Systems Definition: Regulation of high-density lipoprotein particle clearance

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System [edit]

System Name

HDL / Cholesterol clearance regulation system

Description

A system that modulates the rate, frequency or extent of high-density lipoprotein particle clearance. High-density lipoprotein particle clearance is the process in which a high-density lipoprotein particle is removed from the blood via receptor-mediated endocytosis and its constituent parts degraded.

Key associated GO terms (process ontology)

- GO:0034384 (high-density lipoprotein particle clearance)
- GO:0010984 (regulation of lipoprotein particle clearance)
- GO:0010982 (regulation of high-density lipoprotein particle clearance)
- GO:0010983 (positive regulation of high-density lipoprotein particle clearance)
- GO:0010987 (negative regulation of high-density lipoprotein particle clearance)

Concepts [edit]

- High density lipoprotein cholesterol (HDL-C) levels are strongly, inversely and independently associated with coronary heart disease (CHD).[1] This inverse relationship between plasma HDL cholesterol concentrations and the risk of cardiovascular disease is well accepted. The structures and cholesterol transport abilities of HDL particles are determined by the properties of their exchangeable apolipoprotein (apo) components.[2]
- HDL clearance is closely associated with RCT (Reverse Cholesterol Transport).[3] HDL plays an important anti-atherogenic role through reverse cholesterol transport from peripheral cells to the liver.[4]
- Two possible ways for HDL to be cleared from the blood:
  1. Directly through HDL receptors on the liver.
  2. Conversion of HDL to LDL/VLDL and clearance of LDL/VLDL through receptors on the liver.

Adding Genes (Bottom up) [edit]

Symbol	ID	Source	Reference	Role	Notes
LCAT	P04180	STRING	[5]	Enzyme(transferase)	Central enzyme in the extracellular metabolism of plasma lipoproteins. Esterifies cholesterol in plasma.
APOD	P05090	Literature	[5]	Activator	APOD occurs in a macromolecular complex with lecithin-cholesterol acyltransferase. Activator of LCAT.
APOA1	P02647	GO:0034384, STRING	[5] [6]	*Activator*	APOA1 occurs in a macromolecular complex with lecithin-cholesterol acyltransferase. Activator of LCAT. ApoA-I has also been reported to stimulate GPLD1 activity. ApoA-I is the major protein component of HDL in plasma.
APOM	O95445	GO:0034384 Literature	[7]	*Effector*	Predominantly associated with HDL particles. Apolipoprotein M is important for the formation of pre-beta high-density lipoprotein and reverse cholesterol transport.
APOA2	P02652	GO:0034384, STRING	[8]	*Effector*	Apolipoprotein A-II is the second major apo of high-density lipoproteins. It may stabilize HDL structure by its association with lipids, and affect the HDL metabolism.
APOE	P02649	GO:0034384	[9]	*Effector*	Essential for the normal catabolism of triglyceride-rich lipoprotein constituents. Apolipoprotein E (apoE) is a major carrier of cholesterol.
APOC2	P02655	GO:0010983 Literature	[10] [11]	*Activator/Cofactor*	Component of chylomicrons, VLDL, LDL, and HDL in plasma. Plays an important role in lipoprotein metabolism as an activator/cofactor of lipoprotein lipase.
APOC3	P02656	GO:0010987	[12] [13]	*Inhibitor/Cofactor*	LPL activity is finely modulated by several cofactors, including apolipoprotein C-III which acts as a LPL inhibitor. It also inhibits hepatic uptake of triglyceride-rich particles.
GPLD1	P80108	GO:0010983	[14]	*Regulator/unknown!*	Codes for the protein GPI-specific phospholipase D. GPI-PLD associates with high density lipoproteins and with an apoA-I and apoA-IV containing complex.
LIPG	Q9Y5X9	GO:0010983	[15]	*Enzyme*	Has phospholipase and triglyceride lipase activities. Hydrolyzes high density lipoproteins (HDL) more efficiently than other lipoproteins. Carriers of the endothelial lipase gene (LIPG) variant, LIPG Asn396Ser, display significant increases in HDL-C as compared to non-carriers.
SCARB1	Q8WTV0	GO:0034384	[16] [17] [18]	*Receptor*	Scavenger receptor class B member 1 is the primary receptor for the selective uptake of cholesterol from high-density lipoprotein (HDL). SCARB1 also mediates HDL endocytosis.
GPIHBP1	Q8IV16	Literature	[19]	*Regulator*	Required for the transport of lipoprotein lipase LPL into the capillary lumen.
APOA4	P06727	Literature	[14]	*Activator*	ApoA-IV is a potent activator of LCAT in vitro. Required for efficient activation of lipoprotein lipase by apoC-II. APOA4 has been shown to interact with GPLD1.
ABCA1	O95477	Literature	[20] [4]	*Receptor*	Has a role in cellular lipid efflux and high density lipoprotein metabolism. Mutations in the ABCA1 gene interfere with cellular cholesterol efflux.
CETP	P11597	Literature	[21]	*Enzyme*	CETP-inhibitors drugs were found to increase serum HDL-C levels and decrease LDL-C levels.
LPL	P06858	Literature	[22]	*Enzyme*	Lipoprotein lipase is an enzyme that is responsible for the metabolism of core triglycerides of very-low density lipoproteins (VLDL).
LDLR	P01130	Literature	[23] [24]	*Receptor*	A gene, that codes for a low-density lipoprotein (LDL) receptor, involved in cholesterol uptake via receptor-mediated endocytosis.

