INFLAMMATION AND Atherosclerosis

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What determines who will develop atherosclerosis?

LDL-CHOLESTEROL??

OTHER RISK FACTORS???
“ATHEROSCLEROSIS IS AN INFLAMMATORY DISEASE”

......................Dr Peter Libby
Dr. Paul Ridker  (Mr hs-CRP)
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

The Cantos Study

1. Canakinumab- human monoclonal antibody that has been used as an anti-inflammatory medication in certain types of arthritis

2. 10,000 pts who had an average hs-CRP 4.2 and LDL-C of 82 mg/dl were randomized.

3. Study was 48 mo.

4. Primary endpoint: non-fatal MI or stroke, CV death
The Cantos Study con’t

1. THE GOOD NEWS: 15% REDUCTION IN PRIMARY ENDPOINT
2. THE BAD NEWS: INCREASED RATE OF INFECTION AND SEPSIS
3. THE STRIKING NEWS: WITHOUT AFFECTING LDL-C, CANAKINUMAB PRODUCED THE SAME CV RISK REDUCTION AS THE PCSK-9 STUDIES OF FOURIER AND ODYSSEY
hsCRP Levels Risk Stratify for PEP Even When LDL-C<20mg/dL

N=2,707

Adjusted* 3 Year Rate of PEP

LDL-C at 1 month (mg/dL)

<20: 9.0%
20-49: 10.8%
50-69: 12.0%
70-99: 10.4%
≥100: 10.9%

hsCRP (mg/L)

<1: 14.9%
1-3: 14.9%
>3: 18.2%

*Adjusted for age, BMI, sex, race, region, prior MI, prior stroke, PAD, HTN, DM, CHF, smoking, eGFR<60, high-intensity statin, ezetimibe, baseline LDL-C, HDL-C and log(TG)
APPROACHING INFLAMMATION...

THE INFLAMMASOME
THE INFLAMMASOME- A PROTEIN COMPLEX THAT CAN SENSE DANGER

Cholesterol Crystals
Uric Acid
Silica
Asbestos

Crystals and Particles
Microbial Products
Hypoxia
Disturbed Flow
Dead Cells

Caspase-1
The Interleukin-1β converting enzyme, surrounded by the danger sensing domain of the NLRP3 Inflammasome

Pro IL-1β
33 kDa
17 kDa
Active, Mature IL-1β

Rader DJ. Am Society Clin Investigation
FIGURE 1 Selected Actions of IL-1 Related to Atherosclerosis

Interleukin-1 Beta

- WBC Adhesion Molecules
- Tissue Factor Procoagulant

Endothelial Cell

Smooth Muscle Cell

Monocyte/Macrophage

↑ Cytokine, Chemokine Production (e.g., IL-6)

↑ MMPs 2,9 (Erosion)

↑ Proliferation
↑ MMP-3 (Remodeling)
↑ MMPs 2,9 (Migration)

↑ MMPs 1, 8, 13 (Collagenases, Plaque Rupture)

Libby P. JACC Oct 2017
Risk Factors, Pro-Inflammatory Stimuli

IL-1β

Autoinduction
IL-1β

Interleukin-6, Mediator of Atherothrombosis

IL-6

C-Reactive Protein
Gauge of Overall Inflammatory State

hs-CRP

Fibrinogen

Plasminogen Activator Inhibitor

Thrombus Accumulation

Pro-clotting

Anti-Fibrinolytic

Libby P. JACC Oct 2017
**Central Illustration** Some Effects of IL-1 Blockade on Cellular Functions

**Interleukin-1 Blockade**

**Endothelial Cells**
Reduces leukocyte adhesion, procoagulant, inflammatory mediator and pyrogenic prostaglandin production.

**Smooth Muscle Cells:**
Reduces proliferation, inflammatory mediator production.

**Hepatocytes:**
Reduces acute phase reactants: fibrinogen, plasminogen activator inhibitor, CRP.

**Leukocytes:**
Reduces production of inflammatory mediators including cytokines, chemokines, lipids.

**Cancer and Stem Cells:**
Inhibits epithelial to mesenchymal transition implicated in oncogenesis, reduces procoagulant production.

**Tumor and Stromal Cells:**
Reduces production of basement membrane-degrading proteinases involved in cancer invasion and metastasis.

