Beyond LDL Cholesterol, a New Role for PCSK9

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Elevated low-density lipoprotein cholesterol (LDL-C) levels in the plasma is the most important causative factor of atherosclerosis and associated ischemic cardiovascular diseases. The LDL receptor (LDLR) is the preferential pathway through which LDLs are cleared from the circulation. LDLs bound to the LDLR are internalized into clathrin-coated pits and subsequently undergo lysosomal degradation, whereas the LDLR is recycled back to the plasma membrane.

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Familial hypercholesterolemia (FH) is an autosomal dominant disorder associated with elevated LDL levels and premature coronary heart disease. FH is caused primarily by mutations of the LDLR or of apolipoprotein B100 (apoB100), the protein component of LDL that interacts with the LDLR. In 2003, “gain of function” mutations on a newly identified gene, proprotein convertase subtilisin/kexin type 9 (PCSK9), were associated with FH. In 2005, a causative association was established between “loss of function” mutations in PCSK9 and low LDL-C levels in 2% of the African-American population. The coronary heart disease risk in these individuals was reduced by 88%. As a result of these landmark studies (reviewed in Reference 1), PCSK9 became the subject of intensive research to discover the underlying mechanisms.

PCSK9 is a serine protease mainly expressed in the liver and the intestine. It acts by reducing the amount of LDLR in hepatocytes. This was demonstrated in vitro and in mouse models and inferred by genetic studies in patients with PCSK9 mutations (reviewed in Reference 2). In brief, PCSK9 enzymatic activity permits its intracellular maturation, followed by secretion (Figure). Circulating PCSK9 binds the LDLR on the cell surface and is subsequently cointernalized together with the LDLR. This promotes the degradation of the receptor in the lysosome, rather than recycling to the plasma membrane. PCSK9 can also bind the LDLR intracellularly. Thus, by virtue of its role as a major inhibitor of the LDLR, PCSK9 has emerged as a hot new drug target to treat hypercholesterolemia and coronary heart disease.

PCSK9 inhibition has been intensively studied in cell-based systems. A peptide, which mimics the interaction domain of the LDLR with PCSK9, can inhibit PCSK9 binding to the LDLR and prevent its degradation. Likewise, an anti-PCSK9 antibody and an anti-PCSK9 antigen binding fragment disrupt the interaction between PCSK9 and the LDLR, thus restoring cellular LDL-uptake. In vivo, PCSK9 has been inhibited using antisense oligonucleotides or small interfering RNA (siRNA). These treatments dramatically increase hepatic LDLR and lower plasma LDL-C in rodents and monkeys. Another approach has involved infusions of humanized anti-PCSK9 antibodies. A single injection of these antibodies reduced LDL-C by 80% in monkeys. This study also showed that anti-PCSK9 antibodies act synergistically with statins to increase LDLR cell surface expression, indicating that blocking PCSK9 in statin-treated patients will most likely further reduce their LDL-C levels. Thus, PCSK9 inhibitors should prove invaluable for patients at risk of developing recurrent cardiovascular events despite aggressive statin treatment and in patients with FH.

In that respect, the D374Y-PCSK9 gain of function nonsense mutation is at the origin of an extremely severe FH phenotype, particularly hard to treat with statins. Carriers of the D374Y-PCSK9 mutation are affected 10 years earlier than other FH patients by premature coronary heart disease. This mutant was found to bind the LDLR with a 5- to 30-fold higher affinity compared with wild-type PCSK9, by allowing a hydrogen bond to form between the PCSK9 and the peptide domain of the LDLR.

The study by Herbert et al in this issue of Arteriosclerosis, Thrombosis and Vascular Biology demonstrates that the D374Y-PCSK9 mutation causes atherosclerosis as a result of (1) impaired LDL clearance, as well as (2) increased secretion of apoB-containing lipoproteins. In this study, mice lines expressing human PCSK9 (wild type and D374Y) at physiological levels were generated. Transgenes expression was restricted almost exclusively to the liver, and human PCSK9 was detected in the plasma of these animals. As anticipated, plasma cholesterol levels were more elevated in D374Y-PCSK9 transgenics, followed by wild-type PCSK9 transgenics, compared with control mice, and this phenotype was exacerbated on a cholesterol-rich diet. All transgenics had lower hepatic LDLR expression than controls. The plasma lipoprotein profile of wild-type PCSK9 transgenics was characterized by an increase in LDL levels. That of D374Y-PCSK9 transgenics was characterized by an even sharper increase in LDL, as well as by the presence of large very-low-density lipoprotein (VLDL)/intermediate-density lipoprotein particles in the plasma, resulting from an increased production of triglyceride-rich lipoproteins. After 15 weeks on a cholesterol-rich diet, only the D374Y-PCSK9 transgenic mice displayed aortic atherosclerotic lesions. To date, this is the only genetically engineered PCSK9 animal model in which atherosclerosis has been assessed. The D374Y-PCSK9 transgenic mice should prove useful to test the antiathero-
The genetic potential of PCSK9 inhibitors, either alone or in combination with a statin.

Another merit of this study is to unravel a role for PCSK9 on lipoprotein metabolism that does not apparently involve the LDLR. This has been a controversy for some time, depending on the animal model or experimental settings. Because PCSK9 knockout and LDLR/PCSK9 double knockout mice have the same lipoprotein profile, it was concluded that PCSK9 regulates cholesterol homeostasis exclusively via the LDLR. But PCSK9 knockout mice secrete larger chylomicrons and less apoB, and they clear chylomicron remnants faster than control animals. ApoB100 secretion from primary hepatocytes of PCSK9 knockouts is also reduced. Overproduction of apoB100 was reported in FH patients carrying the S127R-PCSK9 gain of function mutation, as well as in hepatoma cells expressing D374Y-PCSK9. In addition, PCSK9 overexpression was associated with increased VLDL hepatic output in mice on fasting, and we have recently reported that fenofibrate concomitantly decreases serum PCSK9 and VLDL particle concentration in statin-treated type 2 diabetics. Lately, 2 studies have indicated that serum triglyceride levels correlate with circulating PCSK9 in humans. Therefore, beside the well-established role of PCSK9, as a bona fide LDLR inhibitor and prime modulator of plasma LDL levels, there is mounting evidence that PCSK9 plays a role in triglyceride-rich lipoprotein metabolism, at least in certain pathophysiological conditions (fasting and gavage), and for 2 gain of function mutants (D374Y and S127R). Whether the LDLR is involved in part, directly or indirectly, in these metabolic pathways certainly merits further investigation.

Disclosures

None.

References


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