System Functions (Bottom up)

[edit]

- Cholesterol efflux promotes HDL clearance from plasma. This efflux happens through **ABCA1** receptors, located on the cell membrane.[20].
- The biogenesis of HDL initially requires functional interaction of **apoA-I** with the **ABCA1** and subsequently interactions of the lipidated apoA-I forms with **LCAT**.[3] **LCAT** mediates the esterification of cholesterol in plasma and exists most likely as a complex with its activators **apoA-I** and **apoD**.[3]
- From published articles, **apo-M** was found to be necessary for the formation of pre-beta high-density lipoprotein.[7] The formation of HDL is simplified in this system and so we will assume that **apo-M** is necessary for HDL formation.
- **apoA-II** is known to be one of the most abundant apo-lipoproteins in HDL particles and necessary for HDL stabilization. Therefore, **apoA-II** is necessary for HDL formation as well.
- **apo-E** is known to be a major carrier of cholesterol.[9] Also, being a subunit of HDL, it was deduced that **apo-E** is necessary for the binding of cholesterol by HDL particles. Once bound to esterified cholesterol, HDL-CE clearance from blood is mediated by **SCARB1** receptors located on the membrane of liver cells.[17]

- HDL can also be indirectly cleared from blood by first transforming into LDL/VLDL and then the consecutive clearance of LDL/VLDL particles.
  - From UniProt, it was found the **CETP** allows the net movement of cholesteryl ester from HDL to VLDL. Moreover, a study showed that mutation in **LIPG** gene causes an increase in plasma HDL levels.[15] This suggests that **LIPG** is necessary for the metabolism of HDL particles. Therefore, it was deduced that the enzymes **LIPG** and **CETP** promote the transformation of HDL into VLDL/LDL. VLDL can in-turn change to LDL with the help of the enzyme **LPL**[22], which is known to be activated by **apoC-II**[10] and repressed by **apoC-III**[12]. From UniProt, it is known that **ApoA-IV** enhances the activation of LPL by **apoC-II**. Also, **GPIHBP1** is known to be necessary for the transport of **LPL** into the plasma, and thus promotes the function of LPL.[19]
  - Once HDL has been transformed into LDL, LDL particles can bind to **LDLR** receptors located on the membrane of hepatic cells. This causes the uptake/clearance of LDL particles, which consecutively results in HDL clearance as well.[23] A study showed that the absence of **apoC-III** improves hepatic clearance via LDLR.[25] This suggests that **LDLR** uptake of LDL particles is inhibited by **apoC-III**.

- **GPLD1** also acts towards HDL clearance. **ApoA-I** and **apoA-IV** are thought to promote GPLD1 activity. However, the mechanism that GPLD1 regulates HDL clearance is still unknown![14]

- The collective actions of **SCARB1** and **LDLR** (along with the positive regulation of GPLD1) cause HDL/cholesterol clearance from the blood.

System Properties (Top down)

[edit]

Name
HDL / Cholesterol clearance regulation system

Purpose
To modulate the rate, frequency or extent of high-density lipoprotein particle clearance from the plasma

