**AN INSIGHT INTO THE ROLE OF EXTRACELLULAR MATRIX IN DETERMINING THE SITE OF AORTIC ANEURYSM, TAA VERSUS AAA**

**Z. Kassiri**

University of Alberta, Edmonton, AB, Canada

Aortic aneurysm is the second most prevalent aortic pathology, and has no direct pharmacological therapy. It can occur in thoracic (TAA) or in abdominal region (AAA). Prevalence, prognostics and risk factors for AAA and TAA are different. However, the mechanism that determines the site of aneurysm formation remains to be determined. Aneurysmal aorta exhibits drastic structural remodeling, including remodeling of the extracellular matrix (ECM). Homeostasis of the arterial ECM (primarily collagen, elastin) is the result of a balance between its MMP-mediated degradation that is negatively regulated by TIMPs (MMP inhibitors), and its replacement with newly synthesized protein. Disruption of any of these processes would adversely influence ECM integrity.

**Objective:** How does extracellular matrix remodeling affect aneurysm formation in the absence of atherosclerosis.

**Method & Results:** Mice lacking a key tissue inhibitor of metalloproteinase (TIMP3) developed AAA after 4 weeks of Angiotensin II infusion. This was associated with thinning of the arterial wall and enlarged aortic lumen, inflammation and increased proteolytic activities, particularly MMP2. Blocking MMP2 by generating *Timp3*/*Mmp2* double knockout mice exacerbated AAA development due to enhanced inflammation. Intriguingly, subjecting *Mmp2*-deficient mice to Ang II result in TAA (but not AAA). Detailed molecular analyses revealed that MMP2 is a key enzyme in proteolytic release/activation of the ECM-bound TGFbeta which is required for de novo synthesis of ECM proteins in response to Ang II.

**Conclusion:**Aberrant degradation of the ECM leads to AAA formation, whereas disruption of *de novo* synthesis of ECM proteins results in TAA formation, perhaps due to regional structural differences.