OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference on
Clinical & Experimental Cardiology

April 15-17, 2013 Hilton Chicago/Northbrook, USA

Loss of tissue inhibitor of metalloproteinase-3 (TIMP3) leads to abdominal aortic aneurysm formation in response to Angiotensin II

Zamaneh Kassiri
University of Alberta, Canada

Aortic aneurysm is dilation of the aorta primarily due to degradation of the aortic wall extracellular matrix (ECM). Tissue inhibitor of metalloproteinases (TIMPs) inhibit MMPs, the proteases that degrade the ECM. TIMP3 is the only ECM-bound TIMP and its levels are altered in the aorta from patients with abdominal aortic aneurysm (AAA). We investigated the causal role of TIMP3 in AAA formation. Infusion of Angiotensin II (Ang II), using micro-osmotic (Alzet) pumps, in TIMP3-/- male mice, but not in wild type control mice, led to adverse remodeling of the abdominal aorta, reduced collagen and elastin proteins but not mRNA, and elevated proteolytic activities suggesting excess protein degradation within 2 weeks that led to formation of AAA by 4 weeks. Intriguingly, despite early upregulation of MMP2 in TIMP3-/-AngII aortas, additional deletion of MMP2 in these mice (TIMP3-/-/MMP2-/-) resulted in exacerbated AAA, compromised survival due to aortic rupture, and inflammation in the abdominal aorta. Reconstitution of WT bone marrow in TIMP3-/-/MMP2-/- mice reduced inflammation and prevented AAA in these animals following Ang II infusion. Treatment with a broad-spectrum MMP inhibitor (PD166793) prevented the Ang II-induced AAA in TIMP3-/- and in TIMP3-/-/MMP2-/- mice. Our study demonstrates that the regulatory function of TIMP3 is critical in preventing adverse vascular remodeling and AAA. Hence, replenishing TIMP3, a physiological inhibitor of a number of metalloproteinases, could serve as a therapeutic approach in limiting AAA development or expansion.

Biography

Kassiri completed her graduate training at University of Toronto in muscle physiology (MSc), electrophysiology and gene therapy (Ph.D.), followed by a post-doctoral training in matrix biology and remodeling in cardiovascular diseases at Ontario Cancer Institute (Toronto). She joined University of Alberta in August 2007 as an independent Investigator, where she currently is an Associate Professor at the Department of Physiology and a member of the Mazankowski Alberta Heart Institute and Cardiovascular Research Centre (CVRC). Her research investigates the role of tissue inhibitor of metalloproteinases (TIMPs) in cardiac and vascular pathologies. Her research has been supported by an Establishment Grant from Alberta Innovates-Health Solutions (AI-HS), and operating grants from Canadian Institute for Health Research (CIHR) and Heart and Stroke Foundation of Canada (HSF).

kassiri@ualberta.ca