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 \( O_2 \) 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).
Potential ligands

TLR4 MyD88-Dependent Signaling

TLR4 MyD88-Independent Signaling

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**

<table>
<thead>
<tr>
<th>4h and 24h - incubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood</td>
</tr>
<tr>
<td>Isolation of heart</td>
</tr>
</tbody>
</table>

- J Mol Cell Cardiol 2010
- Antioxid Redox Signal 2011
Cardiac function of TLR4-KO mice improved following MI

**In-vivo Heart Pressures Measurements**

- **LPS**
  - WT
  - TLR4-KO
  - Time post treatment (h): 4, 24, 72

- **MI**
  - WT
  - TLR4-KO
  - Time post treatment (h): 4, 24, 72

**Heart Pressures Measurements**

- LVP (mmHg)
  - Saline, 4, 24, 72
  - Sham, 4, 24, 72

**Area at risk**

- % of Left ventricle
  - Area at risk
  - Infarct size

**Neutrophils x 10 fields**

- Saline, 4, 24, Sham, 4, 24

**Immunofluorescence Imaging**

- Pale (Necrotic), Red (Ischemic), Blue (Viable)
  - WT, TLR4-KO

**Cardiac function of TLR4-KO mice improved following MI**
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

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

EF=ejection fraction, WBC=white blood cells
Plasma results

**Pro-BNP**

- Control: Low Pro-BNP levels
- HIGH EF: Slightly increased Pro-BNP levels
- LOW EF: Significantly increased Pro-BNP levels

**CRP**

- LOW EF: Elevated CRP levels
- HIGH EF: Normal CRP levels

**LDH**

- LOW EF: Elevated LDH levels
- HIGH EF: Normal LDH levels
Patient with LOW EF

Patient with HIGH EF
P = 0.03

Baseline TLR4 rMFI

LOW EF  HIGH EF

Baseline TLR4 rMFI

LOW EF  HIGH EF

WBC (K/micl)  NEUT (%)  MONO (%)

LOW EF  HIGH EF

Baseline TLR4 rMFI

LOW EF  HIGH EF
Tissue results (auricles)

**TLR4**

- LOW EF: RQ = 2
- HIGH EF: RQ = 2

**NOX4**

- LOW EF: RQ = 2
- HIGH EF: RQ = 1

**TNF-α**

- LOW EF: RQ = 3
- HIGH EF: RQ = 1

**TLR2**

- LOW EF: RQ = 3
- HIGH EF: RQ = 1
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

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