Inhibition of EGFR Decreases Cardiac Rupture and Improves Survival Post-Myocardial Infarction

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Chain of Events Leading to Cardiovascular Mortality

Chain of Events:
1. Risk factors
   - Hyperlipidemia
   - Hypertension
   - Diabetes

2. Atherosclerosis
   - LV Hypertrophy

3. Coronary Artery Disease
   - Coronary Thrombosis

4. Myocardial Infarction
   - Myocardial ischemia
   - Neurohumoral activation
   - Loss of muscle
   - Remodeling
   - Ventricular Dilatation
   - Congestive Heart Failure

5. Cardiac Rupture
6. Sudden Death
Cardiac Rupture post-Myocardial Infarction

- Cardiac rupture is a fatal complication of myocardial infarction resulting in sudden death.
- Incidence of cardiac rupture in patients post-MI is 1-6%.
- Autopsy examination shows that cardiac rupture is 24-65% among acute MI patients.
- Currently there is no specific drug treatment for cardiac rupture.
Infarct Healing After Acute Myocardial Infarction

Inflammatory Phase

- Inflammatory cells
- Macrophages

Angiogenic cytokines
Fibrogenic cytokines

Proliferation
Migration

Fibroblasts
Myofibroblasts

Autocrine factors
Paracrine factors

Collagen synthesis
ECM degradation (MMPs)

Maturation of fibrosis

Infarct healing
Cardiac rupture

Modified from Kusachi & Ninomiya 2005
Cardiac Rupture post-MI in TIMP3\(^{-/-}\) mice

WT

TIMP-3\(^{-/-}\)

1 mm
Incidence of Cardiac Rupture post-MI

% Cardiac Rupture

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>TIMP-3-/-</th>
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<tbody>
<tr>
<td>6/71</td>
<td>27/79</td>
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Minimum Force of Scar Rupture (g)

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<th></th>
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<th>TIMP-3-/-</th>
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<tbody>
<tr>
<td>6</td>
<td>4</td>
<td>*</td>
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</table>
Myocardial MMP Activity post-MI

- **WT**
- **TIMP-3^-/-**

MMP Activity (pmoles substrate cleaved/mg protein)

Sham

MI

* * †
Collagen I Synthesis in the Infarct Region 5 Days post-MI

![Graph showing PINP (ng/mg protein) levels for WT and TIMP-3⁻/⁻ mice in Sham and MI conditions.](image-url)
Survival After Myocardial Infarction

Days After MI

Survival (%)
EGF/EGFR Signaling Inhibits Collagen Synthesis

• Epidermal growth factor (EGF) is a ligand that binds to EGFR
• EGF is synthesized as a transmembrane protein, and is cleaved by MMPs to form active soluble EGFR ligand.
• Activation of EGFR by EGF inhibits collagen synthesis
Effects of EGF on Collagen I Synthesis in Cultured Adult Cardiac Myofibroblasts

![Graph showing the effects of EGF on Collagen I synthesis in cultured adult cardiac myofibroblasts. The graph compares the PINP levels in WT and TIMP-3-/- conditions with and without rEGF (10 ng/ml).]
EGFR Inhibition by Cetuximab Prevents Cardiac Rupture post-MI in TIMP-3⁻/⁻ mice

% Cardiac Rupture

WT TIMP-3⁻/⁻ No Treatment

6/71

27/79

WT TIMP-3⁻/⁻
EGFR Inhibition by Cetuximab Improves Cardiac Function post-MI in TIMP-3−/− mice

