ATHEROSCLEROSIS

AND

THE HDL RECEPTORS

A REVIEW
• **High Density Lipoprotein (HDL)**
  - acts as a cholesterol scavenger
  - probably obtains cholesterol from cell surface membranes using lecithin:cholesterol acyltransferase (LCAT)
  - transfers some cholesterol esters (CE) to VLDL and LDL using cholesterol ester transfer protein (CETP)
  - transport of cholesterol and CE from tissues to liver and steroidogenic cells
    - excrete cholesterol from body
      - in form of bile acids
    - use as building blocks for steroids
IMPORTANCE

- Cardiovascular disease is the #1 killer in the US
  - 40% of all deaths
  - in the US 1.5 million new cases every year
  - chronic illness

- The Framingham Heart Study shows that a 1% reduction in an individual's total serum cholesterol level translates into an approximate 2% reduction in heart disease risk
• HDL RECEPTORS
  • SCAVENGER RECEPTORS
  • CUBILIN
  • MEGALIN
• **SCAVENGER RECEPTORS**

  • There are many classes of these receptors
    
    - Scavenger Receptor Class B Type 1 (SR-B1)
    - Scavenger Receptor Class B Type 2 (SR-B2)
    - Cluster Designation (CD) 36

  • Focus: SR-B1 and CD 36
• **SR-B1**
  
  • identified as a receptor for LDLs
  • greatest expression in hepatic and steriodogenic cells
    • in liver, ovary, lung and adrenal glands

  **FUNCTIONS**
  
  • decreases plasma levels of HDL and non-HDL cholesterol
  • mediates HDL CE selective uptake
  • anchors HDL molecules to plasma membranes without internalizing or degrading them
• STRUCTURE OF SR-B1

- 2 transmembrane domains
- 2 cytoplasmic domains
  - consists of amino and carboxyl terminals
  - C-terminal may facilitate uptake of CE into cells
  - N-terminal responsible for proper targeting of receptor to plasma membrane
- an extracellular domain
  - contains
    - a cysteine rich region
    - 9 putative sites for N linked glycosylation
- binding site for HDL CE
  - greatest efficiency for uptake and binding
- a non-aqueous channel between the HDL and the plasma membrane
• Extracellular domain
  • HDL CE uptake
  • Bi-directional free cholesterol flux
  • alteration of membrane cholesterol mass and distribution
• Cytoplasmic domain : N and C-terminals
  • C-terminal tail is dispensable for activity as well as for targeting to the plasma membrane
  • it does not confer an enhanced HDL CE selective uptake activity
  • N-terminal has no new activity roles
• Intestinal receptor for the endocytosis of intrinsic factor-vitamin B\textsubscript{12} 
• high expression in kidney, yolk sac, placenta and hepatic cells 
• binds to HDL and apolipoprotein A-1 (apo A-1) 
• endocytosis of \textsuperscript{127}I-HDL inhibited by IgG antibodies against apo A-1 and cubilin 
• deficiency results in loss of apo A-1 in urine 
• uptake of apo A-1 and HDL from kidney tubules 
• not a receptor for LDL or its derivatives
• **STRUCTURE OF CUBILIN**
  
  • a short N terminal sequence  
    • this region is involved in membrane association  
    • has a amphipathic helix pattern which is a potential site for hydrophobic interactions  

  • 8 epidermal growth factor repeats  

  • 27 CUB (Complement componentsClr/Cls, Uegf, and bone morphogenic protein-1) domain cluster  
    • ligand binding sites:  
      • domains 5-8 bind intrinsic factor-vitamin B$\textsubscript{12}$  
      • domains 13-14 is a receptor-associated protein binding site
• Cubilin does not have apparent transmembrane and cytoplasmic domains

• **MEGALIN**
  • does not bind to HDL, delipidated HDL or apo A-1
  • co-purifies with cubilin
  • exhibits a coincident pattern of mRNA expression in mouse tissues including kidney, ileum, placenta and yolk sac – same as cubilin
  • suppression of megalin activity results in reduced cell surface expression of cubilin
  • megalin antibodies inhibit HDL uptake
  • may play a role in the intracellular trafficking of cubilin
• **ATHEROSCLEROSIS**

  • the higher the plasma concentrations of HDL the lower the risk
  • mechanism is unknown
  • strong correlation between atherosclerotic lesions and VLDL and LDL levels
  • combination of SR-B1 overexpression and a low fat diet demonstrates strong anti-atherogenic potential
  • overexpression of hepatic SR-B1
    • reduces advanced atherosclerotic lesions
    • decreases HDL cholesterol levels
    • moderately reduces non HDL cholesterol levels
• **FUTURE WORKS**

  - Structure of Megalin
  - Details of its interaction with cubilin
  - Determining the extent to which megalin is involved in HDL uptake
  - Crystalline structure of SR-B1
  - Details of the non-aqueous channel and its function
  - Mechanistic details of relation between atherosclerosis and HDL plasma concentrations
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