TLR4 expression is associated with left ventricular dysfunction in patients undergoing CABG surgery

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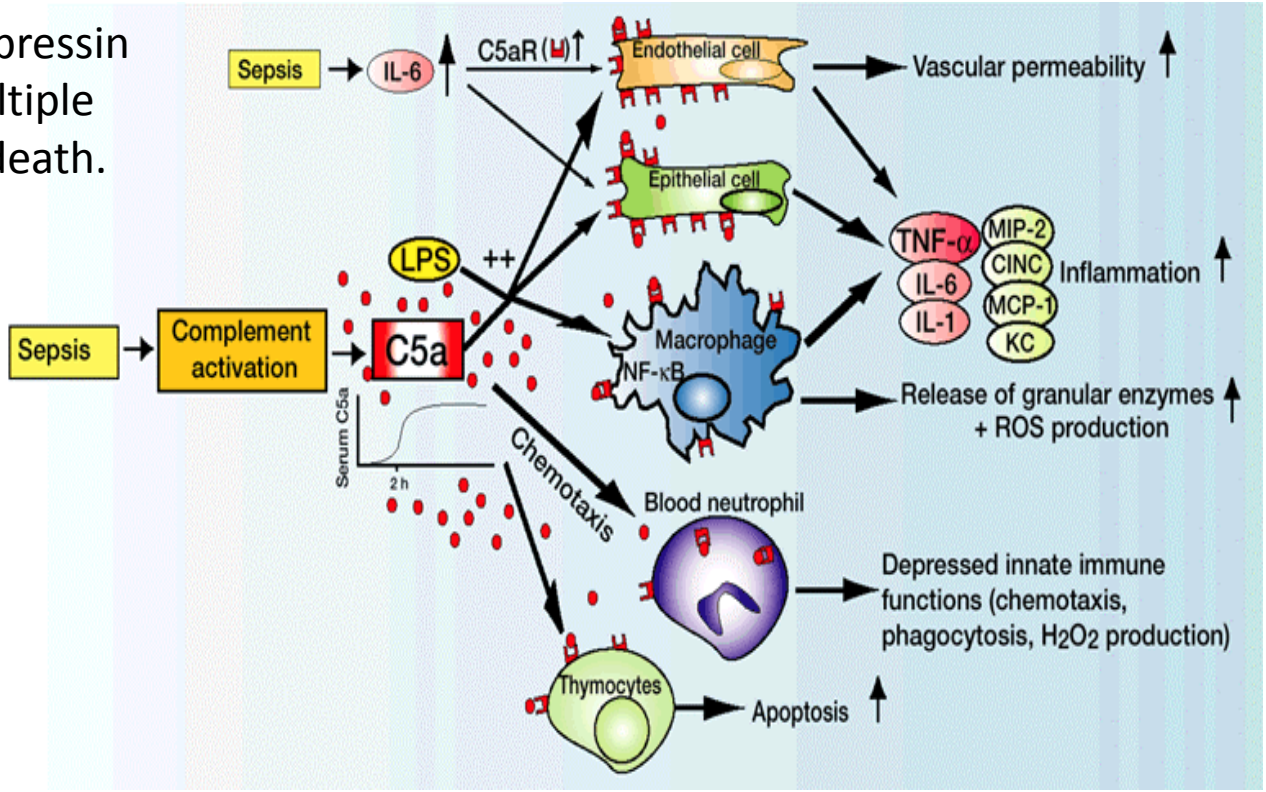
Disclosures

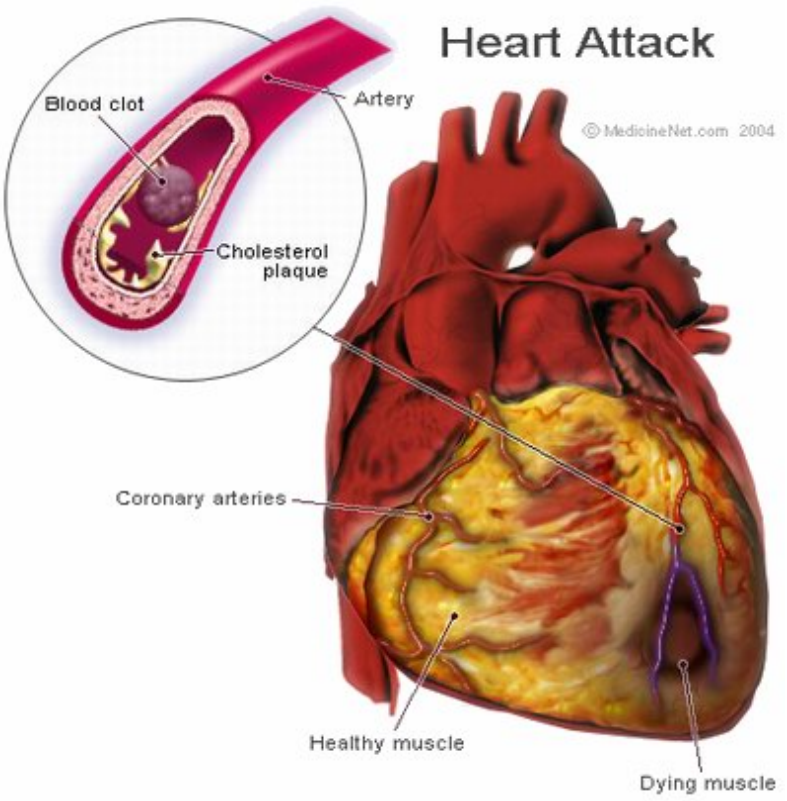
None

Myocardial dysfunction is a well documented feature in myocardial ischemia (MI) and septic shock

Septic shock includes:
sepsis with hypotension that fails to provide adequate blood and 0_2 to organs,
hyperactivity to vasopressin agents leading to multiple organ failure and to death.

