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Review

Low-density lipoprotein receptors in liver: Old acquaintances and a newcomer

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ABSTRACT

The lipoprotein receptors low-density lipoprotein receptor (LDLR), the low-density lipoprotein receptor-related protein 1 (LRP1) and megalin/LRP2 share characteristic structural elements. In addition to their well-known roles in endocytosis of lipoproteins and systemic lipid homeostasis, it has been established that LRP1 mediates the endocytotic clearance of a multitude of extracellular ligands and regulates diverse signaling processes such as growth factor signaling, inflammatory signaling pathways, apoptosis, and phagocytosis in liver. Here, possible functions of LRP1 expression in hepatocytes and non-parenchymal cells in healthy and injured liver are discussed. Recent studies indicate the expression of megalin (LRP2) by hepatic stellate cells, myofibroblasts and Kupffer cells and hypothesize that LRP2 might represent another potential regulator of hepatic inflammatory processes. These observations provide the experimental framework for the systematic and dynamic analysis of the LDLR family during chronic liver injury and fibrogenesis.

1. Introduction

The liver plays the central role in maintaining metabolic homeostasis and is responsible for the energy supply of the whole organism. Besides, the liver represents an important barrier in the immunological defense against antigens infiltrating the body via the gastrointestinal tract. Liver resident macrophages (Kupffer cells) are critical for the homeostasis and regulation of inflammation.

2. The hepatic lipid metabolism

A crucial role of the liver is the regulation of lipid metabolism, including the uptake of lipoproteins from plasma. There are two types of primary lipoproteins: intestinal chylomicrons and hepatic very-low-density lipoproteins (VLDL), which are composed of triacylglycerides (TG), cholesterol, phospholipids, and apolipoproteins. Chylomicrons are assembled postprandially by the intestinal epithelium. The hydrolysis of TG from chylomicrons by lipoprotein lipase (LPL) in the circulation and hepatic lipase (HL) yields chylomicron remnants, which are internalized by hepatocytes in an apolipoprotein (apo) E-mediated process. VLDLs are produced by the liver and are responsible for the transport of TG to other tissues. Through the activity of LPL, fatty acids are released, and VLDLs are converted to VLDL remnants, which exhibit an atherogenic potential. While a main part of these VLDL remnants (more than 50%) are directly internalized by the liver in an apoE-mediated process, further hydrolyzation of VLDL remnants yields low-density lipoproteins (LDL). These LDL reduce their apoE content but contain one apoB100 molecule that is responsible for their internalization into the liver [1–3].

LPL is the rate-limiting enzyme for the hydrolysis of the TG core of circulating TG-rich lipoproteins. LPL is synthesized by parenchymal cells and localized at the inner surface of capillaries of adipose tissue, heart and skeletal muscle via glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 [4,5]. Its activity is modulated by apoproteins and angiopoietin-like proteins (ANGPTL) in dependence of the nutritional state and hormonal signals. Lipoprotein-associated apoA-V activates proteoglycan-bound LPL, whereupon the negatively charged proteoglycan facilitates the interaction with the substrate and accelerates the hydrolysis of TG-rich lipoproteins either directly or via apoC-III [6,7]. ANGPTL-3 and ANGPTL-4 inhibit the activity of LPL by promoting degradation or direct inactivation, respectively [4,8]. In addition to its catalytic function, LPL is a structural element of postprandial apoB-containing lipoproteins and facilitates their hepatic clearance ([9,10]. In addition to its LPL-activating function, apoA-V has been shown to interact with lipoprotein receptors, thereby promoting directly to the endocytic uptake of lipoproteins [7,11]. The identification of human apoAV variants in patients with hypertriglyceridaemia confirms the important role of apoAV in human triglyceride metabolism [12].

Two members of the low-density-lipoprotein receptor (LDLR) family, low density lipoprotein receptor (LDLR) [13] and LDLR-related protein 1

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(LRP1) [14] mediate the endocytotic uptake of VLDL, VLDL remnants, LDL and chylomicron remnants into the liver.

3. The low-density lipoprotein receptor family

The LDLR family consists of a class of closely related endocytotic type I transmembrane cell surface receptors, which are composed of a large extracellular domain, one transmembrane domain, and a relatively short cytoplasmic tail. The core family represents seven members in mammals (LDLR, very-low-density-lipoprotein receptor [VLDLR], LRP1, LRP1B, Megalin/LRP2, LRP4, Apoer2/LRP8), which are characterized by the high structural similarities of their extracellular domains (Fig. 1). The first structural motif is a cluster of ligand-binding repeats, each of which comprises about 40 amino acids, including six cysteine residues involved in disulphide bond formation [15]. The second conserved motif represents the epidermal growth factor (EGF) homology region, which consists of two EGF repeats, followed by six YWTD repeats forming a compact β-propeller [16], and another EGF repeat. This region is responsible for the pH-dependent release of the ligand into the lysosomal compartment and the recycling of the receptor [17] The cytoplasmic tails of the receptors are not very well conserved apart from one to three NPXY consensus sequences, which account for sorting of the receptors [18], coated pit-mediated endocytosis, and the binding of signaling proteins.