TARGETING INFLAMMATION

1- Methotrexate
2- Colchicine
3- Tumor Necrosis Factor Inhibitors (TNF)
4- Phospholipase A2 Superfamily (LP-PLA-2)
5- IL-1 and IL-6

From Bhatt DL Cardiovascular Consultants May 2018
1- Atherosclerosis is an inflammatory disease
2- Immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree
3- Blood borne inflammatory and immune cells constitute an important part of the atheroma
4- Many of the immune cells show signs of activation and produce inflammatory cytokines
THE IMMUNE SYSTEM AND CARDIOVASCULAR DISEASE

Adaptive Immunity
ADAPTIVE IMMUNITY

Occurs after a lag phase where T lymphocytes are exposed to various antigens:

T cells proliferate into:
- T helper cells (Th)- (proinflammatory)

T cells also proliferate into T regulatory cells (Treg)- (anti-inflammatory)
Acute Coronary Syndrome is an Inflammatory Response and Occurs when there is an **imbalance** in T cell immunity

- **Antigen s** (antigen presenting cells
- (microbes, autoantigens, inflammatory molecules)

1- **HELPER T CELLS REGULATE IMMUNITY**
2- **ANTIGEN PRESENTING CELLS ACTIVATE T CELL RECEPTORS**
3- **T CELLS DIFFERENTIATE INTO HELPER T CELLS**
4- **HELPER T CELLS SECRETE INFLAMMATORY SUBSTANCES THAT DESTABILZE CORONARY PLAQUES**

Flego D. JACC 2016:68
KILLER T CELLS:

- Helper T Cells

CD40 AND MMP (MATRIX METALLOPROTEINASE)

DISRUPT ENDOTHELIAL CELLS

Flego D. JACC 2016:68
Acute Coronary Syndrome is an Inflammatory Response

1- HELPER T CELLS REGULATE IMMUNITY
2- ANTIGEN PRESENTING CELLS ACTIVATE T CELL RECEPTORS
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Flego D. JACC 2016:68
REGULATORY T CELLS
(The Hero !)

- Regulatory T cells
  (Good!)

Flego D. JACC 2016:68
1- Capable of suppressing the Immune response by producing anti-inflammatory cytokines (IL-10) and inhibits T cell response
2- ACS occurs when Tregs are defective

Flego D. JACC 2016:68
Regulatory T cells

•

(Good!)

1- When Regulatory T cells cannot suppress the harmful immune response
2- there is HELPER T CELL DYSREGULATION
3- This produces an abnormal immune response which leads to
PLAQUE DESTABILIZATION

Flego D. JACC 2016:68
STABLE PHASE OF THE DISEASE

Low expression of CD31
High expression of PTPN22

Low activation of CREB

High T-cell receptor activation

Increased effector T-cells
(increased immune activation)

Reduced regulatory T-cells
(reduced regulatory immunity)

Central Illustration: Responses to Antigen Presentation Observed in Patients With ACS

High expression of CD31
High expression of PTPN22

High activation of CREB

Normal T-cell receptor activation

Effector T-cells

Regulatory T-cells

ACUTE CORONARY SYNDROME

STABLE PHASE OF THE DISEASE

ADHESION

MIGRATION

ENDOTHELIUM

REGULATORY T CELLS

T CELLS

INHIBITORY CYTOKINES

CYTOKINES

INFLAMMATION

SMOOTH MUSCLE CELLS

ANTIGENS, OXIDIZED LDL, HEAT SHOCK PROTEINS, MICROBES

ANTIGEN PRESENTING CELLS

Libby P. NEJM 2005
THE IMMUNE SYSTEM

Innate Immunity

Adaptive Immunity
THE IMMUNE SYSTEM

Innate Immunity
THE IMMUNE SYSTEM

• INNATE IMMUNITY:

• creates an immediate and general response

• Monocytes are recruited from the bone marrow or spleen by endothelial activation and differentiate into macrophages
THE
Macrophage

M1 Macrophage: express proinflammatory mediators

M2 Macrophages: secrete anti-inflammatory cytokines
**ATHEROSCLEROTIC PROGRESSION**

- **PROINFLAMMATORY**
  - DIRECT
  - INDIRECT
  - Chol crystals
  - Oxidized LDL
  - Inflammasome

- **DIRECT**
  - M1
  - M2

- **INDIRECT**
  - T cell activ.
  - plaque hypoxia

- **Inflammasome**

- **Progressing plaque**

**ATHEROSCLEROTIC REGRESSION**

- **ANTI-INFLAMMATORY**
  - DIRECT
  - INDIRECT
  - Reversal mechanisms – HDL

- **DIRECT**
  - M1

- **INDIRECT**
  - M2

- **IL-10**
- **COLLAGEN**

- **Regressing plaque**

From Peled et al.
Epicardial Fat and Inflammation and HEART FAILURE
Epicardial Fat and HFpEF