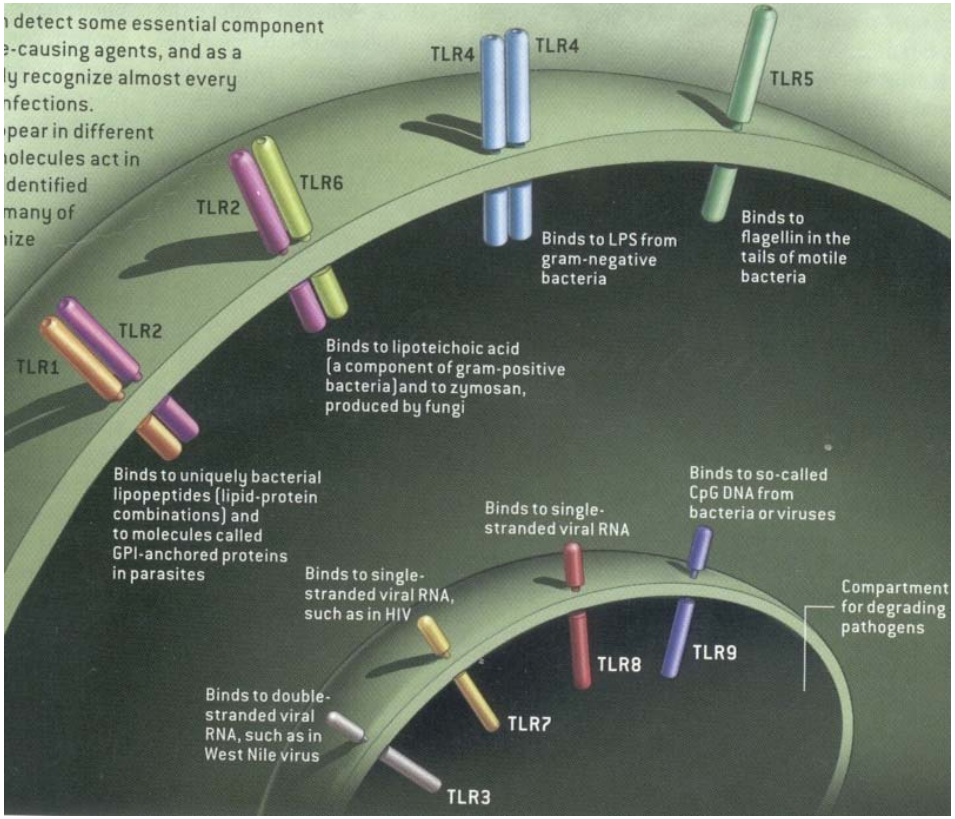


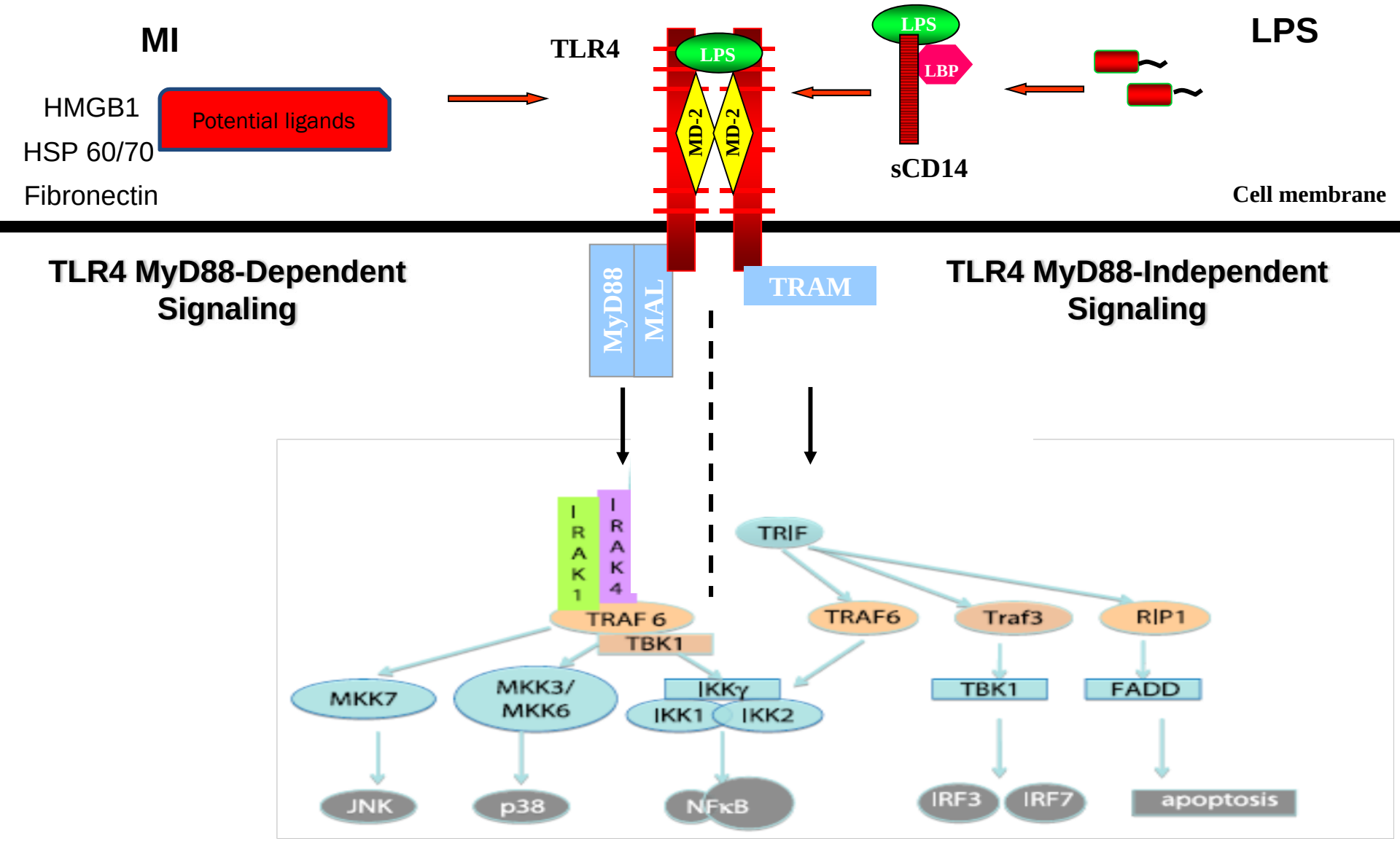
Myocardial ischemia results from the blockade of the coronary arteries caused by atherosclerosis that impairs oxygen delivery.
Innate immune and inflammatory pathways have been implicated in myocardial ischemic injury.



