Regulation of low-density lipoprotein receptors: implications for pathogenesis and therapy of hypercholesterolemia and atherosclerosis

JOSEPH L. GOLDSTEIN, M.D., AND MICHAEL S. BROWN, M.D.

ABSTRACT Low-density lipoprotein (LDL) is the most abundant and the most atherogenic class of cholesterol-carrying lipoproteins in human plasma. The level of plasma LDL is regulated by the LDL receptor, a cell surface glycoprotein that removes LDL from plasma by receptor-mediated endocytosis. Defects in the gene encoding the LDL receptor, which occur in patients with familial hypercholesterolemia, elevate the plasma LDL level and produce premature coronary atherosclerosis. The physiologically important LDL receptors are located primarily in the liver, where their number is regulated by the cholesterol content of the hepatocyte. When the cholesterol content of hepatocytes is raised by ingestion of diets high in saturated fat and cholesterol, LDL receptors fall and plasma LDL levels rise. Conversely, maneuvers that lower the cholesterol content of hepatocytes, such as ingestion of drugs that inhibit cholesterol synthesis (mevinolin or compactin) or prevent the reutilization of bile acids (cholestyramine or colestipol), stimulate LDL receptor production and lower plasma LDL levels. The normal process of receptor regulation can therefore be exploited in powerful and novel ways so as to reverse hypercholesterolemia and prevent atherosclerosis.


IN 1913, a Russian scientist named Anitschkow fed pure cholesterol to rabbits and produced a high level of cholesterol in the blood as well as atherosclerosis in the aorta and coronary arteries.1 He therefore proposed that hypercholesterolemia leads to atherosclerosis. This straightforward demonstration set the stage for the next 50 years of epidemiologic, genetic, and experimental research, which has now established a firm causal link between the blood cholesterol level and coronary atherosclerosis in man.

After the cholesterol connection had been cemented in the late 1950s and early 1960s, the focus of research shifted from measurement of total cholesterol level in blood to mechanistic studies designed to elucidate the factors regulating the level of specific cholesterol-carrying lipoproteins. By the mid 1960s, investigators had established that blood cholesterol is transported in lipoproteins of specific composition.2 The most abundant class of atherogenic lipoproteins in human plasma is low-density lipoprotein (LDL). The 1970s and 1980s saw the discovery of the LDL receptor and the recognition of its role in regulating the level of LDL in plasma.3 The lower the number of LDL receptors, the higher the plasma LDL level and the more florid the atherosclerosis. In this article, we will briefly review recent studies of the molecular biology and genetics of the LDL receptor. We will also discuss how regulatory changes in this receptor may underlie many forms of hypercholesterolemia in man and how this regulatory system can be stimulated by drugs to lower plasma LDL levels.

Receptor-mediated endocytosis of LDL. Two classes of lipoprotein receptors have been identified: (1) those that bind lipoproteins containing exogenous cholesterol absorbed from the intestine, i.e., chylomicron remnant receptors, and (2) those that bind lipoproteins that carry endogenous cholesterol derived from the liver and other nonintestinal sources, i.e., LDL receptors.4-5

The two classes of lipoprotein receptors are produced by different genes that are subject to different forms of metabolic regulation.4-5 Research on the molecular biology and biochemistry of the chylomicron remnant receptor is in its infancy and will not be discussed further in this article.

The LDL receptors were the first lipoprotein receptors to be described; indeed, they are among the best characterized of all mammalian cell surface receptors.
These receptors are present on the surface of essentially all cultured mammalian cells, where they mediate the uptake of plasma LDL, thereby providing growing cells with the cholesterol that they need for membrane synthesis. In the body, most LDL receptors are expressed in the liver, where they supply cholesterol for secretion into bile, conversion to bile acids, and resecretion into the plasma in newly synthesized lipoproteins. LDL receptors are also present in high concentrations in the adrenal cortex and the ovarian corpus luteum, where they function to provide cholesterol for steroid hormone formation.4

