Myocardial Toll-Like Receptor 4 (TLR4) mediates dysfunction in septic shock and myocardial ischemia (MI)

R Fallach [1,2], A Shainberg [1], M Fainblut [2], Y Chepurko [2], E Porat [2], E Hochhauser [2]

[1] Faculty of Life Sciences, Bar-Ilan University, Ramat Gan, [2] The Cardiac Research Laboratory of the Department of Cardiothoracic Surgery, Felsenstein Medical Research Center, Tel Aviv University, Petach Tikva, Israel

TLR4 expressed in myeloid cells plays important role in regulating innate immune responses. TLR4 is also expressed in cardiomyocytes, questioning the relative contribution of both cell types to cardiac dysfunction during septic shock and MI.

To test whether cardiomyocyte TLR4 contributes to cardiac dysfunction, C57Bl and TLR4-deficient (TLR4-def) mice were studied *in vivo* in a septic shock model induced by LPS (i.p.) and MI induced by left anterior descending coronary artery ligation at 4, 24, 72 hours post-treatment and *ex vivo* (Langendorff isolated heart preparation). All C57Bl hearts (n=5, in each time point) displayed reduced left ventricular systolic pressure (Millar pressure transducer), along with increased myocardial levels of IL-1β, TNF-α (ELISA) and the up regulation of mRNA encoding TLR4 (quantitative RT-PCR). TLR4-def mice cardiac function was less affected vs. C57Bl mice post-MI, were unaffected by LPS and did not display significant elevation in heart cytokines. These data indicate that TLR4 plays an important role in myocardial dysfunction following septic shock and MI. Deterioration in cardiac function in wild type hearts and sustained function of TLR4-def hearts under *ex vivo* conditions of asanguineous perfusion, suggest that myocardial TLR4 is a direct mechanism of cardiomyocytes function suppression. TLR4 may therefore constitute a novel target in the treatment of the ischemic and septic heart.

	LPS at 4h			MI at 4h		
	LVP mmHg	IL-1β pg/mg protein	TNF-α pg/mg protein	LVP mmHg	IL-1β pg/mg protein	TNF-α pg/mg protein
C57Bl	67±8	606±167	139.4±12	74±6	691.9±109	193.8±35
TLR4-def	130±15	139.88±55	22.3±3	86±6	160.7±42	43.8±4