Galectin-3 and Plasma Cytokines in Acute Myocardial Infarction

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DISCLOSURES

• Steering Committee Member, LAPTOP clinical trial sponsored by St. Jude Medical
• Steering Committee Member, CardioMEMS Post-Market Approval Clinical Trial
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Cytotoxic Inflammatory Injury after AMI

During Acute MI  7 Days Post-MI

*RED=MAC 387 Stain

Frangogiannis NG Nat Rev Cardiol. 2014; 11: 255–65
TGF-\(\beta\), a Key Mediator of Remodeling after AMI

Frangogiannis NG Nat Rev Cardiol. 2014; 11: 255–65
Fibrosis, Scarring & Adverse Cardiac Remodeling

Myocardial injury (e.g., MI) triggers inflammatory & wound healing response

Macrophages carrying galectin-3 infiltrate necrotic tissue

Macrophages release galectin-3

Galectin-3 binds and activates the myofibroblast leading to collagen synthesis

Collagen deposition results in scar formation

Remodeling & dilatation)
Aldosterone Promotes CV Fibrosis Via Galectin-3

VSMC

Aldosterone

MCR

Nucleus

G-3

LV Growth and Dysfunction

Ventriculo-Vascular Uncoupling

Cardiac and Arterial Stiffening

Cardiovascular Fibrosis
Preclinical Studies:
Effect of Aldosterone on Galectin-3 expression

Mice vascular smooth muscle cells (VSMCs) in vitro

- Aldosterone up-regulates galectin-3
- Aldosterone up-regulation is mediated through mineralocorticoid receptor

N. Lopez-Andres et al., Presented at the ESC-HF Congress 2012, Belgrade, Serbia.
Preclinical Studies:
Tight Relationship between Aldosterone, Galectin-3 & Fibrosis

Mice VSMCs in vitro: galectin-3 RNA specific inhibition

- Galectin-3 involved in the entire chain of fibrogenesis:
  - from enhanced synthesis of procollagen type-I
  - regulation of enzymes involved in collagen maturation
- Aldosterone up-regulates galectin-3 expression via the mineralocorticoid receptor *in vitro* and *in vivo*

N. Lopez-Andres et al., Presented at the ESC-HF Congress 2012, Belgrade, Serbia.
Galectin-3:

Interaction with Pro-inflammatory Cytokines in a HF Population - COACH

- Galectin-3 levels correlated, albeit weakly, with IL-6, CRP and VEGF demonstrating possible involvement in inflammation
- Galectin-3 likely exerts its effects in HF via other pathologic pathways

# Galectin-3 and Plasma Cytokines in AMI Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gal-3 (ng/mL)</th>
<th>TNF-α (pg/mL)</th>
<th>IL-6 (pg/mL)</th>
<th>CRP (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, mean (SD) (^b)</td>
<td>8.24 (1.64)</td>
<td>12.35 (1.52)</td>
<td>140 (11.19)</td>
<td>9.05 (3.24)</td>
</tr>
<tr>
<td>AMI mean (SD) (^b)</td>
<td>10.14 (2.08)</td>
<td>18.62 (1.68)</td>
<td>170 (14.13)</td>
<td>87.81 (29.52)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.005</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Plasma Gal-3 levels were significantly and positively correlated with plasma IL-6 and TNF-α levels \((r = 0.427 \text{ and } r = 0.382 \text{ respectively; } P < .05)\).

Moreover, in the patient and control groups \((n = 58)\), plasma Gal-3 levels were significantly and positively correlated with plasma IL-6, TNF-α, and CRP levels \((r = 0.488, r = 0.514, \text{ and } r = 0.517, \text{ respectively; } P < .01)\).

Positive correlations were also observed between IL-6 and CRP levels and between IL-6 and TNF-α levels \((r = 0.742, r = 0.682 \text{ respectively; } P < .01)\).

Alturfan AA et al. Lab Med Fall 2014; 45: 332-337
Galectin-3 – Early Detection

- Galectin-3 elevations precede the onset of HF symptoms
  - Window of opportunity to detect those at risk of HF development

![Graph showing Galectin-3, Cardiac Fibrosis, and eGFR stages with chronic micro injury highlighted.](image)
Galectin-3 – Early Detection

**PROVE-IT (TIMI 22)**

- **Objective:** In ACS patients receiving therapy that meets current recommendations, is further LDL lowering of major value?
- **Design:** Double-blind randomized multinational trial in which 4162 patients received 80 mg/day of atorvastatin or 40 mg/day of pravastatin after an MI or unstable angina discharge
  - 349 sites in 8 countries
- **Primary end point:** composite endpoint
  - Death from any cause
  - MI
  - Documented unstable angina requiring re-hospitalization
  - Stroke

Galectin-3 – Early Detection

**PROVE-IT (TIMI 22)-Nested Case Control study**

- Galectin-3 showed a graded relationship with risk of HF
- Patients in highest galectin-3 quartile had approximately 4 x higher odds of developing HF than those in the baseline quartile ($P_{trend} = 0.003$)

![Graph showing univariate unadjusted relative odds of heart failure by galectin-3 quartile.]

- 100 cases with hospitalization for new or worsening HF
- 100 controls matched for age, sex, ACS type and randomized treatment
- Galectin-3 measured at baseline (within 7 days post-ACS)

Galectin-3 – Early Detection

PROVE-IT (TIMI 22)

- Nested case-control study: pilot study
- Patients who developed HF had higher median galectin-3 level
  - 16.7 vs 14.6 ng/ml, p=0.004
- Patients with baseline galectin-3 above median have higher risk of developing HF

Elevated Galectin-3 is associated with increased risk of developing HF following ACS

Biomarker-Based Approaches to Target the Inflammatory response after AMI

Frangogiannis NG Nat Rev Cardiol. 2014; 11: 255–65
Conclusions

• In the infarcted myocardium, cardiomyocyte death and degradation of the cardiac extracellular matrix releases signals that activate innate immune pathways and trigger an intense inflammatory reaction.

• The role of post-infarction inflammation in extending ischemic cardiomyocyte injury is controversial; however, inflammatory mediators are implicated in dilative remodeling and in the pathogenesis of post-infarction heart failure.

• Early stimulation of inflammatory signaling is important for clearance of the infarct from dead cells and for repair.

• Timely repression of pro-inflammatory mediators protects the heart from excessive inflammatory injury.

• Patients surviving a large myocardial infarction exhibit pathophysiological heterogeneity, as subpopulations with progressive dilative remodeling and patients with predominant diastolic heart failure are identified.

• Biomarker-based approaches are needed to identify patients with overactive pro-inflammatory signaling, who might benefit from anti-IL-1 or anti-chemokine strategies, and individuals with excessive fibrosis who might benefit from TGF-β/Smad inhibition.