Toll-like receptor 4 –TLR4

TLRs have been identified as the primary innate immune receptors. In the innate immune system, there are receptor proteins that recognize specific patterns (**PRRs)**. These receptors detect pathogen associated molecular patterns (**PAMPs)**.



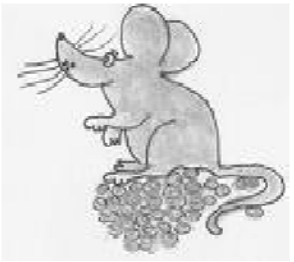


Toll like receptor 4 are expressed in immune cells and cardiac muscle.

In the first part of this study, we examined whether myocardial TLR4 is involved in the acute myocardial dysfunction caused by septic shock or myocardial ischemia.

Control

TLR4-deficient (TLR4-KO)



MI /LPS Injection

4h and 24h - incubation

blood

Isolation of heart

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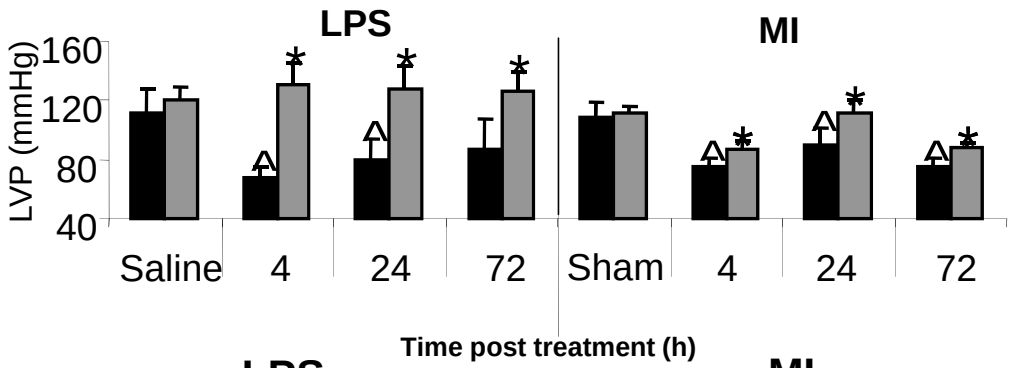
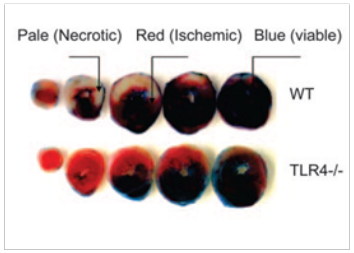
- J Mol Cell Cardiol 2010
- *Antioxid Redox Signal* 2011

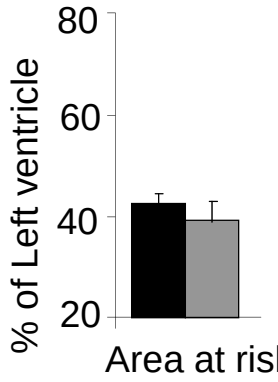
Cardiac function of TLR4-KO mice improved following MI

