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Pharmacological regulation of low density lipoprotein receptor expression: Current status and future developments

Marc Issandou *

GlaxoSmithKline, 25 Avenue du Quebec, 91951 Les Ulis Cedex, France

Abstract

Plasma levels of low-density lipoprotein (LDL) cholesterol are considered to be a major risk factor for the development of cardiovascular diseases. The LDL receptor is the key component in the maintenance of cholesterol homeostasis in the body, playing a pivotal role by regulating the hepatic catabolism of LDL cholesterol. Many clinical studies using statins, which up-regulate the LDL receptor expression via a feedback mechanism, have demonstrated that the reduction of LDL cholesterol levels lowers the incidence of cardiovascular events in both primary and secondary prevention. In this context, new strategies designed to increase hepatic LDL receptor activity can be considered as attractive opportunities for future therapy. Several potential new drugs have been described in the last decade to up-regulate LDL receptor expression in vitro and in vivo, thus allowing the identification of new transcriptional and post-transcriptional mechanisms.

Keywords: Dyslipidemia; LDL cholesterol; Lipid metabolism; LDL receptor

Abbreviations: LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; apoB, apolipoprotein B; SREBP, sterol responsive element binding protein; SCAP, SREBP cleavage activating protein; Insig, insulin-induced gene; NPC, Niemann-Pick Type C; OM, oncostatin M; MAP, mitogen activating protein.

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1. Introduction

Epidemiological data show unequivocally that elevated plasma low density lipoprotein (LDL) cholesterol concentration is a major risk factor for atherosclerosis (Cantos & Iskandrian, 2003; Grundy, 2000; Nabel, 2003). Numerous clinical trials involving cholesterol lowering therapy have established that intervention to reduce LDL cholesterol levels lowers the risk of development of clinical coronary heart disease. Additional lipid-lowering therapies are in clinical and pre-clinical development (Bays & Stein, 2003; Best & Jenkins, 2001; Wierzbicki, 2004), and are aimed at identifying new agents affecting other lipids such as high density lipoprotein (HDL) cholesterol or triglycerides (TG), but at the moment only reduction of LDL cholesterol has been demonstrated to reduce morbidity and mortality from coro-

* Tel.: +33 1 69 29 60 69; fax: +33 1 69 07 48 92.
E-mail address: MI18785@GSK.com.

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nary heart disease (Cholesterol Treatment Trialists Collaborators, 2005; Downs et al., 1998; Scandinavian, 1994). Thus LDL cholesterol can be considered to be the main proven target in lipid-lowering therapy for cardiovascular diseases. LDL lowering has been the key strategy for successful registration of lipid lowering therapies, even those which have significant additional activities. While a great deal of research and development effort is being focussed on the identification of HDL and TG modulating therapies, this review will focus on LDL cholesterol reduction, mainly through LDL receptor up-regulation.

The plasma LDL cholesterol concentration is determined primarily by the liver due to the fact that this tissue is on one hand the site of formation and production of apolipoprotein B (apoB)-containing lipoproteins, considered to be precursors of LDL particles, and on the other hand, the site where the bulk of receptor-mediated clearance of LDL cholesterol takes place (Dietschy et al., 1993). The hepatic LDL receptor is responsible for the binding and subsequent cellular uptake of apoB- and apoE-containing lipoproteins and any disregulation in this process results in hypercholesterolemia. Genetic defects in the LDL receptor are associated with familial hypercholesterolemia. It has been well established, in both homozygous and heterozygous LDL receptor deficiency, that the rate of LDL catabolism is determined by the number of functional LDL receptors present at the cell surface (Hobbs et al., 1992). Increasing surface LDL receptor abundance in the hepatocyte, whether by gene therapy or by a pharmacological intervention, has been demonstrated to increase the hepatic clearance of LDL cholesterol and to reduce serum LDL cholesterol levels (Defesche, 2004; Jeon & Blacklow, 2005; Rudenko & Deisenhofer, 2003). This increase in uptake of extracellular cholesterol by the liver does not lead to cholesterol overloading as a complex series of feedback mechanisms are triggered such as inhibition of de novo cholesterol synthesis and storage of excess cholesterol in the form of cholesteryl esters (Kovanen & Schneider, 1999). Thus the activity of the LDL receptor is considered to be the key factor which determines the concentration of circulating LDL cholesterol. For this reason intensive research over the last decade has been initiated to better understand the mechanism of regulation of LDL receptor expression and to identify points for pharmaceutical intervention.

