Novel non-lipid anti-atherosclerotic Therapies

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Disclosures

- Department of Cardiac Sciences and Libin Cardiovascular Institute – U of Calgary

- Grant support by Alberta Innovates – HS
  – Merck, Amgen
Objectives

• Understand new insights into pathophysiology of atherosclerosis and plaque instability
• Review approaches to target identification
  – Genetics
  – Molecular Imaging
  – miRNA
• Targets
  – Anti-inflammatory therapies
  – Others
Nitric oxide signaling

Murad NEJM 2006;355:2003
Secondary messenger cell signaling

Calo et al. J Hypert 2007;25:259
Pathophysiology

Libby et al.
Nature 2011;473:317
Objectives

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• **Review approaches to target identification**
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• **Targets**
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Potential CV Biomarkers

**Imaging**
- Angiography
- IVUS
- Virtual Histology
- Palpography
- Coronary CT angio
- Carotid US – IMT, plaque
- MRI
- PET
- Aortic CT
- Scintigraphy (thallium, sestimibe)
- Intracoronary Ach
- Brachial ultrasound – FMD
- Brachial hyperemic velocity
- Plethysmography
- TEE (aortic)
- Monoclonal antibody imaging
- Pulsatile flow visualization (aorta)
- Regional aortic distensibility
- Aortic stiffness (Doppler)
- Coronary thermography
- Coronary elastography
- Coronary NIR spectroscopy

**Immunology**
- Anti-oxLDL IgG

**Genetics**
- ACE polymorphism
- PCSK9
- 9p21
- rs 20455 in K1F6

**Lipids**
- lipoproteins
- lipoprotein subfractions (L1-3, V1-6, H1-5)
- Apolipoproteins (CIII, All:E, LpB…)
- Lp(a)
- Lipid ratios

**Immunoglobulins**
- IgG, IgM, IgA

**Inflammation and Proliferation**
- CRP
- Lp-PLA2
- MCSF
- PDGF
- FDF
- FGF
- Interleukins (1,6,8,10,12,15)
- MMPs (1,2,3,9)
- Heat shock proteins - 27
- TNF alpha
- Proliferating cell nuclear antigen
- Hyaluronan receptors
- SR-A, SR-B1
- TGF
- SM myacin heavy chains
- CD 11, 18, 36, 40, 68
- MCP-1
- CCR2
- Pentraxin-3
- C4b binding protein
- I kappa B-alpha
- Total sialic acid
- Osteopontin

**Coagulation**
- VWF
- tPA
- PAI-1
- PF4
- D-dimer
- Tissue factor
- Fibrinogen
- Beta thromboglobulin
- Erythrocyte sed. Rate
- RBC adhesiveness/aggregation

**Adapted from T Heinonen**
Genetic basis of atherosclerosis

• Genome
  – 9p21 - ? Cyclin dependent kinase inhibitors
  – PCSK9 – genotype and protein levels
  – GWAS – CXCL12 (chemoattractant cytokine)
  – Cancer genes such as BRCA1

• Transcriptome
  – Myeloid related protein (MRP 14) found in platelets

• Proteome
  – CRP, PLA2, MPO
  – ? Of the hundreds with association with athero

• Metabolome
Genetic basis of atherosclerosis

- 100 genes have been shown to affect atherosclerosis in mice models
- About 1/3 work through lipids, 2/3 of KO decrease atherosclerosis
- Tend to use LDLr or apoE KO mice
- Human studies use GWAS or candidate gene approach
- Linkage studies and mendelian randomization
microRNA and atherosclerosis

• Highly conserved non-coding RNA
• Development and disease
• Post-transcriptional modulators of gene regulation
• Dysregulation results in cellular abnormalities including calcification, hypertrophy, remodeling etc.
• Inhibitors are being developed
microRNA and atherosclerosis

Small et al. Nature 2011;469:336
Molecular imaging of atherosclerosis

# Molecular imaging of atherosclerosis

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<td>...</td>
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<td>$\alpha\nu\beta3$ integrin</td>
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<td>PET, MRI, optical imaging, CEU</td>
<td>Neoangiogenesis</td>
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<td>Glycoprotein IIb/IIIa</td>
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<td>Fibrin</td>
<td>$^{64}$Cu, Gd</td>
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<td>Factor XIII</td>
<td>Gd, SPIO, NIRF</td>
<td>MRI, optical imaging</td>
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Atherosclerosis

Anti-inflammatory targets
Anti-inflammatory targets – inflammasome

Nod like receptor
Anti-inflammatory targets – IL1B

- Mouse studies have demonstrated the role of the inflammasome in atherosclerosis development
- Human biomarker studies have shown association
- Genetic validation not firmly established
- Clinical studies have demonstrated benefit in other inflammatory diseases
- Ongoing randomized trials in human atherosclerosis
Anti-inflammatory targets

• Cardiovascular Inflammation Reduction Trial
  – Stable post-MI patients
  – High dose statins
  – Randomized to Mtx (10-15 mg/week) or placebo

• Canakinumab Anti-inflammatory Thrombosis Outcomes Trial
  – IL1-beta inhibition in stable CAD patients
  – Cholesterol crystals stimulate the NLRP3 inflammasome that stimulates IL1-beta
Lp-PLA2 and atherosclerosis

**Stable Plaque**
- Low Lp-PLA2 content (reddish-brown staining)
- May have significant stenosis
- Thick fibrous cap / high collagen content
- Small lipid pool
- Few inflammatory cells

**Ruptured Plaque**
- High Lp-PLA2 content (reddish-brown staining)
- May have minimal stenosis
- Thin fibrous cap / low collagen content
- Large lipid pool
- Many inflammatory cells

Corson et al AJC 2008;101:41F
Inflammation - Leukotrienes

Inflammation - Resveratrol

Li et al. Nitric Oxide 2012;26:102
Anti-inflammatory targets

- Translating the extension data set from mice has proven difficult
- NSAIDs – increase risk
- Statins – have anti-inflammatory properties
- Inflammasome – IL1B antagonists or IL1ra agonists
- Lp PLA\textsubscript{2} antagonists – Darapladib – STABILITY and SOLID TIMI 52
- Methotrexate CIRT study
- Lipoxygenase pathway inhibitors
- Resveratrol
Anti-atherosclerotic targets

• Vitamin D
• Incretin based diabetes therapy
• Lipid targets
• S100A1
• Heat shock proteins – HSP 27
• Thyroidmimetics
Summary

- Can think of risk at the plaque, artery or patient level
- Current therapy aimed at lipid targets and have been successful but still 60% of the risk remains
- Novel therapies offer opportunity over the next decade but the bar is very high to show benefit
- Personalized medicine approach remains a desired goal for the future