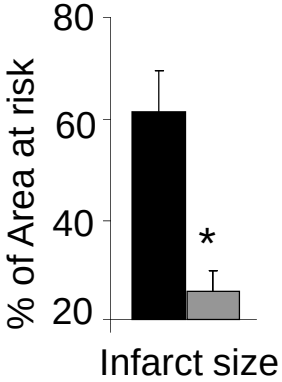
In-vivo Heart Pressures Measurements

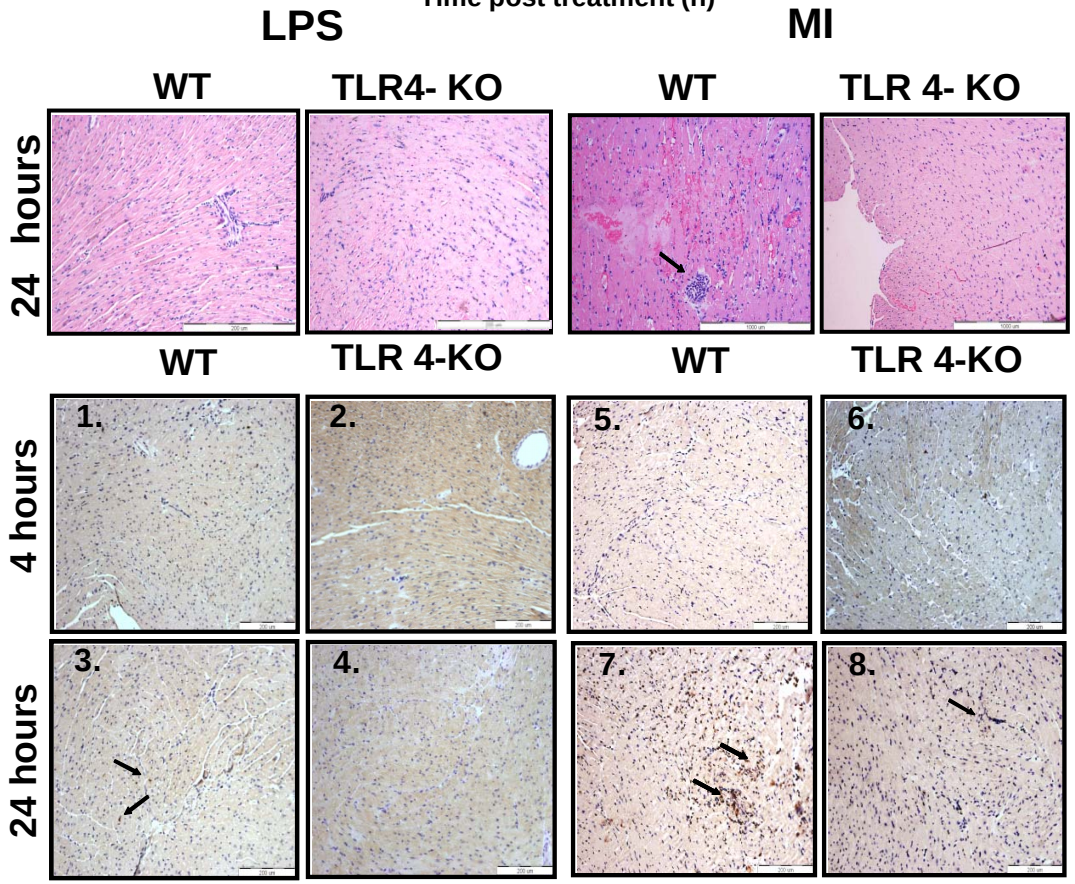


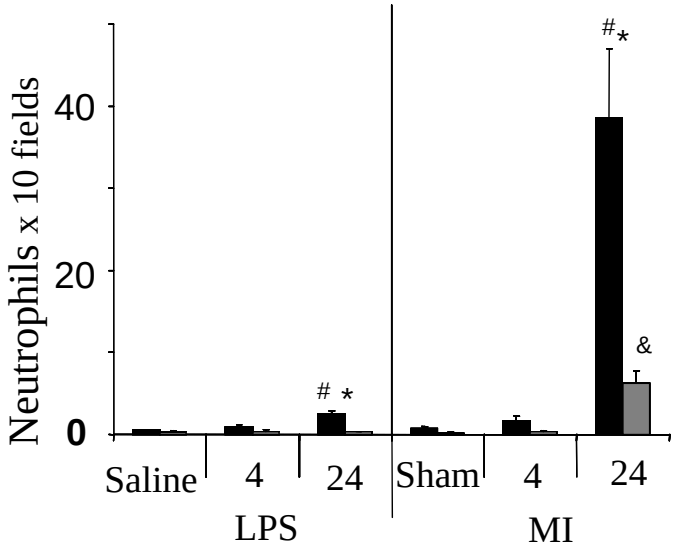


WT
TLR4-KO









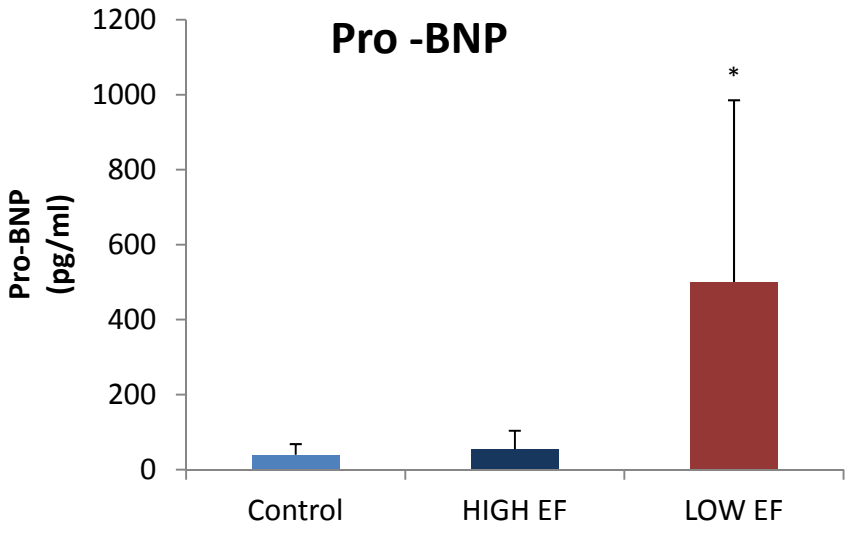
In the second part of this study, we tested the hypothesis that TLR4 can be great interest as a therapeutic target against myocardial dysfunction.