The human LDL receptor is a single-chain transmembrane glycoprotein of 839 amino acids (figure 1). It specifically binds lipoproteins that contain apolipoprotein B-100 or the active form of apolipoprotein E. The ligand-binding domain of the LDL receptor comprises the NH₂-terminal 292 amino acids and is composed of a cysteine-rich sequence of 40 amino acids that is repeated seven times with minor variations. The cytoplasmic domain, composed of 50 amino acids at the COOH-terminal end of the protein, serves to direct the receptor to coated pits, where the bound LDL is rapidly internalized. In addition to the ligand-binding domain, the extracellular portion of the receptor contains a 400–amino acid region that is homologous to the precursor for epidermal growth factor and a 58–amino acid region that contains up to 18 O-linked carbohydrate chains attached to serine or threonine residues. The other domain of the receptor is a 22–amino acid membrane-spanning region.6–8

To carry its bound LDL into cells, the cell surface LDL receptor must localize in coated pits, the portals by which many receptor-bound ligands enter cells.6

These pits are regions in which the surface membrane is indented and coated on its cytoplasmic face with the protein clathrin. Within minutes of their formation, the pits invaginate to form coated endocytic vesicles that rapidly shed their coats and fuse with another to become endosomes. Within the endosomes, the LDL dissociates from its receptor, an event that allows the receptor to return to the surface where it binds and internalizes another LDL particle in a process known as receptor recycling.6 After it dissociates from the receptor in...
endosomes, the LDL is carried to lysosomes, where its cholesterol ester component is hydrolyzed and the free cholesterol is liberated for metabolic purposes.3

Genetic defects in the LDL receptor. Genetic defects in the LDL receptor produce familial hypercholesterolemia, a common cause of premature heart attacks.9 Approximately one in every 500 persons inherits a single copy of a mutant LDL receptor gene and therefore suffers from heterozygous familial hypercholesterolemia. The cells of these individuals produce approximately half the normal number of LDL receptors. As a result, LDL is removed from the circulation at half the normal rate, the lipoprotein accumulates in blood to levels twofold above normal, and heart attacks occur typically in the fourth and fifth decades of life. Heterozygous familial hypercholesterolemia causes approximately 5% of all heart attacks in people less than 60 years of age.9

Rarely, two individuals with heterozygous familial hypercholesterolemia marry and both transmit their mutant LDL receptor genes to their offspring. These children have homozygous familial hypercholesterolemia, even though most of them inherit two different mutant LDL receptor genes and therefore are technically compound heterozygotes. These patients have a much more severe clinical syndrome than those with heterozygous familial hypercholesterolemia. Their cholesterol levels are sixfold to 10-fold above normal, and they usually suffer heart attacks in early childhood.

Four classes of mutations in the LDL receptor gene have been identified in patients with familial hypercholesterolemia.5 One class of mutant genes produces no detectable receptors (so-called null alleles). The second class produces receptors that are synthesized in the rough endoplasmic reticulum but cannot be transported to the cell surface and therefore cannot perform their normal function (so-called transport-deficient alleles). The third class of mutations produces receptors that move to the cell surface normally but are unable to bind LDL because of an abnormality in the binding domain (so-called binding-deficient alleles). The fourth class of mutations produces receptors that are transported to the surface and bind LDL but are unable to enter coated pits and therefore cannot carry LDL into cells (so-called internalization-defective alleles).

The precise molecular defects in 11 patients with familial hypercholesterolemia have been elucidated through cloning and sequencing of the relevant portions of the mutant LDL receptor genes.3,6 Study of these mutations has revealed the functions of various domains in the receptor protein. These investigations have also revealed the features of the protein that are required for normal transport to the cell surface.

Lowering plasma LDL by raising LDL receptors. Understanding of the LDL receptor has provided a rational basis for treatment of familial hypercholesterolemia. Patients with heterozygous familial hypercholesterolemia have one copy of the normal receptor gene that can be stimulated to produce an increased number of receptors, thereby overcoming the genetic deficiency.3 The normal gene can be stimulated by capitalizing on the observation that production of LDL receptors is under feedback regulation.10 When cells accumulate excess cholesterol, they reduce their receptors. Conversely, when cells are deprived of cholesterol, they transcribe the LDL receptor genes at a high rate, and they produce increased amounts of the receptor.10–12

