**NEGATIVE REGULATION OF TOLL LIKE RECEPTOR (TLR)/ INTERLEUKIN-1 (IL-1) SIGNALING IN CARDIAC REPAIR**

**N.G. Frangogiannis**

Albert Einstein College of Medicine, Bronx, NY, USA

Myocardial infarction activates innate immune pathways triggering an intense inflammatory reaction that is required for cardiac repair. However, exaggerated and prolonged inflammation following cardiac injury may increase protease activity promoting dilative remodeling of the infarcted ventricle. Activation of inhibitory signals that prevent uncontrolled post-infarction inflammation may play an important role in cardiac repair. Adverse remodeling in patients with myocardial infarction may reflect impaired activation of the endogenous pathways involved in suppression and containment of the inflammatory response. Our ongoing work is aimed at identifying key endogenous protective signals that limit the innate immune response following myocardial infarction. Interleukin (IL)-1beta is markedly upregulated in the infarcted myocardium and triggers pro-inflammatory and matrix-degrading pathways acting through the type 1 IL-1 receptor (IL-1R1). IL-1R1 signaling promotes recruitment of inflammatory Ly6Chi monocytes and increases fibroblast-derived MMP synthesis while inhibiting myofibroblast transdifferentiation; these actions play an important role in the pathogenesis of post-infarction remodeling. Induction of Interleukin Receptor Associated Kinase (IRAK)-M in infarct mononuclear cells and fibroblasts is a potent inhibitory mechanism that prevents uncontrolled monocyte inflammatory activity and limits cytokine-stimulated matrix metalloproteinase synthesis in fibroblasts. Endogenous pathways that inhibit the innate immune response protect from the development of adverse remodeling following cardiac injury.