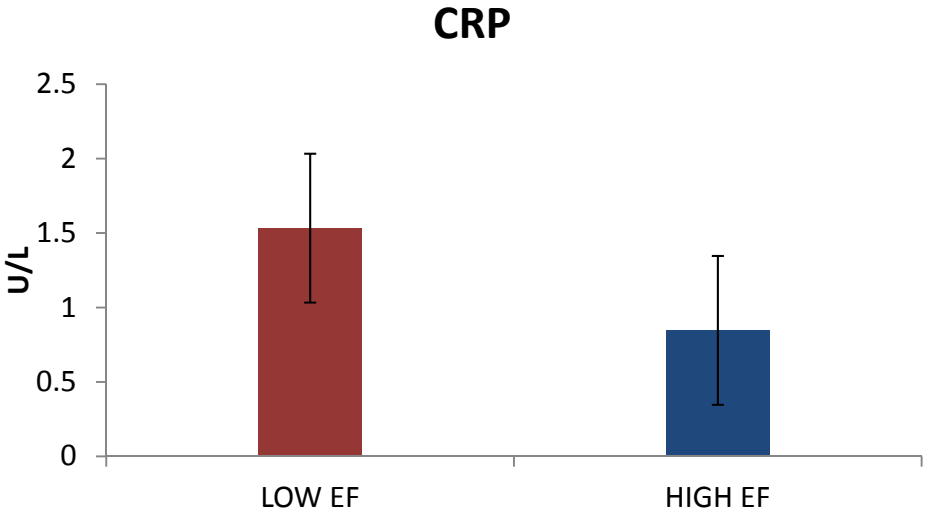
Table: Baseline characteristics of the study population

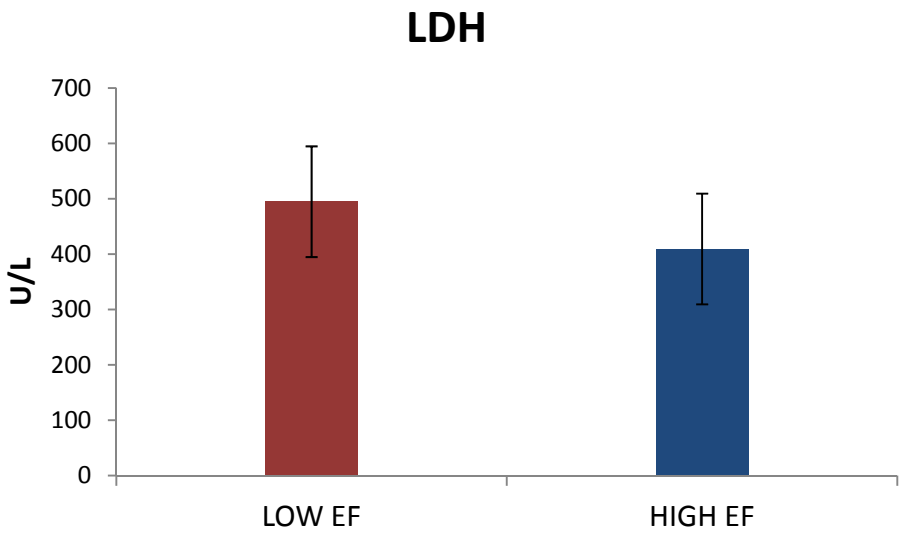
	LOW EF (n=18)	HIGH EF (n=23)	P value
AGE (YEAR)	58±9	65±9.2	0.06
Female (%)	5	8.7	1
Monocyte (%)	4.6±2.9	4.9±2.9	0.8
EF (%)	36.6±6.9	56.8±4.03	0.001
Smoking (%)	50	60.8	0.53
Serum creatinine (mg/dl)	0.9±0.2	1.0±0.35	0.27
Serum sodium(mmol /l)	137±1.83	138.1±1.99	0.5
WBC (K/micl)	9.3±1.4	8.4±2.24	0.15

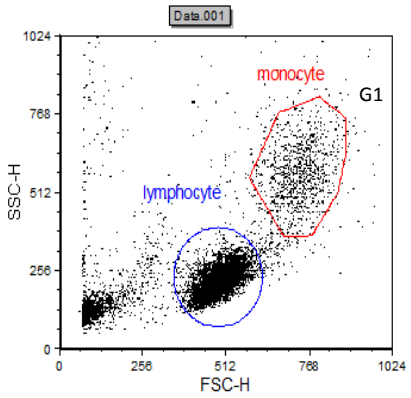
EF=ejection fraction, WBC=white blood cells