4. The low density lipoprotein receptor (LDLR) and its function in lipoprotein metabolism

The LDLR was first described by Brown and Goldstein [13] about 40 years ago as the receptor responsible for the uptake of cholesterol-rich LDL particles. Several years later the genes encoding LDLR in humans and mice were identified [15,19]. The deduced primary structures of the proteins encompass 839 or 841 amino acids, respectively, yielding a molecular weight of the receptor of 95 kDa. LDLR exhibits a relatively simple structure as compared to larger members of the LDLR family. The extracellular domain of the glycoprotein receptor is composed of one cluster of seven ligand-binding repeats, followed by one EGF homology region and one O-linked sugar domain with 18 serin/threonine-linked oligosaccharides. A membrane spanning region of 22 amino acids anchors the protein into the cell membrane. The cytoplasmic tail (CT) of LDLR encompasses 50 amino acids and one FXNPXY motif, which is important for the apoB-100-mediated uptake of LDL (Fig. 1) [20,21].

An important regulator of hepatic LDLR is the secreted proprotein convertase subtilisin-like/kexin type 9 (PCSK9), which binds to the extracellular EGF homology region of the receptor and promotes receptor degradation instead of recycling. This regulatory mechanism might prevent the reuptake of nascent VLDL by the liver, and rare *PCSK9* 'gain-of-function' mutations have been identified as cause of autosomal-dominant hypercholesterolemia [22–24].

The endocytosis of the receptor and its ligand is characterized by the aggregation in clathrin coated pits and subsequent internalization. Classical models of clathrin coated pits described them as aggregates of clathrin and the assembly protein AP-2 [25,26]. Consistently, binding of peptides containing the FXNPXY motif to the clathrin adaptor AP-2 or to clathrin was demonstrated using surface plasmon resonance and UV crosslinking [27] and nuclear magnetic resonance measurement [28], respectively. Therefore, LDLR can directly interact via clathrin or AP-2 with the internalization machinery of coated pits for cargo uptake. However, further work in this field provided evidence for alternative sorting proteins. RNA interference experiments demonstrated that LDLR chimera containing the LDLR tail were internalized into AP-2 depleted HeLa cells but not into clathrin depleted cells [29], thus indicating an AP-2 independent internalization mechanism. The protein Disabled-2 (Dab2) represents an alternative pathway, as it colocalizes together with clathrin, AP-2 and LDLR in coated pits [30]. In vitro studies demonstrated the binding of fusion proteins containing the protein-interaction domain/phosphotyrosine-binding domain (PID/PTB) of Dab2 and peptides containing the FXNPXY

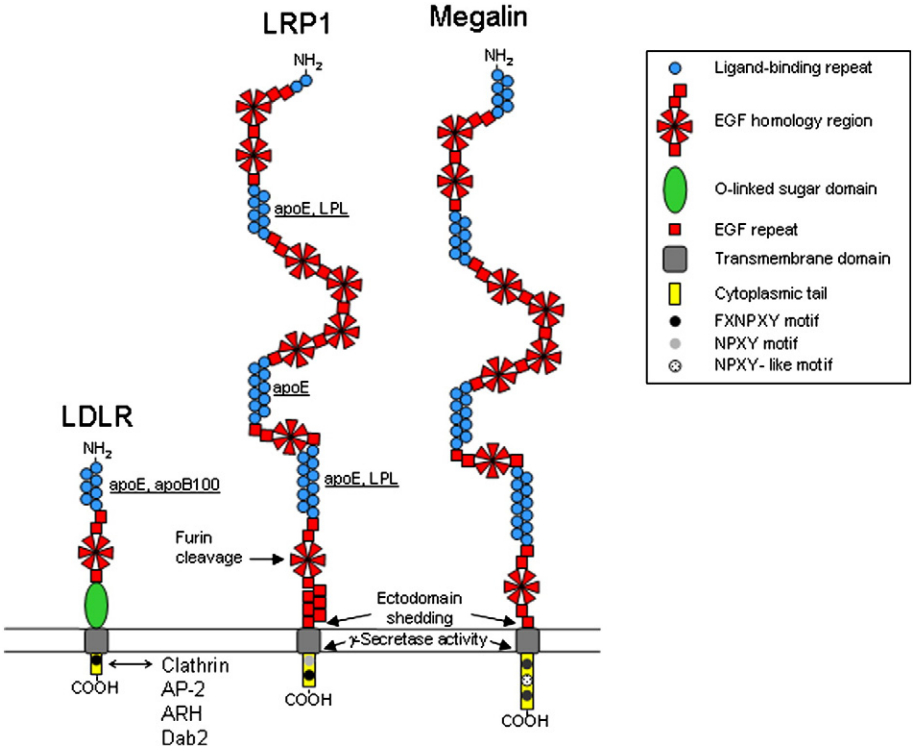

Fig. 1. Schematic presentation of the low-density lipoprotein receptor (LDLR), the LDLR-related protein 1 (LRP1), and megalin (LRP2). The illustration highlights the composition of the receptors and their common structural elements. The interactions of the cytoplasmic tail of LDLR with adapter proteins are depicted by the double arrow. Possible cleavage sites yielding posttranslational modification or truncated forms of the receptors are indicated by arrows. Ligand-binding domains of apoE, apoB100 and LPL are marked. AP-2, assembly polypeptide 2; ARH, autosomal recessive hypercholesterolemia protein; Dab2, disabled-2; and EGF, epidermal growth factor.