Modeling Lesion Growth in Atherosclerosis

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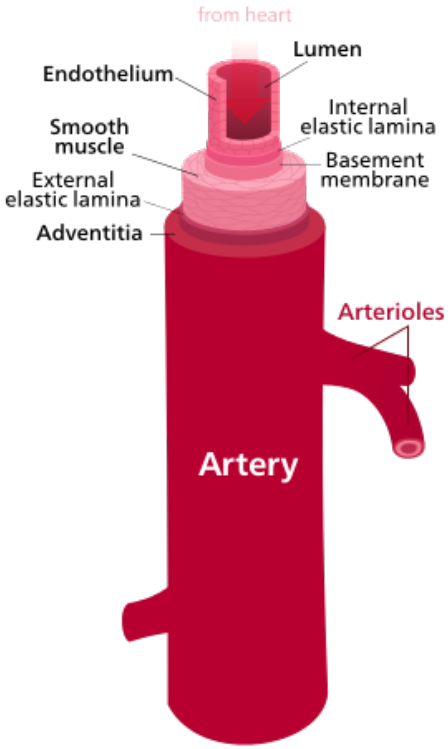
Definitions

- Atherosclerosis
  - Hardening of the arteries
  - A build up of fatty cells in the wall of the artery
- Lesion
  - Collection of fatty cells (foam cells) in the artery wall
- Atherogensis
  - The start of atherosclerosis
  - A lesion starts growing

Artery

- Endothelium
  - One cell thick
  - Holes form to make leaky spots



http://en.wikipedia.org/wiki/Artery

Key Players

- Immune Cells = I
  - Example: Macrophages
  - Eat oxidized LDL and HDL to create foam cells
  - Can also remove some foam cells from lesion
- Foam Cells = D (Debris)
  - Collection of fatty cells (foam cells) in the artery wall
- Chemoattractant = C
  - Released when foam cells are present
  - Macrophages are attracted towards chemoattractant
- Free Radicals = R
  - Produced as a biproduct of metabolism
  - Oxidize LDL and HDL

Key Players

- LDL $= L$
  - Low density lipid protein
  - "Bad cholesterol"
- Oxidized LDL $= L_{ox}$
  - LDL after free radicals have oxidized it
- HDL $= H$
  - High density lipid protein
  - "Good cholesterol"
- Oxidized HDL $= H_{ox}$
  - HDL after free radicals have oxidized it

Atherogenesis

- Hole in endothelium
- LDL, HDL, Macrophages flow into hole
- LDL and HDL are oxidized by free radicals
- Macrophages eat oxidized LDL and HDL
  - Become so fat, they cannot leave through the hole
  - Become foam cells
- Chemoattractant is released
- Macrophages are attracted to the chemoattractant

Healthy State

- Definition
  - $I = D = C = 0$
  - That is, no immune cells, foams cells, or chemoattractant.
- Stability
  - Stable $\Longleftrightarrow$ small perturbation goes back to the healthy state
  - Unstable $\Longleftrightarrow$ Atherogenesis
- Theorems
  - Healthy state exists and is an equilibrium solution
  - Given all other parameters, A_{ox} can be made sufficiently large to make the healthy state stable.

Different Models

Boundary Transport

- Transport from blood stream
- Transport from vaso vasorum

Incorporating HDL

- Kelly's model

Equations

- Model with boundary transport from blood stream

$$\dot{I} = Div(\mu_I \nabla I - \chi(I, C)\nabla C) - d_{11} I - a_{15} I L_{ox} - a_{12} I D$$
$$\dot{D} = Div(\mu_D \nabla D) + c_{15} I L_{ox} - a_{21} I D - d_{22} D$$
$$\dot{C} = Div(\mu_C \nabla C) + p_{32} - a_{31} C I - d_{33} C$$
$$\dot{L} = Div(\mu_L \nabla L) - a_{46} L R + b_4 A_{ox} r_4 L_{ox}$$
$$\dot{L}_{ox} = Div(\mu_{L_{ox}} \nabla L_{ox}) + c_{46} L R - A_{ox} r_4 L_{ox} - b_{15} I L_{ox}$$
$$\dot{R} = Div(\mu_R \nabla R) - b_{46} R L - A_{ox} b_6 R + p_R$$

On S_I:

$$\mathbf{q}_I = -\alpha_I(C)$$
$$\mathbf{q}_C = \alpha_C$$
$$\mathbf{q}_L = -\alpha_I(C)$$
$$\mathbf{q}_j \cdot \hat{\mathbf{n}} = 0 \quad \text{for} \quad j = D, L_{ox}, R$$

On S_O:

$$\mathbf{q}_j \cdot \hat{\mathbf{n}} = 0 \quad \text{for} \quad j = I, D, C, L, L_{ox}, R$$

Equations

- Model with boundary transport from vaso vasorum

$$\dot{I} = Div(\mu_I \nabla I - \chi(I, C)\nabla C) - d_{11} I - a_{15} I L_{ox} - a_{12} I D + p_{13} C$$
$$\dot{D} = Div(\mu_D \nabla D) + c_{15} I L_{ox} - a_{21} I D - d_{22} D$$
$$\dot{C} = Div(\mu_C \nabla C) + p_{32} - a_{31} C I - d_{33} C$$
$$\dot{L} = Div(\mu_L \nabla L) - a_{46} L R + b_4 A_{ox} r_4 L_{ox}$$
$$\dot{L}_{ox} =$$
$$Div(\mu_{L_{ox}} \nabla L_{ox}) + c_{46} L R - A_{ox} r_4 L_{ox} - b_{15} I L_{ox} + p_{44}(L_B - L)$$
$$\dot{R} = Div(\mu_R \nabla R) - b_{46} R L - A_{ox} b_6 R + p_R$$

On S_I:

$$\mathbf{q}_j \cdot \hat{\mathbf{n}} = 0 \quad \text{for} \quad j = I, D, C, L, L_{ox}, R$$

On S_O:

$$\mathbf{q}_j \cdot \hat{\mathbf{n}} = 0 \quad \text{for} \quad j = I, D, C, L, L_{ox}, R$$

Programming

- Previously
  - Explict method in Cartesian coordinates (1-D)
  - Implicit method in cylindical coordinates (1-D)
- New
  - No Boundary Transport Model (implicit, cylindrical, 1-D)
  - HDL model (implicit, cylindrical, 1-D, from Kelly)

Equilibria

- Implications of multiple equilibria
  - Unhealthy to healthy vs. always healthy
  - Limits on curing abilities
- Numerical results on multiple equilibria
  - None found in boundary transport model
  - Found in model with no boundary transport

Sensitivity Analysis

- α_C, α_I, L_B
  - All have same order of magnitude effect on athergenesis
  - All have same order of magnitude effect on lesion size
- α_L
  - Appears to have no effect on atherogenesis
  - However, does affect the size of lesion if it grows

Applications of Research

- Multiple equilibria
- Give directions for medical research
  - Sensitivity analysis
  - What to target for treatment / prevention
- Personal medicine

Current Research Direction

- HDL Model
  - Quantify the effects of HDL on the system
  - Look at HDL being helpful vs hurtful

Thanks for listening!