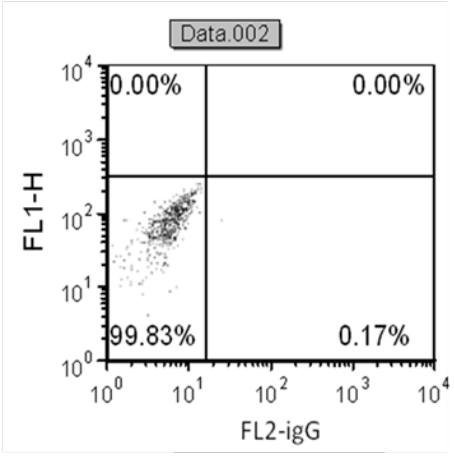
Plasma results

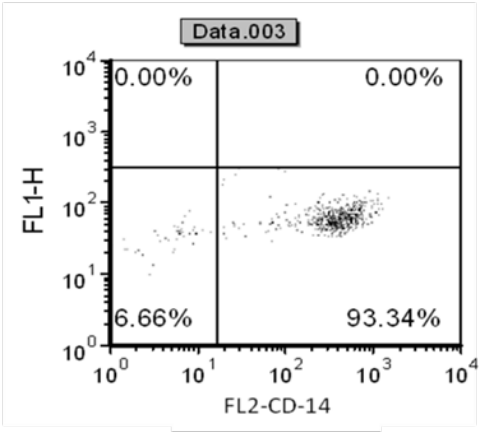


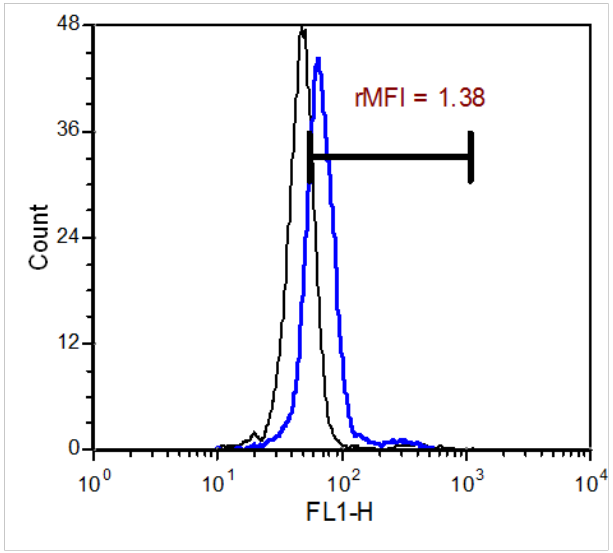


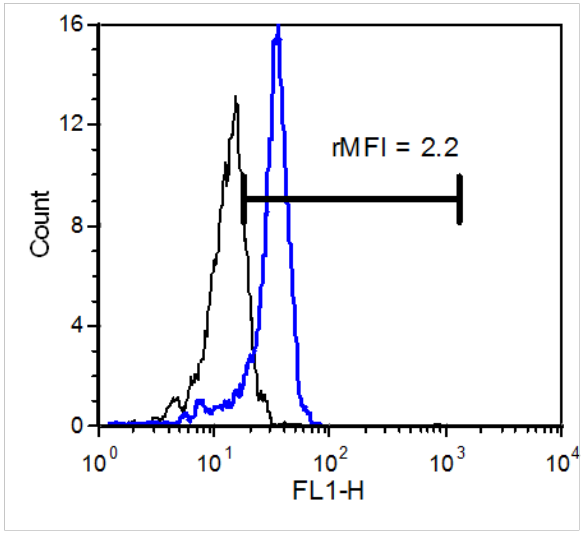






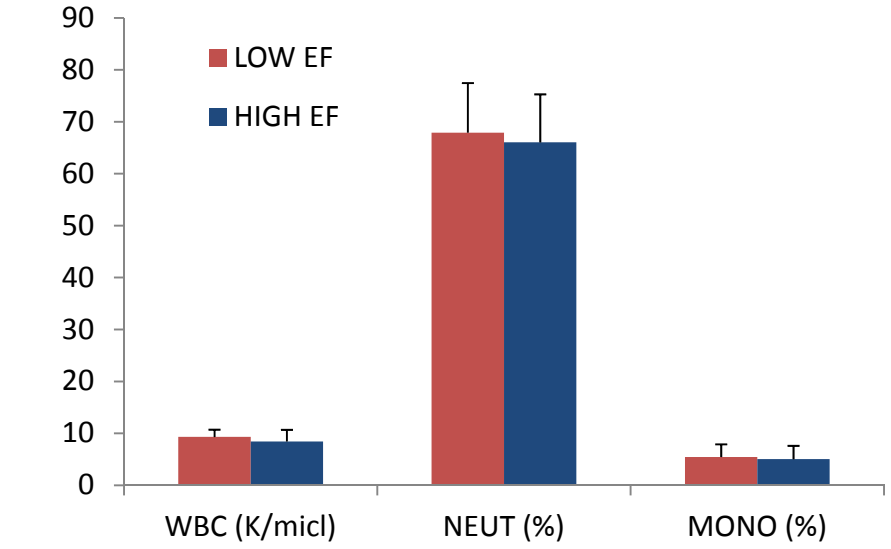


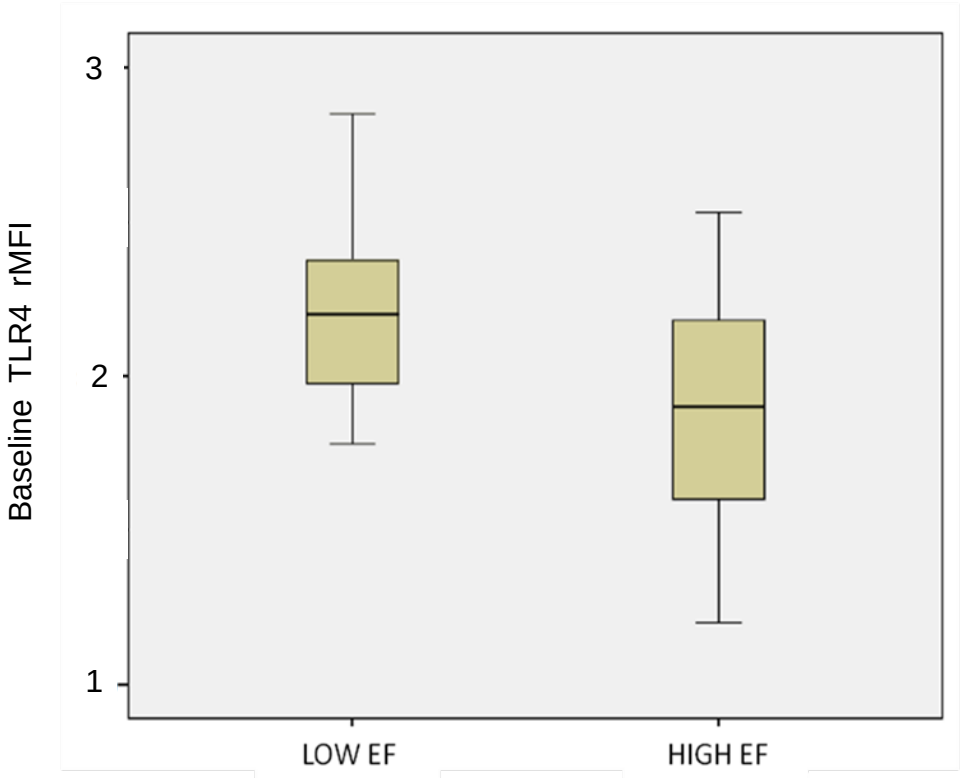


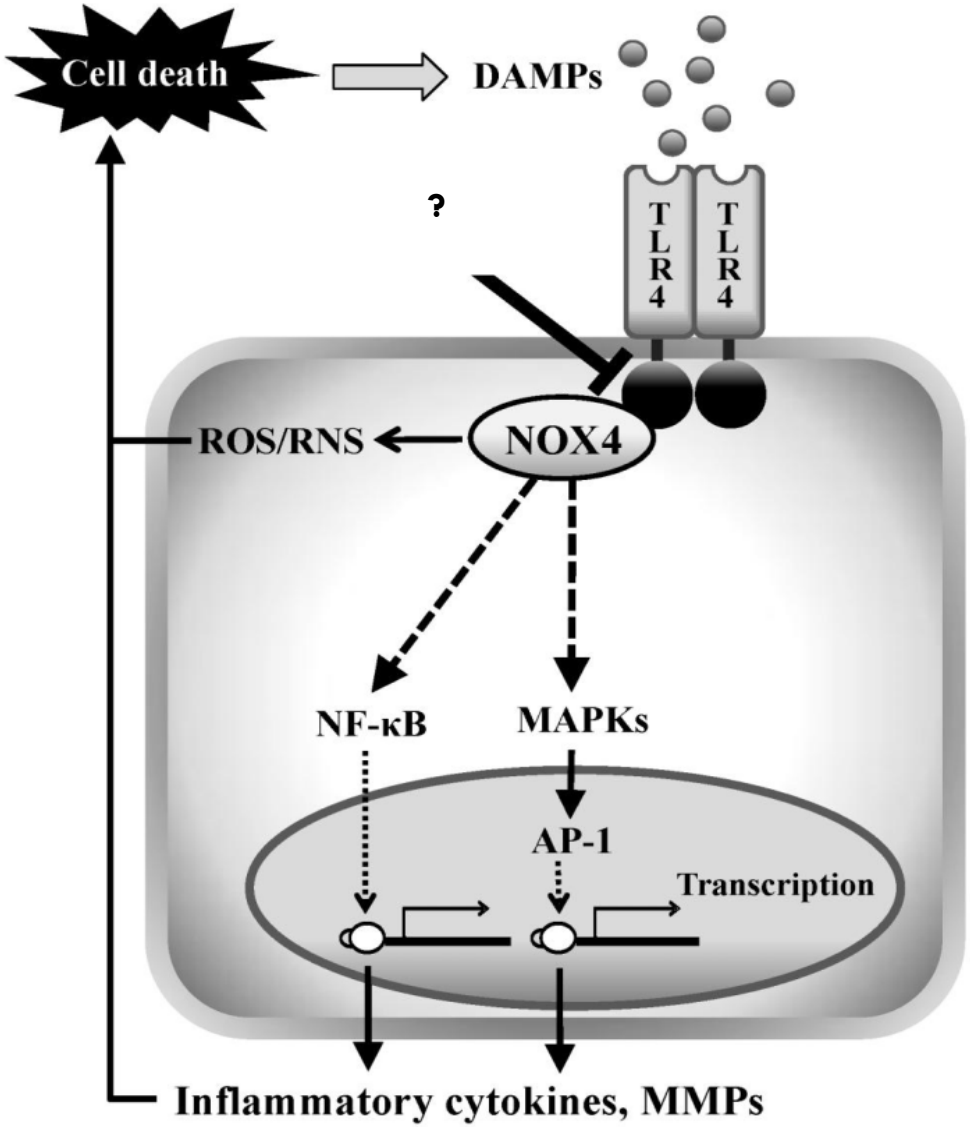


Patient with HIGH EF

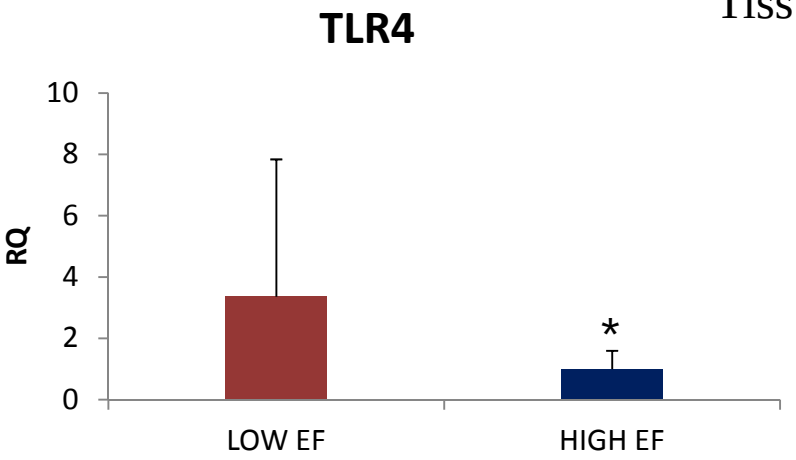
Patient with LOW EF

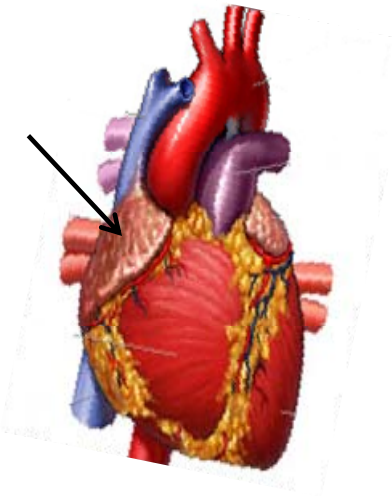

90
80
70
60
50
40
30
20
10
0
LOW EF
HIGH EF
WBC (K/micl)
NEUT (%)
MONO (%)

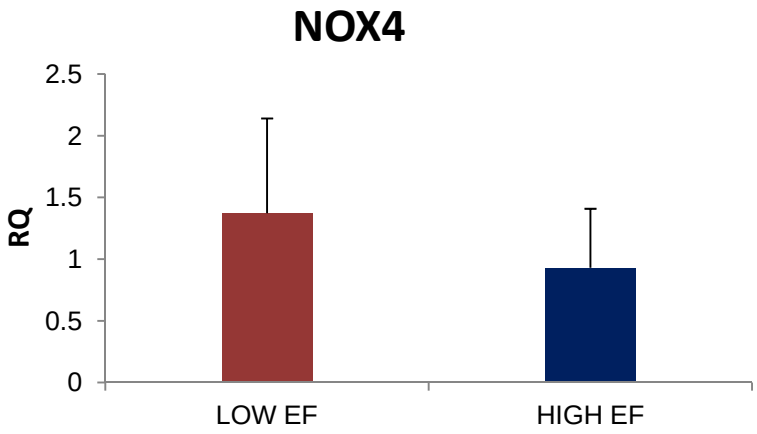

