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COMMENTARY

Unappreciated role of low-density lipoprotein receptor-related protein 1 in pancreatic β cells: Multiple roles of low-density lipoprotein receptor-related protein 1 in glucose and lipid metabolism

The low-density lipoprotein receptor (LDLR)-related protein 1 (LRP-1) belongs to the LDLR family, which includes LDLR, LRP-2/megalin, very low-density lipoprotein receptor and apolipoprotein E (apoE) receptor 2. Previous studies showed that these receptors have distinct physiological roles in various organs. LRP-1 was originally identified as an endocytic receptor for apoE and α2-macroglobulin; however, accumulated evidence showed that LRP-1 binds not only to these two molecules, but also to various ligands, such as lipoprotein lipase and tissue plasminogen activator. In addition, LRP-1 is now known to function not only as an endocytic receptor, but also as a mediator of cellular signal transduction[1]. LRP-1 is abundantly expressed in hepatocytes, adipocytes, vascular smooth muscle cells and neurons, all of which play a role in systemic metabolism and are closely associated with diabetic complications. The mode of action of LRP-1 clearly suggests its multiple physiological roles in various cells.

In hepatocytes, LRP-1 is known to mediate the endocytosis and degradation of chylomicron remnants, very low-density lipoprotein and so on. Indeed, the *in vivo* ablation of LRP-1 expression in hepatocytes results in decreased insulin-mediated clearance of chylomicron remnants. In addition, mice in which LRP-1 is specifically deleted in the liver showed diet-induced insulin resistance with dyslipidemia and hepatic steatosis, probably as a result of increased hepatic lipogenesis and reduced very low-density lipoprotein secretion. These mice also showed reduced expression of insulin receptors (IRs) on the surface of hepatocytes, as well as decreased glucose transporter 2 translocation. These data suggest that cell surface expression of IRs in hepatocytes seems to be LRP-1 dependent, and that LRP-1 plays an essential role in IR signaling in the liver[2].

LRP-1 is also highly expressed in adipocytes. Considering that LRP-1 mediates the endocytosis and degradation of lipoproteins in hepatocytes, it is not difficult to imagine that LRP-1 in adipocytes plays an important role in lipid accumulation in adipocytes. Indeed, mice in which LRP-1 was specifically inactivated in adipose tissues showed delayed postprandial lipid clearance, reduced bodyweight with smaller fat stores and elevated energy expenditure with lipid-depleted brown adipocytes. These findings show that LRP-1 plays a critical role in adipocyte energy homeostasis. Reduced lipid accumulation in brown adipocytes was shown to result in a shift from fat to muscle tissues for body core temperature maintenance[3]. In contrast, LRP-1 is known to be expressed in glucose transporter (GLUT4)-containing vesicles and to be essential for insulin-dependent glucose transport through GLUT4 translocation from the cytosol to the cell surface in adipocytes. Indeed, LRP-1-depleted adipocytes showed reduced GLUT4 expression and decreased insulin-stimulated glucose uptake[4].

In addition to these roles of LRP-1 in lipid and glucose metabolism in the liver and adipocytes, Ye *et al.*[5] very recently showed a previously unidentified role of LRP-1 in pancreatic β-cells. This group first became interested in LRP-1 because they found that its expression in pancreatic islets was positively associated with plasma glucose levels and negatively associated with insulin levels in *ob*/*ob* mice. Thus, to investigate the causal relationship between decreased islet expression of LRP-1 and decreased β-cell function, they generated β-cells specific LRP-1 knockout (LRP-1-βKO) mice, in which doxycycline was used to specifically knock out LRP-1 in pancreatic β-cells. Under a high-fat diet, LRP-1-βKO mice showed deterioration of glucose tolerance as a result of decreased insulin levels. In addition, these mice showed an insufficient increase in β-cell volume and a decreased β-cell proliferation rate under the high-fat diet. Next, Ye *et al.*[5] explored the reasons for insufficient increase of β-cell volume responding to the insulin resistance induced by the high-fat diet. First, the islets of LRP-1-βKO mice under the high-fat diet showed decreased expression of IR substrate (IRS) 2, IR and IRS1, as well as key transcription factors for β-cell differentiation, such as pancreatic and duodenal homeobox-1, v-maf

