Inflammation: Novel Target for Cardiovascular Risk Reduction

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Why inflammation?

- **Population-based studies:** low grade inflammation predicts CV events:
  - $1^0$ prevention ("healthy"): leukocyte count, hsCRP, IL-18, Lp-PLA$_2$...
  - $2^0$ prevention (e.g., ACS): hsCRP, IL-6, CD40L...

- **Pathology:** Inflammatory cells accompany all stages of atherosclerosis in humans:
  - macrophages, T cells
  - neutrophils (late stage)

- **Therapies:** emerging link between pharmacologic reduction of inflammatory burden and CV events:
  - soluble biomarkers: e.g., hsCRP, CD40 ligand
  - cell-associated: e.g., chemokines, chemokine receptors
CRP adds prognostic information

• Is there a need for additional treatments in patients at risk of CV events?

• What are potential therapeutic targets that are directed at inflammatory processes?
CV Events: unmet medical needs

- **Maximizing therapy:** in ACS patients (PROVE-IT):
  - revascularization (~70%)
  - antiplatelet Rx (~100%)
  - early statin therapy (100%)

- **Aggressive atorvastatin Rx to new goals:**
  - on treatment LDL=62 mg/dL

- **Events continue to accrue:**
  - Death and CV events at 2 years: 22%
PROVE-IT: Among patients with ACS, rapid reduction in CRP to <2mg/L is associated with fewer events at all levels of LDL cholesterol achieved.

A-to-Z trial: LDL lowering without CRP reduction has not conferred early clinical benefit.

• Is there a need for additional treatments in patients at risk of CV events?

• What are potential new therapeutic targets that are directed at inflammatory processes?
Inflammation: target for CV risk reduction

- Reverse cholesterol transport
- Oxidized LDL

- Insulin resistance
- Local & systemic inflammation
In patients with AMI, coronary levels IL-6, SAA are increased at the site of plaque rupture.

Maier et al. Circ 2005;111:1355
Targeting macrophage foam cell

- Cholesterol accumulation
- Inflammation

Li and Glass. *Nat Med* 2002;8:1235
Reverse cholesterol transport

- **Removal of cholesterol**
  - activation of ABCA1 transporter (PPARs, LXR)
  - apoA-I acceptor (apoA-I<sub>M</sub>/PL, apoA-I mimetics)
  - CE transfer to the liver (CETP inhibitor)

- **HDL effects**
  - inhibit adhesive molecules on EC (E-selectin, VCAM, ICAM-1)
  - protect LDL from oxidation
  - neutralize effects of CRP

“Anti-inflammatory” effects of HDL

HDL protects LDL from oxidation: “the size matters”

ApoA-I/PL prevents adhesion of monocytes to EC: “composition matters”

Kontush. ATVB 2003;23:1881; Wadham Circ 2004;109;2116
ApoA-I: reverse cholesterol transport

- **Lipid poor ApoA-I**: effective acceptor of free cholesterol

- **Medical genetics**: ApoA-I\textsubscript{M} (Cys173Arg) variant → protection against CHD

- **Experimental biology**:  
  - apoA-I\textsubscript{M}/PL reduces  
    - arterial cholesterol and  
    - macrophage content (48 hrs)

- **Clinical experience**:  
  - restoration of endothelial function (4 hrs)  
  - apoA-I\textsubscript{M}/PL suggestion of plaque regression by IVUS (5 weeks)

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Rye and Barter ATVB 2004;24:421; Spieker Circ 2002;105:1399; Shah Circ 2001;103:3047; Nissen JAMA 2003;290:2292
Lipoprotein-associated PLA$_2$

- produced by leukocytes
- associated with circulating LDL (~80%)
- hydrolysis of oxidized LDL to proinflammatory mediators
- promotes monocyte chemotaxis and death

### Lp-PLA₂: CV events

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
<th>Difference in mean Lp-PLA₂ levels</th>
<th>Multivariate-adjusted risk*</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>CV death, MI, revasc.</td>
<td>Yes</td>
<td>Yes</td>
<td>0.005</td>
</tr>
<tr>
<td>WHS</td>
<td>CV death, MI, stroke</td>
<td>Yes</td>
<td>No</td>
<td>NS</td>
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<tr>
<td>MONICA</td>
<td>CV death, MI, sudden death</td>
<td>Yes</td>
<td>Yes</td>
<td>0.04</td>
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<tr>
<td>ARIC</td>
<td>CV death, MI, revasc.</td>
<td>Yes</td>
<td>LDL &lt;130 mg/dL</td>
<td>0.05</td>
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<tr>
<td>ARIC</td>
<td>Stroke</td>
<td>Yes</td>
<td>Yes</td>
<td>0.015</td>
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<tr>
<td>Rotterdam</td>
<td>CV death, MI, revasc., VFib, CHF</td>
<td>Yes</td>
<td>Yes</td>
<td>0.02</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>Stroke</td>
<td>Yes</td>
<td>Yes</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Covariates: age, gender/race (where appropriate), DM, smoking, BMI, systolic BP, LDL, HDL, TG and/or total cholesterol. Several studies further adjusted for WBC and/or CRP and/or fibrinogen.
**Localization:** elevated expression in human plaques (macrophage/T cells);

**Association:** Lp-PLA₂ expression correlates with genes that confer increased CV risk (MMP-9, 5-LO);

**Clinical trials:** selective inhibitors reduce Lp-PLA₂ activity in human plasma/plaque
Inflammation: target for CV risk reduction

- Reverse cholesterol transport
- Oxidized LDL

- Insulin resistance
- Local & systemic inflammation
Adipose tissue signaling

Endothelial activation

Perivascular inflammation: “outside-to-inside” signaling (?)

Wellen and Hotamisligil JCI 2003;112:1785
Epicardial fat inflammation in CAD

IL-6

MCP-1

mRNA

protein

Epicardial Subcut

Epicardial Subcut

Epicardial Subcut

Epicardial Subcut

Mazurek et al Circ 2003;108:2460
PPAR-γ agonists: “from the belly to the heart”

- **Downregulate inflammation:**
  - adipose tissue (TNFα, FFA)
  - monocytes (cytokines, iNOS)
  - vessel wall (TNFα, MMPs, adhesion molecules)

- **Restore insulin sensitivity:**
  - >50% of CHD patients have metabolic syndrome;
  - >60% of post-MI patients have abnormal glucose metabolism;
  - relationship between glucose metabolism and severity of CAD

PPARγ activation: “from the fat to the heart”

- **Plasma biomarkers:**
  - ↓ inflammatory biomarkers
    - T2DM: CRP, CD40L, MMP-9;
    - non-T2DM: CRP, vWF, E-selectin

- **Atherosclerosis progression:**
  - carotid IMT: CHICAGO (pioglitazone)
  - coronary IVUS: APPROACH (rosiglitazone), PERISCOPE (pioglitazone);

- **CV outcomes:**
  - PROactive=5,000,
  - RECORD; n=4200,
  - BARI-2D: n=2800, f/u 5-6 yrs.

Haffner Circ 2002;106:679; Sidhu JACC 2003;42:1757; Raji Diab Care 2003;26:172; Sidhu ATVB 2004;24:930
Quo vadis: inflammation and beyond….

- **Human tissue studies**
  - mechanisms of disease
  - novel targets → more effective Rx (?)

- **Clinical index of risk** (intermediate endpoints)
  - plaque imaging: structural vs compositional
  - plasma biomarkers & global approach…omics

- **Outcome studies**: closing therapeutic gap in “post HPS/PROVE-IT era”:
  - high risk populations: post ACS, metabolic syndrome/diabetes, renal impairment…. 