Atherosclerosis is an Inflammatory Disease: Does it Matter?

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No Conflicts of Interest to Disclose
Inflammation
The Key Biological Response to Lipoprotein Retention

Plaque necrosis
Amplified LP retention

Tabas et al., Circulation, 2007

Twenty and Beyond

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Twenty and Beyond
Defective Inflammation Resolution
The Response That Promotes Plaque Progression

Plaque necrosis
Mature DC
Amplified LP retention
Tissue damage (DAMPs)
Persistent LP retention

Resolving Inflammation

Anti-Inflammatory Therapy in Chronic Disease: Challenges and Opportunities

Review
Resolving Inflammation

DAMP Tissue damage

Resolution and repair

Pathogens cleared by Resolution and repair

Tissue damage

Normal tissue

Inflammation Resolution

AC100 Inflammatory response

Inflammation

Resolving Tissue

Necroptosis

Leukocyte recruitment

Necrosis

Tissue death
Resolving Inflammation

Non-resolving Inflammation

Non-resolving Inflammation
Non-resolving Inflammation

Atherosclerosis
Hallmarks of Defective Inflammation Resolution in Atherosclerosis

- Persistent DAMPS (apoB LPs)
- Persistent monocyte influx
- Defective Mφ egress

(adapted from Tabas Nature Rev. Immunol 2010)
Persistent DAMPS (apoB LPs) and persistent monocyte influx are hallmarks of defective inflammation resolution in atherosclerosis. This process is associated with the thinning of the fibrous cap. The diagram is adapted from Tabas, Nature Rev. Immunol. 2010.
Hallmarks of Defective Inflammation Resolution in Atherosclerosis

persistent monocyte influx

defective Mφ egress

defective efferocytosis → necrosis

thin fibrous cap

Therapeutic Opportunities in Atherosclerosis?

persistent DAMPS (apoB LPs)

defective inflammation

oxidative stress

persistent inflammation

oxidative stress

adapted from Tabas Nature Rev. Immunol. 2010
Therapeutic Opportunities in Atherosclerosis?

Persistent monocyte influx → Defective macrophage (Mφ) egress → Defective efferocytosis → Necrosis → Additional DAMPS → Thinning of fibrous cap

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

50 210 70 190 170 150 130 110 90

% with CAD event

LDL-C (mg/dL)

HPS

WOSCOPS

AFCAPS

CARE

4S

LIPID

HPS

50 210 70 190 170 150 130 110 90

% with CAD event

LDL-C (mg/dL)

HPS

WOSCOPS

AFCAPS

CARE

4S

LIPID

HPS

A TVB 2012

Induction of Anti-Anti-Id type Antibodies Against Sulfated Glycosaminoglycans Reduces Atherosclerosis in Apolipoprotein E-Deficient Mice

Vitor Brito, Karla Nóbilo, Simon Gross Portugal, Adelina Pinto, Yeundol Sim, Dania da Silva, Valéria Marques, Ana Maria Vignato
Therapeutic Opportunities in Atherosclerosis?

- Persistent monocyte influx
- Defective macrophage egress
- Defective efferocytosis → necrosis → additional DAMPS
- Thinning of fibrous cap
- Persistent DAMPs (apoB LPs)
- Persistent inflammation
- Oxidative stress

DAMP Tissue damage

Specialized proresolving mediators (SPMs)

- Therapeutic Opportunities
  - Dampen inflammation and restore homeostasis
  - ↓ monocyte influx
  - ↑ efferocytosis
  - ↑ fibrous cap
  - ↓ oxidative stress

Nature's Solution

Barriers to Therapeutic Translation in Chronic Inflammatory Diseases

Host Defense and the Therapeutic Window
Specialized Proresolving Mediators (SPMs): The Push and Pull of Pro-Inflammatory and Pro-Resolving Mediators

Pro-inflammatory mediators

Leukotrienes
Cytokines
Chemokines
Fight infection

Endogenous SPMs

Annexin A1
IL-10
Lipoxins
Resolvins

Homeostasis

Leukotrienes
Cytokines
Chemokines
Fight infection

Temper pro-inflammatory signals but are not immunosuppressive
Enhance efferocytosis and tissue repair
The Push and Pull of Pro-Inflammatory and Pro-Resolving Mediators

- Endogenous SPMs: Temper pro-inflammatory signals but are not immunosuppressive. Enhance efferocytosis and tissue repair.
- Annexin A1, IL-10, Lipoxins, Resolvin: Homeostasis.
- Pro-inflammatory mediators: Leukotrienes, Cytokines, Chemokines, Fight infection.

Inflammatory Disease

- Leukotrienes Cytokines Chemokines

Therapeutic SPMs

- Rx with exogenous SPMs
- Enhance efferocytosis and tissue repair.

The Potential of SPM Therapy in Atherosclerosis

- Pre-TEENS: Monocyte influx, Efferocytosis, Fibrous cap, Oxidative stress.
- Therapeutic SPMs:
  - ↓ Monocyte influx
  - ↑ Efferocytosis
  - ↓ Oxidative stress

Thinning of fibrous cap

Permissive inflammatory

Inflammatory stress

Protective inflammatory

Protective efferocytosis

Protective oxidative stress

Inflammatory efferocytosis

Inflammatory oxidative stress
Atherosclerosis is an Inflammatory Disease: Does it Matter?

Yes—but only if viewed in the context of the balance between inflammation and its resolution and the narrow therapeutic window limited by compromising host defense.