The Role of PCSK9 in the Regulation of LDL Cholesterol
Hepatic Low-Density Lipoprotein Receptors (LDLRs) Play a Central Role in Cholesterol Homeostasis

- Low-density lipoprotein (LDL) particles consist mostly of cholesteryl esters packaged with a protein moiety called apolipoprotein B (apoB), with 1 apoB molecule in each LDL particle.\(^1\,^2\) LDL particles are the primary carriers of plasma cholesterol in humans,\(^1\) and high LDL levels have a strong and direct relationship with the development of atherosclerosis.\(^3\)

- The liver is responsible for the clearance and catabolism of plasma LDL,\(^2\) and hepatocyte expression of LDL receptors (LDLRs) is central to this process by binding and removing LDL from the plasma.\(^4\,^5\)

- The LDL/LDLR complex is internalized into the hepatocyte via clathrin-coated vesicles, thereby removing LDL from the blood.\(^1\,^5\,^6\) The affinity of the hepatic LDLR for apoB on LDL enables LDLRs to clear plasma LDL effectively.\(^2\)
Recycling of LDLRs Enables Efficient Clearance of LDL Particles

- Clathrin-coated vesicles containing internalized LDL/LDLR complexes fuse with endosomes, resulting in dissociation of the LDL particles from the LDLRs due to the acidic environment. The free LDLRs then recycle back to the surface of the hepatocyte to bind and clear additional LDL from the blood.

- Free LDL particles in the endosomes are transported to the lysosomes and degraded into lipids and amino acids.

- The ability of hepatic LDLRs to be recycled is a key determinant of hepatic efficacy in lowering plasma LDL levels.
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Regulates the Recycling of LDLRs by Targeting the LDLR for Degradation

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proprotein produced in hepatocytes and secreted into the plasma as functional PCSK9. Extracellular PCSK9 binds to the LDLR on the surface of the hepatocyte and is internalized within the endosome.

- The LDLR/PCSK9 complex is then routed to the lysosome for degradation, thereby preventing the recycling of LDLR back to the hepatocyte surface.

- By preventing LDLRs from recycling back to the surface, PCSK9 reduces the concentration of LDLRs on the surface of the hepatocytes, resulting in a lower LDL clearance rate and elevated levels of plasma LDL.
Gain-of-function mutations result in increased LDL-C

- The role of PCSK9 in the regulation of plasma LDL levels is supported by a significant amount of genetic evidence.\(^7,9\)

- Gain-of-function mutations in PCSK9 result in increased PCSK9 function, which leads to decreased LDLR recycling to the cell surface.\(^7,9\)

- This results in an autosomal-dominant hypercholesterolemia with increased plasma LDL levels.\(^7,9\)
Loss-of-function mutations are associated with decreased LDL-C\textsuperscript{11}

- Mutations in the human PCSK9 gene that lead to a loss of PCSK9 function are found in 1\% to 3\% of the representative populations.\textsuperscript{10,11}

- These loss-of-function mutations have been associated with lower levels of circulating PCSK9,\textsuperscript{12} lower plasma LDL levels.\textsuperscript{10}
List of References