Basic Mechanisms of Atherosclerosis and Plaque Rupture: Clinical Implications

Ira Tabas, M.D., Ph.D.
Richard J. Stock Professor of Medicine, Cell Biology, and Physiology
iat1@columbia.edu

No Conflicts of Interest to Disclose
Progression of Atherothrombotic Vascular Events

Years: common; asymptomatic

Rare; acute vascular events

Mechanisms of atherogenesis

Overview

Clinical implications

Advanced plaque progression

The maladaptive inflammatory response: defective inflammation resolution

Summary and conclusions
The Macrophage Foam Cell

Defective inflammation resolution due to persistent LP retention
Basic Mechanisms of Atherosclerosis and Plaque Rupture

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Clinical Predictions

- Lowering apoB-LPs should decrease heart disease
- The fallacy of terms like “low” or “healthy” levels of plasma LDL
- Lower is better
- Earlier is better
Atherogenesis

“High” levels of apoB-lipoproteins in the bloodstream

+ A “susceptible” arterial wall (i.e., susceptible to apoB-LP retention or responses to retention)

Therapeutic Approach to Prevent and Reverse Atherosclerosis

“High” levels of ApoB-lipoproteins in the bloodstream

↓↓ ↓↓ Probability of ApoB-LP entry and then retention in the subendothelium

Lowering Plasma LDL Decreases Coronary Artery Disease

Clinical Predictions

- Lowering apoB-LPs should decrease heart disease
- The fallacy of terms like “low” or “healthy” levels of plasma LDL
- Lower is better
- Earlier is better
Lower is Better and "Safe"

- Hunter-gatherer societies (and other mammals)
- Cord blood
- Familial hypobetalipoproteinemia
- "Zero-risk" extrapolation of LDL-lowering trials
- LDL-lowering trial subgroups (PROVE-IT, JUPITER)
- LDL receptor is 50% saturated at 10 mg/dl

Clinical Predictions

- Lowering apoB-LPs should decrease heart disease
- The fallacy of terms like "low" or "healthy" levels of plasma LDL
- Lower is better
- Earlier is better
Earlier is Better

- Genetic syndromes that lower LDL at birth (PCSK9)
- Clinical studies where intervention is early vs. late

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Acute Atherothrombosis
The Trigger for Acute Coronary Syndromes
The Plaque Rupture Theory of Acute Atherothrombosis

Mild-to-Moderate Lesions that Rupture are the Most Common Cause of Cardiac Events

Plaque Morphology is More Important than Plaque Size

Plaque Rupture

Ruptured plaque at area of thinned fibrous cap

Necrotic Core

Thrombus
The Problem

"Benign" atherosclerotic lesion

Ruptured "vulnerable" plaque

Heart attack
Sudden cardiac death
Unstable angina

2-3% sudden cardiac death
Heart attack
Stroke
Unstable angina

The Necrotic Core
An Essential Feature of Vulnerable Plaques

Necrotic Core
Inflammation
Coagulation
Thrombosis
Proteases
Stress on fibrous cap

How Does the Necrotic Core Form?

Necrotic Core
"graveyard of dead M"
What is the link between Mφ death and necrotic core formation?

Necrotic Core
"graveyard of dead Mφs"

Mφ Death in Atherosclerosis

Tabas ATVB Nov 2005

Mφ Death in Atherosclerosis

Tabas ATVB Nov 2005
Other Processes in Plaque Instability

Defective Efferocytosis

Efferocytosis

- Safe disposal of apoptotic cells
- Anti-inflammatory signaling, including TGFβ
Pathologically defective efferocytosis in advanced atheromata

Thorp & Tabas 2009 / J Leuk Biol

post-apoptotic necrosis

induces inflammation

apo-Mφ

effecocytic Mφ
Presence of apoptotic cells (TUNEL) + tissue necrosis (collection of post-apoptotic cells) = defective efferocytosis

Pathologically defective efferocytosis in advanced atheromata

Arterioscler Thromb Vasc Biol. 2005;25:1256-1261
Phagocytosis of Apoptotic Cells by Macrophages Is Impaired in Atherosclerosis
Dorien M. Schrijvers, Guido R.Y. De Meyer, Mark M. Kockx, Arnold G. Herman, Wim Martinet

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WHAT IS THE MECHANISM?
Basic Mechanisms of Atherosclerosis and Plaque Rupture

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Hallmarks of Defective Inflammation Resolution in Atherosclerosis

Therapeutic Opportunities in Atherosclerosis?
Therapeutic Opportunities in Atherosclerosis?

Persistent monocyte influx → Defective Mφ egress → Necrosis → Additional DAMPS → Thinning of fibrous cap

Persistent apoB lipoproteins (apoB LPs) → Persistent inflammation → Oxidative stress

Therapeutic Opportunities in Atherosclerosis?

Dampen inflammation and restore homeostasis

- Boost natural regulatory mechanisms (e.g., Tregs)
- Lower apoB lipoproteins or block retention
- Monocyte influx ↓
- Efferocytosis ↑
- Fibrous cap ↓
- Oxidative stress ↓
Examples of Treg-mediated strategies that reduce atherosclerosis in mice

- "Vaccination" with HSP60/65, oxLDL, apoB, β2-GP
- Inject tolerogenic DCs: pre-treat with IL-10 or rapamycin, then pulse with above antigens
Nature’s Solution to the Challenge of Host Defense

DAMP Tissue damage → Resolution of inflammation

Specialized proresolving mediators (SPMs)

Can RvD1 improve atherosclerosis?

Resolvin D1 (RvD1)
→ ALX receptor
→ RESOLUTION OF INFLAMMATION

RvD1 Treatment of Fat-Fed \textit{Ldlr}^{\text{−/−}} Mice Lowers the Extent of Advanced Atherosclerosis

Fredman, unpublished data
Can another type of ALX agonist improve atherosclerosis?

Annexin A1 (Ac2-26) → Resolvin D1 (RvD1) → ALX receptor → RESOLUTION OF INFLAMMATION

Nanoparticle-mediated drug delivery to areas of arterial "injury"

Ac2-26 Col IV NP

Karmaly, Fredman, et al., PNAS 2013

Ac2-26 NP Treatment of Fat-Fed Ldlr−/− Mice Suppresses Advanced Plaque Development

scrambled peptide NPs

Ac2-26 NPs
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Atherosclerosis

Defective Inflammation Resolution

- Oxidative stress
- Persistent inflammation
- Inhibition of fibrous cap
- Persistent DAMPS (danger signals)
- Defective efferocytosis
- Defective inflammation resolution
- Reduced plaque necrosis
Therapeutic Opportunities

Persistent monocyte influx → defective Mφ egress → necrosis → additional DAMPS → thinning of fibrous cap

Therapeutic Opportunities
- lower apoB lipoproteins or block retention
- boost natural regulatory mechanisms (vaccines) or administer mediators of inflammation resolution

WHY?

Aging and aging-related diseases evolve because natural selection favors genes that confer benefits early in life, even though those genes may prove detrimental to an organism later in life.

Antagonistic Pleiotropy
G. C. Williams, Evolution, 1957
Atherosclerosis as Example of Antagonistic Pleiotropy

persistent stimulus (apoB LPs) non-resolving

inflammation

calcification

thrombosis

fights infection and promotes resolution

heals broken bones

prevents bleeding

transient stimulus resolving

broken bones

heals

prevents bleeding
Atherosclerosis as Example of Antagonistic Pleiotropy

Getting Caught in the Therapeutic Window

A Possible Opening of the Therapeutic Window