Atherosclerosis Progression and Regression: Biological Mechanisms and Molecular Imaging Targets

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Disclosures

• Speakers Bureau: Merck
• Advisory Boards: Merck, Takeda
• I like fine wine
From Good to Bad to Worst

Progression

From Bad to Better?
A Mouse Model to Achieve the Rapid Normalization of the Plasma Lipid Profile

Chow: TC 500; HDL 30
WD: TC 1500; HDL 30
(mg/dL)

APO E -/-

WT

TC 100
HDL 65
e.g., J. Vasc. Surgery, Circulation, ATVB, PNAS
Absence of CD68+ cells 4 weeks after placing lesions into a “regression” environment

Trogan et al, ATVB, 2004
Monocyte-derived Cells Rapidly Leave Plaques Under Regressive, But Not Progressive Conditions

Llodra et al., PNAS 2004
CCR7 mRNA is induced in plaque CD68+ cells only under regression conditions.

Trogan, Feig, et al., PNAS 2006
Blocking the CCR7 Pathway Prevents Regression

Pre-transplant

control antibody

CCL19/21 antibody

Trogan, Feig, et al., PNAS 2006
Favorable Lipoprotein Changes in the Regression Model

<table>
<thead>
<tr>
<th></th>
<th>Donor (apoE-/-)</th>
<th>Recipient (wild type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol:</td>
<td>1000 mg/dL</td>
<td>100 mg/dL</td>
</tr>
<tr>
<td>HDL-C:</td>
<td>25 mg/dL</td>
<td>75 mg/dL</td>
</tr>
</tbody>
</table>

*Feig et al., in progress*
ApoE-/-
HDL 25

hAI/EKO
HDL 75

Rong et al, Circ 2001
HDL modulates CCR7 levels in Plaque CD68+ cells

J. Feig, PhD thesis
human CCR7

mouse CCR7

SRE activity

HDL

cell cholesterol content
Overly Simplified View of Macrophages in Tissues

**M1**
- Tumor resistance
- Killing of intracellular parasites
- Tissue destruction

IL-12\textsuperscript{high}, IL-23\textsuperscript{high}, IL-10\textsuperscript{low}; ROI; RNI; TNF\textsuperscript{high}, IL-1\textsuperscript{high}; M1 chemokines (e.g. CXCL10).

**M2s**
- Angiogenesis
- Immunoregulation
- Parasite encapsulation
- Tissue remodeling
- Tumor promotion

IL-12\textsuperscript{low}, IL-23\textsuperscript{low}, IL-10\textsuperscript{high}, arginase-1; TNF\textsuperscript{low}; IL-1ra\textsuperscript{high}, decoy IL-1 R1\textsuperscript{high}; scavenger, mannose, galactose receptor\textsuperscript{high}; M2 chemokines (e.g. CCL22).
HDL enriches M2 markers in plaque CD68+ cells

**The Macrophage Cholesterol Exporter ABCA1 Functions as an Anti-inflammatory Receptor**

Received for publication, July 21, 2009, and in revised form, September 7, 2009. Published, JBC Papers in Press, September 25, 2009, DOI 10.1074/jbc.M109.047472

Chongren Tang, Yuhua Liu, Peter S. Kessler, Ashley M. Vaughan, and John F. Oram

From the Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington, Seattle, Washington 98195

*J. Feig, PhD thesis*
Normalization of HDL Promotes the Formation of the Fibrous Cap

Rong, J. X. et al. Circulation 2001;104:2447-2452

α-actin staining
Absence of CD68+ cells and the formation of a fibrous cap 4 weeks after placing lesions into a “regression” environment

Trogan et al, ATVB, 2004
VSMC                                      Macrophage

Rong et al, PNAS 2003; Vengrenyuk, Miano, Fisher

cholesterol loading

cholesterol unloading
The Beginning of Mouse Plaque Imaging By MRI

Fayad et al., Circulation 1998
A

B

Progression

Regression

9 weeks

Trogan et al., ATVB 2004
Effect of nicotinic acid on clinical atherosclerosis

Figure 2: Effects of NA Treatment on Change in Mean Wall Area of the Carotid Arteries Quantified by MRI

Lee et al. J Am Coll Cardiol, 2009.54:1787-1794
Pre-contrast

1 hr post-contrast

24 hr post-contrast

apoE-KO mice

4.36 μmol/kg

9.4T MRM

rHDL-Gd-DTPA-DMPE

A. Barazza, D. Cormode, Z. Fayad, E. Fisher, submitted
A. Early events

- Cell adhesion molecules e.g. VCAM-1, ICAM-1, CD40
- Selectins, cadherins, e.g. P-selectin
- Lipoproteins e.g. HDL, ox-LDL
- Endothelial cell

B. Fatty streaks

- Macrophage foam cells
- Glycolytic activity
- Chemokines & cytokines
- Macrophage receptors e.g. MSR-A

C. Advanced lesions

- Platelets
- $\alpha_{\text{IIB}}\beta_3$ integrin
- Fibrin
- Plaque hemorrhage
- Proteolysis e.g. Cathepsins, MMPs

D. Complicated plaque

- New vessels
- $\alpha_v\beta_3$ integrin
- Calcification
- Fibrous cap
- Lipid-rich necrotic core

Choudhury RP and Fisher EA. ATVB, 2009
Regression model - Reversa mouse

Prevention
Inactivation of Mttp

apoB is degraded

Lieu et al., Circulation 2003

Feig, Mick, Rong, et al., submitted

Feig, Mick, Rong, et al., submitted
CD68+ Content                         Plaque Size

*S. Parathath et al, submitted*
Collagen Content

S. Parathath et al, submitted
EP-3533: collagen targeting peptide, which binds to collagen I/III/IV/V

HDL-EP3533: discoidal HDL nanoparticles conjugated with EP-3533 peptides via a DMPC-PEG spacer embedded into the lipid layer of particles

HDL-EP3533 nanoparticles target the collagens in the extracellular matrix, which enhances the MR signal for collagen-rich plaques

W. Chen, E. Fisher, Z. Fayad
Imaging at day=0 of lipid lowering

W. Chen, E. Fisher, Z. Fayad
28 days later……

W. Chen, E. Fisher, Z. Fayad
Emerging targets for atherosclerosis drugs may alter plaque biology without affecting plaque size
Microarray Studies

Baseline adjusted for resolver error p<0.05
Final signatures
Combined replicates

12530_N8 final filter(ANOVA P>0.1 & P<0.05 & error P<0.05) 1379seq

Thanks!
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Gwen Randolph (MSSM)
Jianhua Liu
Kevin Jon Williams (Temple)
Stephen Young (UCLA)

Zahi Fayad (MSSM): J.C. Frias, David Cormode, Wei Chen
Summary

• Regression of plaques can be achieved by altering the plasma lipoprotein profile, including the selective normalization of HDL
• The CD68+ cells in plaques acquire enhanced migratory ability and become enriched in markers of tissue remodeling macrophages
• Imaging of dynamic changes in plaques can be accomplished by MRI with improved capabilities by adapting HDL

• The plaque changes now detectable non-invasively include compositional and molecular alterations that would otherwise have been missed by currently available clinical modalities