Baseline TLR4 rMFI
3
2
1
LOW EF
HIGH EF

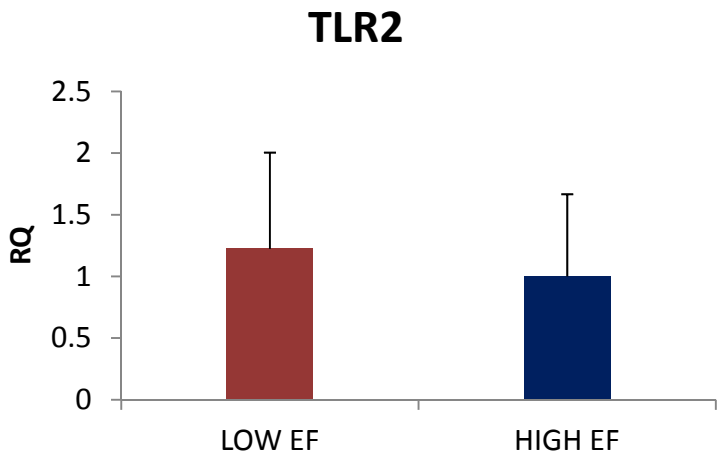

Cell death
DAMPs
?
TLR4
TLR4
ROS/RNS
NOX4
NF-κB
MAPKs
AP-1
Transcription
Inflammatory cytokines, MMPs

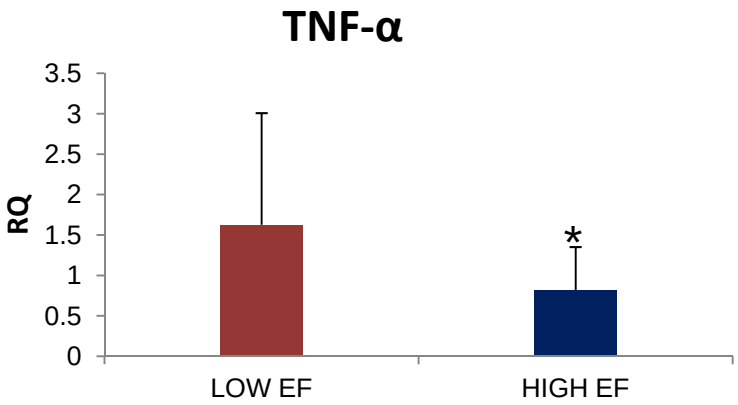
Tissue results (auricles)











Summary

- Cardiac function of TLR4-KO mice improved following sepsis or MI.

- Reduced myocardial production of interleukins, neutrophil recruitment and inflammatory markers in TLR4-KO mice compared to WT mice.

Increased expression of TLR4 may contribute to the activation of innate immunity in the injured myocardium leading to the depression of cardiac function

- Patient with low EF has high TLR4 expression in the blood and heart tissue.

- TLR4 can be used as additional biomarkers for HF.

TLR4 has been proven to be of great interest as a therapeutic target against myocardial dysfunction

Thank you

Acknowledgements:

•Prof. Edith Hochhauser Prof. Asher Shainberg

•Laboratory of Cardiac Research

•Cardiothoracic Surgery Department Under Prof. Dan Aravot Management

Villarrica *2,847m Chile*