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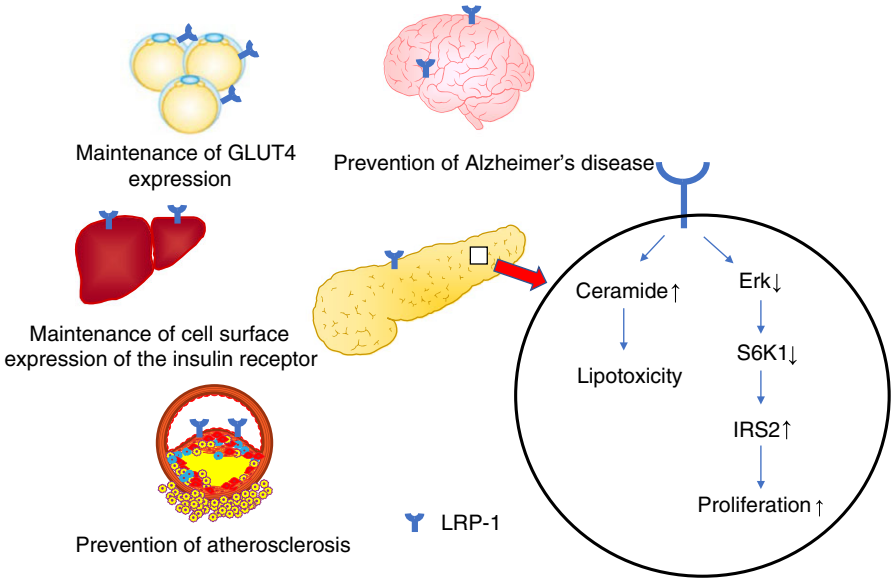

Figure 1 | Schematic representation of multiple roles of low-density lipoprotein cholesterol receptor-related protein 1 (LRP-1) in various tissues. The roles of LRP-1 in various tissues based on the phenotypes of mice with LRP-1 deleted in specific tissues are shown. Ye *et al.*[5] recently showed that LRP-1 in pancreatic β-cells is essential for the proliferation and lipotoxicity of pancreatic β-cells.; Erk, extracellular regulated mitogen-activated protein kinase; GLUT4, glucose transporter 4; IRS2, insulin receptor substrate 2; S6K1, ribosomal protein S6 kinase.

musculoaponeurotic fibrosarcoma oncogene family, protein A and neuronal differentiation 1 (NeuroD1). As previously described, IRS2 in β-cells plays a critical role in the compensatory increase of β-cell volume under an insulin-resistant state[6]. Thus, the decrease in IRS2 expression by LRP-1 deletion seems to be an upstream defect in the insufficient increase in β-cell volume in LRP-1-βKO mice. Furthermore, regarding the cause of decreased IRS2 expression by LRP-1 deletion, extracellular regulated mitogen-activated protein kinase (Erk) and ribosomal protein S6 kinase (S6K1) were activated in the islets of LRP-1-βKO mice receiving the high-fat diet. Given the fact that Erk activates S6K1 and that S6K1 reduces the expression of IRS-2, Erk activation by LRP-1 deletion might be an additional upstream factor that decreases insulin signaling in β-cells. Although reduced IR and GLUT4 expression were observed in LRP-1-deleted hepatocytes and adipocytes, respectively, reduced IRS-2 expression was observed in LRP-1-deleted β-cells. Taken together, this accumulated evidence suggests that LRP-1 deletion impairs insulin signaling by reducing the expression of key factors of insulin signaling in various tissues, but the responsible molecule in each tissue is variable.

LRP-1 plays an important role in lipoprotein endocytosis in hepatocytes and adipocytes. Therefore, the deletion of LRP-1 results in the alteration of the accumulation of lipids in both cell types. Regarding β-cells, exposure to high-fat levels is known to induce β-cell dysfunction, a phenomenon known as "β-cell lipotoxicity." Although the underlying mechanism has not yet been elucidated, several studies suggest that it involves the accumulation of ceramide in β-cells. Intriguingly, decreased ceramide levels have been shown in LRP-1-βKO, suggesting the mitigation of β-cell lipotoxicity.

In addition to its central role in organs and tissues involved in systemic metabolism, LRP-1 plays a key function in other tissues. For instance, LRP-1 is abundantly expressed in smooth muscle cells, and mice in which LRP-1 is specifically deleted in these cells develop aneurysms due to disruption of the elastic layer, proliferation of smooth muscle cells and marked susceptibility to cholesterol-induced atherosclerosis[7]. In addition, mice in which LRP-1 is specifically deleted in macrophages show susceptibility to cholesterol-induced atherosclerosis[8]. Finally, although LRP-1 regulates the apoE gene, a variation of which is the strongest genetic risk factor for Alzheimer's disease, accumulating evidence suggests that LRP-1 in neurons, microglia, astrocytes, vascular smooth muscle cells and pericytes in the brain regulates the metabolism of amyloid-β peptide both in the brain and the periphery[9].

In summary, LRP-1 was originally identified as an endocytic receptor for apoE and α2-macroglobulin. However, this molecule plays broader roles in the metabolism of glucose and lipids, and the diseases associated with diabetes mellitus (Figure 1). Of note, an important hepatokine, selenoprotein P, decreases muscle responsiveness to exercise though LRP-1[10]. As the LRP-1 signal transduction pathway seems to differ markedly among cell types, gaining a clear understanding of the mode of action of LRP-1 is difficult, but understanding this mechanism could provide useful information for new treatment strategies for diabetes and its complications.

DISCLOSURE

The authors declare no conflict of interest.

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