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Lowering Plasma Cholesterol by Raising LDL Receptors—Revisited

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Thirty-one years ago, Mabuchi and coworkers[1] reported in the *NEJM* that compactin, an HMG-CoA reductase inhibitor (a statin), reduced plasma low-density lipoprotein (LDL) cholesterol levels in familial hypercholesterolemia (FH) heterozygotes by 29%. In an accompanying editorial,[2] entitled "Lowering cholesterol by raising LDL receptors," Michael Brown and Joseph Goldstein noted that FH heterozygotes have a deficiency of LDL receptors on cells, resulting in reduced cholesterol uptake by cells and high levels of cholesterol in the plasma. They emphasized that cholesterol levels within cells are tightly controlled, in part by LDL receptors, and pointed out that the cell's machinery for regulating LDL receptors can be harnessed for therapeutic purposes. In the case of statins, blocking an early step in sterol synthesis deprives hepatocytes of cholesterol, leading to upregulated LDL receptors, increased cholesterol uptake by cells, and lower cholesterol levels. They predicted that statins, if proven safe, would delay the onset of atherosclerotic heart disease.[2]

The most optimistic hopes for statins were fulfilled, but additional strategies are needed. Some patients cannot tolerate statins and maximal cholesterol lowering by statins, typically 40–55%, does not allow many high-risk patients to achieve the recommended target for LDL cholesterol (<70 mg/dl).

For the past 31 years, the LDL receptor and other molecules controlling cholesterol metabolism have been investigated intensely, driven by hopes that the cell's regulatory machinery, if fully understood, could be manipulated for therapeutic purposes. In this regard, PCSK9, a regulator of LDL receptors, has received considerable attention.[3] PCSK9 is secreted into the plasma by the liver and binds to an EGF repeat within the extracellular domain of the LDL receptor. After internalization, the binding of PCSK9 to the LDL receptor strengthens, preventing LDL receptors from recycling to the cell surface and leading to their destruction inside cells.[3] Overexpression of PCSK9 in transgenic mice, or infusions of recombinant PCSK9 into mice, lowers LDL receptor levels on the surface of hepatocytes, leading to hypercholesterolemia.[3] Parabiosis experiments showed that the PCSK9 produced by one mouse enters the circulation of the other mouse and virtually eliminates LDL receptors on hepatocytes.[4] The implication of these studies was obvious: blocking PCSK9's capacity to destroy LDL receptors could lead to more LDL receptors on cells and lower plasma cholesterol levels.[3]

Human geneticists have played the leading role in the PCSK9 story. PCSK9 was first uncovered with the discovery that some kindreds with autosomal-dominant hypercholesterolemia have gain-of-function missense mutations in *PCSK9*.[5] Some of the these "cholesterol-raising" mutations alter the structure of PCSK9's "EGF-binding

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interface" so as to increase affinity for LDL receptors and enhance PCSK9's capacity to mediate their destruction.[3] Two years later, Hobbs and Cohen[6,7] identified loss-of-function *PCSK9* mutations in subjects with low plasma cholesterol levels, and it was their studies that spurred interest in PCSK9 therapeutics. Heterozygosity for *PCSK9* nonsense mutations, found in 2% of African-Americans, lowers LDL cholesterol levels by 28% and coronary heart disease risk by 88%. Two young women with a complete loss of PCSK9 had LDL-cholesterol levels of 14 and 16 mg/dl[3]—levels far lower than those achievable with stain therapy. Both women were healthy, and one, a college graduate, worked as an aerobics instructor! Others found no increase in the frequency of *PCSK9* loss-of-function mutations in patients with cancer. These observations were music to the ears of pharmaceutical scientists.

Thus far, most of the effort has focused on developing PCSK-specific monoclonal antibodies that block PCSK9's capacity to destroy LDL receptors. These antibodies bind to PCSK9 with very high affinity, and preclinical studies in primates have been encouraging.[8] In the current issue of the *Journal*, Stein and coworkers[9] report Phase I clinical trials of REGN727, a human PCSK9 monoclonal antibody from Regeneron Pharmaceuticals. REGN727 was administered, intravenously or subcutaneously, to healthy control subjects, FH heterozygotes on atorvastatin, and nonfamilial hypercholesterolemia patients (on or off atorvastatin). In a dose-dependent fashion, REGN727 lowered LDL cholesterol levels by up to 64%, and the percent lowering was similar in patients on or off statin therapy. Cholesterol lowering was prompt, persisted for weeks, and the antibody was well tolerated. At this point, the status of PCSK9 therapeutics appears to be "full-speed ahead." Soon, we can expect more human trials, dissecting the properties of different PCSK9 antibodies and assessing the impact of these agents on lipids, lipoprotein fractions, and biomarkers of atherosclerosis. In the end, evidence of long-term safety, along with data showing protection from coronary disease, will be needed to define the role of these agents in the clinic. High-risk patients who are "not at goal" and statin-intolerant patients could benefit greatly. Patient selection will undoubtedly be influenced by cost-benefit considerations.

In their 1981 editorial,[2] Brown and Goldstein concluded that the "important lesson" of the compactin studies was that "normal regulatory mechanisms can be exploited to lower plasma LDL." The PCSK9 story reinforces this paradigm in an emphatic fashion. And while PCSK9 is an exciting chapter in the cholesterol story, no one should assume it is the last. Indeed, Tontonoz and coworkers recently identified an intracellular protein, IDOL, that (like PCSK9) targets LDL receptors for degradation.[10] As trials of PCSK9 monoclonal antibodies race ahead in lipid clinics, efforts to identify IDOL inhibitors are probably already underway.

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