Atherosclerosis: Modeling the Effects of Functional and Dysfunctional High Density Lipoproteins

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Outline

Introduction

- Atherosclerosis
  - Build-up of Lipids and Debris in Arteries
- Sad Truth
  - 16 million Americans have CAD
  - 8 million of them have had heart attacks
  - One-third of all deaths in Americans older than 35 are due to coronary artery disease.
- Some of the Causes
  - Dyslipidemia
  - Smoking
  - Low-Excersize Lifestyle
  - Hypertension

Hope

Changes in lifestyle and some medications have been shown to lower mortality rates in humans.

Major Players

- Immune Cells: Monocytes
- Debris: Foam Cells
- Chemoattractant: Immune cell signals
- Reactive Oxygen Species: Free Radicals
- Low Density Lipoproteins: Bad Choloesterol
- Oxidized Low Density Lipoproteins: Really Bad Cholesterol
- High Density Lipoproteins: Good Cholesterol
- Dysfunctional High Density Lipoproteins: Really Really Bad Cholesterol

Video

▸ Link

Functional HDL

Formation of HDL

A heterogenous mix of apolipoproteins collectively having discoidal shape uptake cholesterol becoming esterified by Lecithin-Cholesterol Acyltransferase generating HDL.

Roles of HDL

- Removes Debris in the Atheroma
- Removes Natural and Oxidized LDL from the Atheroma
- Removes Radical Oxygenating Species
- Diminishes the Quantity of Chemoattractant and Vascular Cell Adhesion Molecules
- Prevents the Accumulation of Lipid Hydroperoxides in LDL
- Directly Renders LDL Resistant to Oxidation

Corruption of HDL

- Causes
  - Acquisition of Oxidized Sterols and Phospholipids during RCT
  - Changes in Protein Composition due to Serum Amyloid A Occur during Infection, Regular Inflammation, and Acute Phase Reactions to Surgery, Influenza, Sepsis, or Choronic Systemic Inflammation.
  - HDL is naturally dysfunctional in patients who suffer from Diabetes, Obesity, Coronary Artery Disease, and Cardiovascular Disease
  - Oxidation by Myeloperoxidase and Hypoclourous acid in the atheroma

Runs to Failure

HDL works like a garbage truck removing all the atherogenic materials from the atheroma until the the "trash" raises the cytotoxicity of the HDL high enough for it to dysfunction.

Dysfucional HDL

When Good HDL Goes Bad

- Promotes Endothelial Expression of Adhesion Molecules and Chemoattractant Increasing Monocyte Entry into the Arterial Wall Contributing to the Formation of Atherosclerotic Lesions
- No Longer Able to Perform Reverse Cholesterol Transport Effectively
- Less Effective at Mobilizing Oxidized Sterols and Lipids from Foam Cells
- Causes Increased Selective Uptake of Cholesteryl Esters by Macrophages Forming more Debris
- Promotes Transfer of Lipid Hydroperoxides which Oxidize LDL

Litter Bug

Paradoxically, Atherosclerotic lesions progress with the introduction of HDL if the parameters permit corruption of our little garbage trucks.

Processes

- Extensive Literature Review
- Determine Significance of HDL Dynamics
- Represent Biological Proceses as Mathematical Equations using Mass-Action Laws
- Modify the Existing Model to Account for Functional and Dysfunctional HDL
- Determine whether or not a Healthy-State Equilibrium Exists (Analytic)

My Model

$$\dot{I} = P_{13}C - a_{15}IL_{ox} - a_{13}IC - a_{12}ID - k_1IH_{ox}$$

$$\dot{D} = c_{15}IL_{ox} - a_{21}ID - k_3HD + k_2k_1k_{17}IH_{ox}$$

$$\dot{C} = \frac{P_{32}D(1 + k_4H_{ox})}{(1 + k_5H)} - a_{31}IC - d_{33}C$$

$$\dot{L} = P_{44}(L_B - L) + b_4A_{ox}r_4L_{ox} + \beta_1HL_{ox} - k_6HL - a_{46}RL - d_{44}L$$

$$\dot{L}_{ox} = \frac{c_{46}LR}{(1 + k_{12}H)} - b_{15}IL_{ox} - A_{ox}r_4L_{ox} - k_9HL_{ox} - d_{55}L_{ox}$$

$$\dot{R} = P_R + P_KD - b_{46}RL - A_{ox}b_6R - k_{13}HR - d_{66}R$$

$$\dot{H} = P_{77}(H_B - H) + A_{ox}k_{15}H_{ox} - k_{16}HD - k_8HL_{ox} - k_{10}HL - d_{77}H$$

$$\dot{H}_{ox} = k_{19}k_{13}\gamma_1RH + k_3k_{16}\theta_1HD - k_{17}IH_{ox} - k_{18}A_{ox}H_{ox} - d_{88}H_{ox}$$

Examples

Biological Process	Mathematical Representation
Natural HDL Source	$P_{77}(H_B - H)$ [$\dot{H}$ Equation]
Apoptotic HDL Death	$-d_{77}H$ [$\dot{H}$ Equation]
Removal of Oxidated LDL by HDL	$-k_9 HLox$ [$\dot{L}_{ox}$ Equation]

Table 1 : Biology $\rightarrow$ Mathematics Examples

Problems

- With 52 symbolic parameters and 8 state variables, the computer was unable to find an explicit analytic solution.
- With algebra, I was able to simplify all equations into terms of only two variables(LDL and HDL).
- The final two equations,lead to a fifth order rational polynomial with square roots. U-G-L-Y!
- Strategic algebraic manipulations and graphical techniques led to the proof of the existance of a healthy state equilibrium!

Future Directions

Run numerical simulations to find healthy state equilibrium given certain parameters. Determine the stability of the healthy state equilibrium.

Thank you!

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