**MULTI-FACETED CONTRIBUTION OF TIMPs TO MYOCARDIAL REMODELING**

**Z. Kassiri**

Physiology, University of Alberta, Edmonton, AB, Canada

Tissue inhibitor of metalloproteinases (TIMPs) are best known as inhibitors of matrix metalloproteinases (MMPs) that degrade extracellular matrix (ECM) proteins. While a disturbance in the MMP/TIMP balance is often considered as the underlying mechanism responsible for adverse ECM remodeling in heart disease, such data do not always provide a full explanation of the disease outcomes. Therefore, the aim of our research has been to uncover novel functions of TIMPs in heart disease.

**Objective:**  To discover novel function of TIMPs in different heart disease models.

**Method & Results:**  In a series of studies, we have found that TIMP1, TIMP2, and TIMP3 regulate myocardial fibrosis through distinct and MMP-independent pathways. We used knockout mice (for each TIMP), and 3 models of fibrosis: agonist induced (Ang II-infusion) and pressure overload (transverse aortic constriction, TAC), and myocardial infarction (MI). We found that TIMP1 triggers myocardial fibrosis not by inhibiting MMPs, but by activating the CD63-integrin interaction and de novo collagen synthesis. In response to Ang II, TIMP2-deficiency did not alter fibrosis, whereas TIMP3-deficiency augmented myocardial fibrosis mainly through inducing matricellular proteins and post-translational regulation of collagen fibers. Data from explanted human hearts with dilated cardiomyopathy also revealed the importance of matricellular proteins in ECM remodeling. Following myocardial infarction, overexpression of TIMP3 enhanced angiogenesis, limited infarct expansion and significantly improved cardiac function.

**Conclusion:** The function of TIMPs extends beyond MMP inhibition and therefore, the beneficial effects of targeting TIMPs in heart disease can be many fold.