

American College of Surgeons
2009 Clinical Congress
October 11-15, 2009 Chicago IL

Scientific Exhibit Abstract

Category: General Surgery

Title: Adiponectin Deficiency Profoundly Exacerbates Sepsis-related Mortality through Endothelial Activation: A Novel Mechanistic Link between Adiposity and Sepsis

First-named author: Hwee Teoh, PhD

Tel: 4168646060
4168645997

E-mail: teohh@smh.toronto.on.ca
vermasu@smh.toronto.on.ca

Co-Authors: Adrian Quan, MPhil, K. W. Annie Bang, MSc, Vivian Vu, MSc, Jack J. Haitzma, MD, PhD, Haibo Zhang, MD, PhD, Lawrence Chan, MD, DSc, John Freedman, MD, Gary Sweeney, PhD, Subodh Verma, PhD

Institute name, city/state/country: St. Michael's Hospital, Toronto, , Canada

Introduction: Sepsis is a multifactorial, and often fatal disorder, characterized by widespread inflammation with resultant endothelial activation. Adiposity and diabetes are strong negative predictors of sepsis related cardiovascular dysregulation and mortality, however, the mechanisms remain unclear. We postulated that alterations in adipokine biology, particularly adiponectin, are essential modulators of survival and endothelial activation in sepsis.

Methods: We evaluated both loss-of-function (adiponectin gene-deficient mice) and subsequent gain-of-function (recombinant adiponectin reconstitution) strategies in two well-established inflammatory models, cecal ligation perforation (CLP) and thioglycollate-induced peritonitis.

Results: Adipoq^{-/-} mice, subjected to CLP, exhibited a profound (~8 fold) reduction in survival compared to their wild-type Adipoq^{+/+} littermates after 48 hours. Furthermore, compared to wild-type controls, thioglycollate challenge resulted in a markedly greater influx of peritoneal neutrophils in Adipoq^{-/-} mice accompanied by an excess production of key chemoattractant cytokines (IL-12p70, TNF-alpha, MCP-1 and IL-6) and upregulation of aortic endothelial adhesion molecule expression, VCAM-1 and ICAM-1. Importantly, all of these effects were blunted by recombinant total adiponectin administration given three days prior to thioglycollate challenge. The protective effects of

adiponectin were largely ascribed to higher order adiponectin oligomers, since administration of recombinant trimeric adiponectin did not attenuate endothelial adhesion molecule expression in thioglycollate-challenged Adipoq^{-/-} mice.

Conclusions: These data suggest a critical role of adiponectin as a modulator of survival and endothelial inflammation in experimental sepsis and suggest one of the first mechanistic links between adiposity and sepsis related death.