Epicardium is adjacent to myocardium and share the microcirculation

In obesity healthy brown epicardial fat (protective) is converted into harmful white adipose fat

White adipose fat by lipolysis releases fatty acids and inflammatory mediators (IL-1, IL-6, TNF)

Promotes macrophage infiltration destroying the microvascular system and activating profibrotic pathways
Epicardial Fat Accumulation and Inflammation Causes

<table>
<thead>
<tr>
<th>Inflammation and fibrosis of underlying tissue</th>
<th>Atrial dysfunction and arrhythmia</th>
<th>Heart failure with preserved ejection fraction</th>
<th>Accelerated atherosclerosis</th>
</tr>
</thead>
</table>
Chronic systemic inflammatory disorders

Hypercholesterolemia and oxidation of circulating lipoproteins

Epicardial fat accumulation and perivascular inflammation

Enhanced inflammation within vessel walls

Development and acceleration of coronary atherosclerotic disease

Pina, IL JACC May 2018
Potential Role of Epicardial Adipose Tissue in Heart Failure With a Preserved Ejection Fraction

Obesity and other chronic systemic inflammatory disorders

Drugs that may promote epicardial adipose tissue accumulation or inflammation:
- Insulin
- Dipeptidyl peptidase-4 inhibitors

Systemic secretion of proinflammatory cytokines

Drugs that may inhibit epicardial adipose tissue accumulation and inflammation:
- Statins
- Metformin
- Sodium-glucose cotransporter-2 inhibitors
- Mineralocorticoid receptor antagonists

Organ dysfunction and comorbidities

Migration and transformation of mesenchymal stem cells

Heart failure with a preserved ejection fraction

Accumulation and inflammation of epicardial adipose tissue

Local secretion of proinflammatory cytokines

Inflammation, microvascular rarefaction and fibrosis of underlying myocardium

The Effects of Pharmacologic Agents

Accumulation and Inflammation of Epicardial Fat

Cardiac Fibrosis and Impaired Distensibility

HEART FAILURE WITH PRESERVED EF

Pina, IL JACC May 2018
INFLAMMATION AND ATHEROSCLEROSIS AND WHAT WE EAT.....
WHAT IS THE GUT MICROBIOME?

The gut microbiome—the trillions of microbes that reside in the GI tract and influence health by helping digest food, making vitamins, and providing protection against disease-causing microorganisms.
Does our microbial ecosystem drive health and disease?
• When people ingest certain nutrients, such as choline (abundant in red meat, egg yolks, and dairy products) and L-carnitine (found in red meat as well as some energy drinks and supplements), the gut bacteria that break it down produce a compound called trimethylamine (TMA). The liver then converts TMA into the compound, trimethylamine N-oxide (TMAO).

Chronic Dietary Choices Impact TMAO Levels

De Filippis et al, Gut 2015
High levels of TMAO contribute to a heightened risk for clot-related events such as heart attack and stroke—even after researchers take into account the presence of conventional risk factors and markers of inflammation that might skew the results.

TMAO and the Vulnerable Patient

POSSIBLE DIETARY SOLUTIONS -
Lowering Your TMAO levels:

• 1- minimizing the consumption of full-fat dairy products, including whole milk, egg yolk, cream cheese, and butter
POSSIBLE DIETARY SOLUTIONS - Lowering Your TMAO levels:

2- Lower your consumption of both processed and unprocessed red meat (beef, pork, lamb, and veal), as well as nutritional supplements and energy drinks containing choline, phosphatidylcholine (lecithin), and/or L-carnitine. ((Vegetarians and vegans, who avoid meat products, for instance, produce little TMAO)).
POSSIBLE DIETARY SOLUTIONS -
Lowering Your TMAO levels:

3- consuming a diverse diet rich in plant foods and fiber

4- Consume a Mediterranean diet, and include red wine and extra virgin olive oil.
Dimethyl-1-butanol (DMB)

DMB inhibits microbial trimethylamine (TMA) formation in human feces, thereby reducing plasma TMAO levels after choline or carnitine supplementation.

It consequently inhibits choline enhanced endogenous macrophage foam cell formation and atherosclerotic lesion development.

Wang, Zeneng, Hazen et al. CELL 163(7) 1585-1595 2015
Sources of DMB
Olives/Cold-pressed extra virgin olive oil

Grape seed oil

Guinness Lager Stout
BEWARE! It’s what we eat that counts!
Coronary arteries in cross section
LIVE AS IF YOU WERE DIE TOMORROW.
LEARN AS IF YOU WERE TO LIVE FOREVER

......Gandhi