

**Targeting Toll-Like Receptor 4 (TLR4) Protects Against Lipopolysaccharide (LPS) Bacterial Like Sepsis and Myocardial Infarction**

*Avlas, O<sup>1</sup>; Fallach, R<sup>1</sup>; Shainberg, A<sup>2</sup>; Fainblut, M<sup>3</sup>; Chepurko, Y<sup>3</sup>; Porat, E<sup>3</sup>; Hochhauser, E<sup>3</sup>*  
*<sup>1</sup>Bar-Ilan University, Rabin Medical Center, Tel Aviv University, Ramat Gan, Petah Tikva, Israel;*  
*<sup>2</sup>Bar-Ilan University, Ramat Gan, Israel; <sup>3</sup>Rabin Medical Center, Tel Aviv University, Petah Tikva, Israel*

Toll like receptors are expressed in immune cells and cardiac muscle. We examined whether the cardiac TLR4 is involved in the acute myocardial dysfunction caused by septic shock and myocardial ischemia. Wild type mice (WT), TLR4-deficient (TLR4-ko) mice and chimeras that underwent myeloablative bone marrow transplantation to dissociate between TLR4 expression in the heart (TLR4-ko/ WT) and the immuno-hematopoietic system (WT/TLR4-ko) were tested. Mice were injected with LPS (septic shock model) or coronary artery ligation (MI model) and tested for function, histopathology proinflammatory cytokine and TLR4 expression. WT mice challenged with LPS and MI displayed reduced cardiac function, increased myocardial levels of IL1 $\beta$  and TNF $\alpha$  and upregulation of mRNA encoding TLR4 prior to myocardial leukocyte infiltration. TLR4-ko mice sustained significantly smaller infarctions compared with control mice given similar areas at risk. Cardiac function of TLR4-ko mice was not affected by LPS and demonstrated reduced suppression by MI compared to WT. Chimeras deficient in myocardial TLR4 were resistant to suppression induced by LPS and the heart function was less depressed, compared to the TLR4-ko, following MI in the acute phase (4 hours). In contrast, hearts of chimeras deficient in immune-hematopoietic TLR4 expression were suppressed both by LPS and MI, exhibiting increased myocardial cytokine levels, similar to WT mice. The cardiac function of TLR4-ko and chimeric mice that express TLR4 in the immune-hematopoietic system but not in the heart, revealed resistance to LPS and reduced depression following MI, suggesting that TLR4 expressed by the cardiomyocytes plays a key role in these events.