TRAF5 deficiency accelerates atherogenesis in mice by increasing inflammatory cell recruitment and foam cell formation
TRAFs are intracellular adaptor proteins and part of the TNF/IL-1/toll-like-superfamily

- Apoptosis
- Inflammation
- Proliferation
- Migration
TRAF5: a proinflammatory molecule?

TRAF5 is overexpressed in human and mouse atheromata.

Zirlik et al., ATVB 2007
TRAF5 deficiency accelerates atherogenesis in mice

AORTIC ROOTS

AORTIC ARCHES

![Images of aortic roots and aortic arches with and without TRAF5 deficiency]

![Graphs showing intimal lesion area (mm²) with and without TRAF5 deficiency]

- TRAF5^{+/+}/LDLR^{-/-} vs. TRAF5^{-/-}/LDLR^{-/-}: p=0.02
- TRAF5^{+-}/LDLR^{-/-} vs. TRAF5^{-/-}/LDLR^{-/-}: p=0.01
TRAF5 deficiency enhances macrophage content in atherosclerotic plaques

Mac-3-positive staining / total wall area (%)

- TRAF5⁺⁺ / LDLR⁺⁺ (AORTIC ARCHES)  
  - p = 0.005

- TRAF5⁻⁻ / LDLR⁻⁻ (AORTIC ARCHES)  
  - p = 0.3

- TRAF5⁺⁺ / LDLR⁻⁻ (AORTIC ROOTS)

- TRAF5⁻⁻ / LDLR⁻⁻ (AORTIC ROOTS)

Oil-red-O-positive staining / total wall area (%)

- TRAF5⁺⁺ / LDLR⁺⁺ (AORTIC ARCHES)  
  - p = 0.4

- TRAF5⁻⁻ / LDLR⁻⁻ (AORTIC ARCHES)  
  - p = 0.07
How do monocytes accumulate in plaques?

- Extravasation
- Rolling
- Adhesion
- Migration

- Apoptosis
- Differentiation
- Foam cell formation
Enhanced rolling and adhesion of inflammatory cells TRAF5-deficient mice

TRAF5+/+ /LDLR-/-

TRAF5-/- /LDLR-/-
TRAF5-deficient leukocytes adhere more to the vessel wall
TRAF5 deficiency increases expression of adhesion molecules
TRAF5-deficient mice show enhanced leukocyte infiltration of the peritoneal cavity.
TRAF5 deficiency enhances expression of the chemokines KC and MCP-1.
TRAF5 deficiency promotes lipid uptake in bone marrow-derived macrophages
TRAF5 deficiency mediates atherosclerosis independently of TRAF2
Clinical study design

325 patients undergoing coronary angiography

- No CHD
- CHD
- ACS

Whole Blood RNA

TRAF5 mRNA expression
TRAF5 expression is reduced in blood of patients with CHD and ACS
Conclusion

- TRAF5 deficiency increases plaque size \textit{in vivo}, most likely by enhanced monocyte recruitment to the vessel wall.

- TRAF5 might be a protective factor in atherosclerosis and other chronic inflammatory diseases.
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# Study Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TRAF5&lt;sup&gt;+/+&lt;/sup&gt; LDLR&lt;sup&gt;-/-&lt;/sup&gt; n=19</th>
<th>TRAF5&lt;sup&gt;-/-&lt;/sup&gt; LDLR&lt;sup&gt;-/-&lt;/sup&gt; n=23</th>
<th>p-value</th>
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<tr>
<td><strong>Cholesterol (mg/dl)</strong></td>
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<tr>
<td>BD</td>
<td>209±12</td>
<td>200±12</td>
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<td>607±63</td>
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<td><strong>Triglycerides (mg/dl)</strong></td>
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<td><strong>Body weight (g)</strong></td>
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TRAF5 deficiency enhances adhesion under flow conditions in TRAF5 deficient mice.