TOBACCO SMOKE COOPERATES WITH INTERLEUKIN-1β TO ALTER β-CATENIN TRAFFICKING IN VASCULAR ENDOTHELIUM RESULTING IN INCREASED PERMEABILITY AND INDUCTION OF CYCLOOXYGENASE-2 EXPRESSION IN VITRO AND IN VIVO

Silvia S. Barbieri*, Elena Tremoli|| and Babette B. Weksler*

*Division of Hematology-Medical Oncology, Weill Medical College of Cornell University, New York, NY, USA; ||Department of Pharmacological Sciences, University of Milan, Milan, Italy

Cigarette smoking impacts all phases of atherosclerosis from endothelial dysfunction to acute occlusive clinical events. We explored activation by exposure to tobacco smoke of two genes, β-catenin and COX-2, that play key roles in inflammation and vascular remodelling events. Using both in vivo and in vitro smoke exposure, we determined that tobacco smoke (TS) induced nuclear β-catenin accumulation and COX-2 expression and activity, moreover, interacted with IL-1β to enhance these effects. Exposure of cardiac endothelial cells to tobacco smoke plus IL-1β (TS/IL-1β) enhanced permeability of endothelial monolayers and disrupted membrane VE-cadherin/β-catenin complexes, decreased β-catenin phosphorylation, and increased phosphorylation of GSK-3β, Akt and EGFR. Transfection of endothelial cells with β-catenin-directed siRNA suppressed TS/IL-1β-mediated effects on COX-2 modulation. Inhibitors of EGFR and phosphatidylinositol-3-kinase also abolished both the TS/IL-1β-mediated modulation of the Akt/GSK-3β/β-catenin pathway and enhancement of COX-2 expression. Moreover, increased levels of Akt and GSK-3β phosphorylation, nuclear β-catenin accumulation, COX-2 expression, and IL-1β were observed in cardiovascular tissue of ApoE-/- mice exposed to cigarette smoke daily for two weeks. Our results suggest a novel mechanism by which cigarette smoking can induce proinflammatory and proatherosclerotic effects in vascular tissue.