

**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**

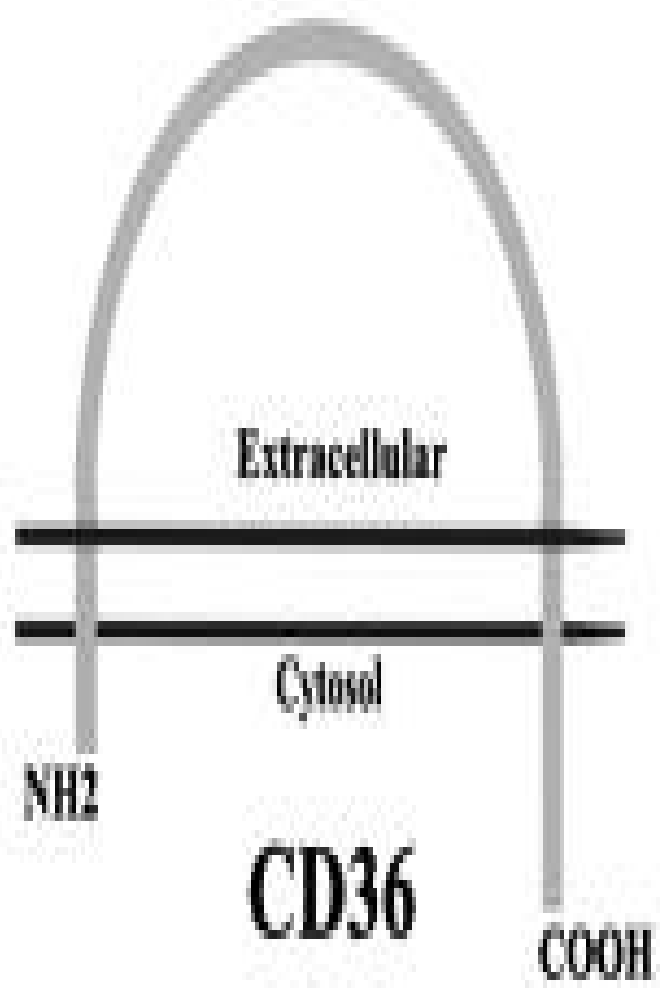
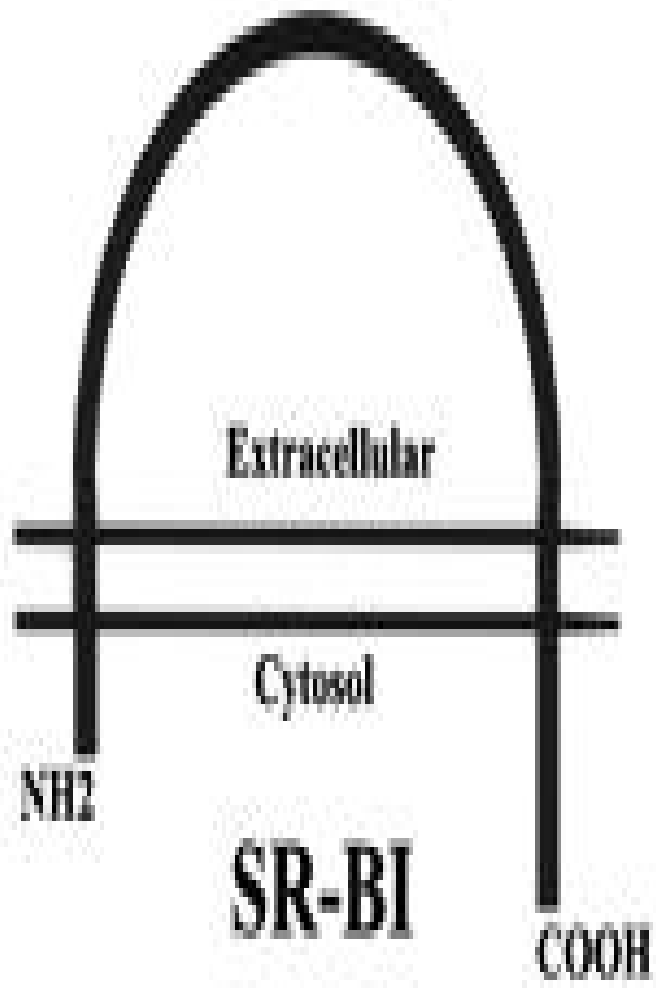
- identified as a receptor for LDLs
- greatest expression in hepatic and steroidogenic cells
  - in liver, ovary, lung and adrenal glands

- **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



# • **HOT OF THE PRESS!**

- 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

## • CUBILIN

- Intestinal receptor for the endocytosis of intrinsic factor-vitamin B<sub>12</sub>
- high expression in kidney, yolk sac, placenta and hepatic cells
- binds to HDL and apolipoprotein A-1 (apo A-1)
- endocytosis of <sup>127</sup>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 components Clr/Cl<sub>s</sub>, Uegf, and bone morphogenic protein-1) domain cluster
  - ligand binding sites:
    - domains 5-8 bind intrinsic factor-vitamin B<sub>12</sub>
    - 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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