Input
High tissue cholesterol levels

Biological components
Intracellular space
Plasma
Liver

Interfaces
ABCA1, SCARB1, and LDLR receptors

Enzymes
LCAT, LIPG, CETP, LPL, GPLD1

Lipoproteins
HDL, LDL, VLDL

Apolipoproteins
apoA-I, apoA-II, apoA-IV, apoC-II, apoC-III, apoD, apoE, apoM

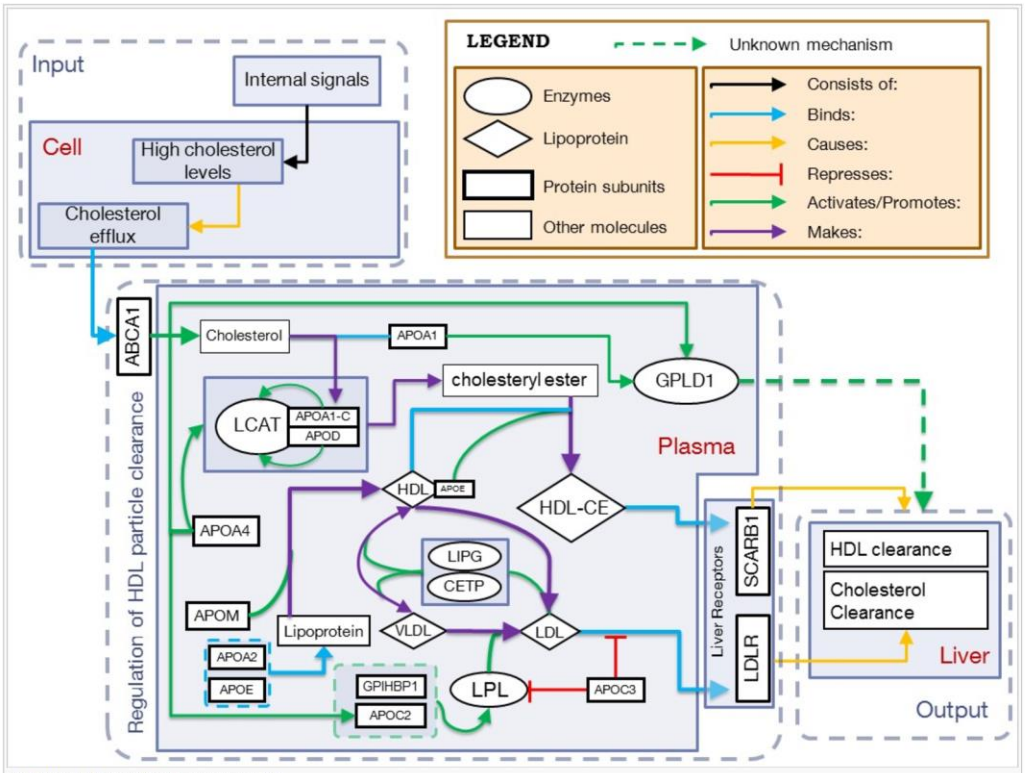
Other proteins
GPIHBP1

Other molecules
Cholesterol, Cholesteryl ester

Output
HDL particle clearance from the blood
Cholesterol clearance from the blood

Architecture

[edit]



Regulation of high-density lipoprotein clearance system
The color, shape, arrow, and box conventions are shown in the legend. Red text represents biological components involved in the system.

Documentation [edit]

Gene Discovery [edit]

GOA [edit]

- The system name `Regulation of high-density lipoprotein particle clearance` was searched in GOA.
- All child terms were searched in GOA.
- Ancestors of the GOA term that concerned HDL were also searched.
  - All unique human genes found in the three searches above were noted.

STRING [edit]

- All proteins found from the GOA searches were entered into the STRING database.
- Any interactors/genes (not found from the GOA search) that had functions concerning HDL were noted.

Literature [edit]

- Some genes were found when reading published articles about HDL clearance.
- Also, many genes were found when reading published articles about the function/role of genes found from GOA and STRING.

PDB [edit]

- Discovered genes were also searched in PDB but no new genes were discovered this way.

Facts [edit]

- All of the discovered genes were searched in UniProt and their functions were recorded.
- All discovered genes were searched in PubMed and published articles were used to further deduce the functions of the genes and how exactly they contribute to HDL clearance.

Gene Interactions [edit]

- Relationships/interactions between different genes were found from published articles.
- Some interactions were also discovered/confirmed using the STRING database.
- GPLD1 was the most challenging to find the function for. From published articles, it was found that the protein product GPI-PLD is closely associated with apoA-I and apoA-IV.[14] Although, I could not find an article that mentions the role of GPLD1 in regulating cholesterol/HDL levels, it is clear from GOA that GPLD1 is involved in the positive regulation of high-density lipoprotein particle clearance. Also, in a study, apoA-I and apoA-IV have been reported to stimulate GPI-PLD activity in vitro.[14] Therefore, we can deduce that apoA-I and apoA-IV act as activators for GPLD1 and that GPLD1 works towards HDL clearance. However, how exactly GPLD1 regulates HDL clearance is still unknown!

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