular endothelium.
- (2) To determine the molecular regulatory mechanisms of IL-4-induced IL-6 expression in vascular endothelium.
- (3) To elucidate the p38 MAPK-mediated signaling pathways responsible for IL-6 induction in IL-4-stimulated vascular endothelium.

The significance of this application is that the proposed studies will contribute to a better understanding of the cellular and molecular signaling mechanisms of IL-4-mediated initiation

and progression of atherosclerosis. Additionally, the elucidation of possible involvement of antioxidant-sensitive mechanisms in this process will have significant clinical implications for the development of therapeutic drugs for atherosclerosis specifically targeted against inflammatory pathways. Moreover, the proposed project will make a special effort to stimulate biomedical research by both undergraduate and graduate students. In particular, undergraduate students involved in the proposed studies will benefit from exposure to and active participation in biomedical research project and be encouraged to pursue graduate studies in the health-related sciences.