In patients with heterozygous familial hypercholesterolemia, the blood level of cholesterol falls in response to agents that lower the content of cholesterol in liver and thereby stimulate the production of LDL receptors.3 Most commonly, this stimulation is achieved through the oral administration of resins, such as cholestyramine and colestipol, that bind bile acids in the intestine, preventing their normal reabsorption and reutilization. With its normal source of bile acids blocked, the liver responds by converting more cholesterol into bile acids, which depletes the liver of cholesterol and causes it to produce increased receptors.13 The effectiveness of bile acid–binding resins can be enhanced by the simultaneous administration of experimental drugs such as compactin and mevinolin that inhibit 3-hydroxy-3-methylglutaryl CoA reductase, an enzyme in the cholesterol biosynthetic pathway. When hepatic cholesterol synthesis is inhibited, the liver develops an even larger increase in LDL receptors to supply needed cholesterol. With a combination of bile acid–binding resins and cholesterol synthesis inhibitors, it is possible to stimulate the normal LDL receptor gene sufficiently to lower plasma LDL cholesterol levels into the normal range in patients with heterozygous familial hypercholesterolemia.14,15

Regulation of LDL receptors: implications for “garden-variety” hypercholesterolemia. Most “normal” individuals living in industrialized countries have plasma LDL cholesterol levels that are severalfold higher than the level necessary to saturate the LDL receptor system for physiologic cholesterol delivery to body cells.3 Epidemiologic and experimental evidence strongly suggests that these levels are in a range that predisposes to atherosclerosis, especially when coupled with another risk factor such as hypertension or smoking. Epidemiologic evidence also suggests that excessive dietary intake of saturated fat and cholesterol is the major factor
responsible for the high levels of blood cholesterol among people living in industrialized countries.\(^3\)

How does a high intake of exogenous saturated fats and cholesterol lead to an increase in plasma LDL, an endogenous lipoprotein that originates in the liver and not in the intestine? Recent biochemical studies have suggested two mechanisms to explain this paradox. Delivery of excessive dietary saturated fat and cholesterol to the liver via the chylomicron remnant receptor may stimulate the liver to produce increased amounts of very low-density lipoproteins (VLDLs) and perhaps LDL. In the face of a fixed removal capacity that is limited by the number of receptors, the increased production causes the plasma LDL level to rise. The problem is made worse because the elevated level of hepatic cholesterol suppresses the activity of the LDL receptor via the feedback mechanism discussed above. The net result of this saturation and suppression of LDL receptors is a marked rise in plasma LDL levels.

The ability of a given individual to resist the “double trouble” of saturation and suppression of LDL receptors in the face of dietary challenges is dictated, in part, by hormonal, nutritional, pharmacologic, and genetic factors (table 1). These factors control the degree to which hepatic LDL receptors are suppressed. The more receptors an individual produces, the lower the plasma cholesterol level. If all other risk factors for atherosclerosis are held constant (for example, smoking, high blood pressure, and platelet aggregation), the individual with the most LDL receptors will have the lowest cholesterol level and therefore will be least vulnerable to a high-fat diet.

**TABLE 1**

Factors that influence the expression of LDL receptors in the liver

<table>
<thead>
<tr>
<th>Factors increasing LDL receptors</th>
<th>Factors decreasing LDL receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal</td>
<td>Genomic</td>
</tr>
<tr>
<td>Thyrroxine</td>
<td>Familial hypercholesterolemia</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Cholesterol feeding (enhanced</td>
</tr>
<tr>
<td>Cholesterol deprivation</td>
<td>by saturated but not polynsaturated fatty acids)</td>
</tr>
<tr>
<td>Starvation (rats and dogs, but not rabbits)</td>
<td>Nonfat diet of casein and wheat starch</td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>Starvation (rabbits, but not rats and dogs)</td>
</tr>
<tr>
<td>1/2-ethyl estradiol</td>
<td>Bile acid-binding resins (cholesterol and colesterol)</td>
</tr>
<tr>
<td>Inhibitors of HMG CoA reductase (compakcin and mevinolin)</td>
<td></td>
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</tbody>
</table>

The common “garden-variety” or polygenic forms of hypercholesterolemia that are so prevalent in industrialized societies are likely to be explained by the interplay of genetic and environmental factors discussed above. This genetic-environmental interaction may also explain why some large-scale epidemiologic studies that do not consider genetic and hormonal variability fail to show a direct relation between dietary fat intake and plasma LDL levels. Differences in individual responses to dietary fat and cholesterol may underlie much of the current confusion and controversy that surrounds the formulation of nutritional recommendations for the population at large. A diet that is well suited to some individuals may be ill advised for others.

**References**

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