The current pharmacological agents of choice for LDL cholesterol lowering in the clinic are the statins, a class of drugs which act through inhibition of cholesterol synthesis and subsequent increase in hepatic LDL receptor expression (Endo, 1992; Jones et al., 1998; Kreisberg & Oberman, 2003). Various other small molecules have recently been described to up-regulate LDL receptor expression or activity and some of them may represent attractive approaches for future therapy in dyslipidemia. Some have been shown to regulate LDL receptor at the transcriptional level while others may act at a post-transcriptional level. This review focuses on new agents that affect the activity of the LDL receptor in hepatic cells and considers their potential utility as lipid-lowering therapies.

2. Regulation of the LDL receptor by a sterol-dependent mechanism

Expression of the LDL receptor is predominantly controlled at the transcriptional level by the intracellular cholesterol pool acting through a negative-feedback mechanism (Brown & Goldstein, 1986; Goldstein & Brown, 1990). This process involves a family of proteins named sterol responsive element binding proteins (SREBPs) (Brown & Goldstein, 1997). SREBPs directly activate the expression of the LDL receptor as well as some 30 genes involved in the metabolism of cholesterol, fatty acids, TG and phospholipids. SREBPs belong to the basic helix-loop-helix-leucine zipper family of transcription factors, which are synthesized as inactive precursor proteins in the endoplasmic reticulum. To reach the nucleus and modulate transcription, SREBPs undergo two proteolytic cleavage steps to release the NH_2-terminal domain that constitutes the mature active form of SREBP which is able to bind to a sterol responsive element (SRE) located in the promoter/enhancer regions of the target genes (Briggs et al., 1993). Three isoforms of SREBP have been identified; two of them, SREBP1a and SREBP1c, are produced from a single gene by alternative splicing, while the third one, SREBP2, is encoded by a different gene. It is generally accepted that SREBP1 regulates the expression of genes involved in fatty acid and TG metabolism while SREBP2 regulates the expression of genes involved in cholesterol homeostasis (Horton, 2002; Horton et al., 2002; McPherson & Gauthier, 2004; Shimano, 2001; Weber et al., 2004). Recently, two additional proteins, named SREBP cleavage activating protein (SCAP) and insulin-induced gene (Insig), have been described as playing a role in the maturation process of SREBPs (Attie, 2004; Edwards et al., 2000; Loewen & Levine, 2002). SCAP retains SREBP in the endoplasmic reticulum and when cholesterol concentration falls in the cell the complex of SCAP and SREBP transfers to the Golgi prior to proteolytic cleavage (Fig. 1) (Brown et al., 2002; Espenshade et al., 2002; Sakai et al., 1998). Insig retains the SCAP/SREBP complex in the endoplasmic reticulum when the cholesterol concentration is high, thus preventing its translocation to the Golgi (Fig. 2) (Adams et al., 2004; Yabe et al., 2002; Yang et al., 2002).

There is still some uncertainty as whether cholesterol acts directly on Insig or on another protein which could be the sterol sensor of the cell (Radhakrishnan et al., 2004; Sun et al., 2005). Thus the Insig/SCAP/SREBP complex monitors the intracellular cholesterol concentration and regulates the expression of genes involved in cholesterol homeostasis including LDL receptor.

Pharmacological agents have been described to up-regulate the expression of LDL receptor by interfering in the Insig/SCAP/SREBP pathway, most notably the statins. Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzymeA reductase, the rate-limiting enzyme in cholesterol synthesis. Inhibition of this enzyme results in a decreased intracellular cholesterol concentration and allows maturation of SREBP leading to increased transcription of the LDL receptor gene, an increase in its activity and subsequently enhanced uptake of