<table>
<thead>
<tr>
<th></th>
<th>WT (n = 9)</th>
<th>MI (n = 9)</th>
<th>MI + Cetux (n = 5)</th>
<th>TIMP-3−/− (n = 8)</th>
<th>MI (n = 6)</th>
<th>MI + Cetux (n = 5)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Sham</td>
<td>MI</td>
<td>MI + Cetux</td>
<td>Sham</td>
<td>MI</td>
<td>MI + Cetux</td>
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<tr>
<td>5 days post-MI</td>
<td></td>
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<tr>
<td>Heart rate (bpm)</td>
<td>369 ± 13</td>
<td>427 ± 20</td>
<td>429 ± 35</td>
<td>401 ± 23</td>
<td>390 ± 28</td>
<td>412 ± 14</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>85.6 ± 6.0</td>
<td>72.4 ± 5.0*</td>
<td>62.1 ± 4.5*</td>
<td>93.8 ± 7.2</td>
<td>69.3 ± 9.8*</td>
<td>67.0 ± 4.5*</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>110.4 ± 5.7</td>
<td>86.6 ± 3.6*</td>
<td>76.5 ± 4.9*</td>
<td>104.7 ± 9.7</td>
<td>84.3 ± 8.0*</td>
<td>72.5 ± 3.9*</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>5.1 ± 0.9</td>
<td>8.2 ± 1.1</td>
<td>9.8 ± 2.5</td>
<td>5.3 ± 0.8</td>
<td>6.3 ± 1.2</td>
<td>7.1 ± 0.9</td>
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<tr>
<td>LV +dP/dt (mmHg s⁻¹)</td>
<td>6,257 ± 538</td>
<td>4,593 ± 365*</td>
<td>4,428 ± 676*</td>
<td>5,911 ± 542</td>
<td>4,988 ± 745*</td>
<td>4,981 ± 885*</td>
</tr>
<tr>
<td>LV −dP/dt (mmHg s⁻¹)</td>
<td>6,021 ± 458</td>
<td>4,501 ± 367*</td>
<td>3,974 ± 455*</td>
<td>5,760 ± 433</td>
<td>4,468 ± 587*</td>
<td>4,206 ± 568*</td>
</tr>
</tbody>
</table>

|                  |WT (n = 8)        |MI (n = 13)       |MI + Cetux (n = 7) |TIMP-3−/− (n = 8) |MI (n = 7)        |MI + Cetux (n = 7) |
|50 days post-MI   |                  |                  |                   |                  |                  |                   |
|Heart rate (bpm)  |435 ± 21          |421 ± 11          |381 ± 17           |434 ± 11          |396 ± 19          |371 ± 17           |
|MAP (mmHg)        |99.0 ± 7.5        |77.0 ± 4.2*       |74.9 ± 3.7         |98.4 ± 5.9        |65.0 ± 5.8*       |79.9 ± 4.2*        |
|LVSP (mmHg)       |114.2 ± 6.0       |93.5 ± 3.1*       |94.3 ± 7.0         |112.4 ± 6.9       |87.1 ± 6.0*       |117.7 ± 11.8*      |
|LVEDP (mmHg)      |5.9 ± 1.6         |9.2 ± 1.0         |11.5 ± 2.6         |4.4 ± 0.2         |7.0 ± 1.2         |9.0 ± 2.8          |
|LV +dP/dt (mmHg s⁻¹) |9,106 ± 722      |5,572 ± 305*      |5,523 ± 376        |9,155 ± 722       |5,422 ± 571*      |7,312 ± 463*       |
|LV −dP/dt (mmHg s⁻¹) |8,833 ± 702      |5,295 ± 284*      |5,767 ± 391        |9,184 ± 907       |5,328 ± 595*      |6,996 ± 931        |

Data are mean ± SEM

MAP mean arterial pressure, LVSP left ventricular systolic pressure, LVEDP left ventricular end-diastolic pressure
* P < 0.05 vs. sham within genotype, †P < 0.05 vs. MI in TIMP-3−/− mice
EGFR Inhibition by Cetuximab Improves Survival post-MI in TIMP-3⁻/⁻ mice
Role of TIMP-3 and EGFR in Infarct Healing post-MI

TIMP-3

MMPs

EGF/EGFR

Cetuximab

Synthesis

Degradation

Collagen

Infarct Healing
Conclusions

• Deficiency in TIMP-3 results in a significantly higher incidence of cardiac rupture and mortality post-MI.

• EGF inhibits collagen synthesis.

• Inhibition of EGFR signaling by cetuximab decreases the incidence of cardiac rupture and improves survival post-MI in TIMP-3-/- mice.
EGF/EGFR Signaling Inhibits Collagen Synthesis

Cardiac myofibroblast

TIMP-3 → MMPs → EGF → EGFR → SP-1 → JNK → TGFβ Expression

Collagen synthesis