Unique Pathway for Cholesterol Uptake in Fat Cells
Sergio Fazio, MacRae F. Linton

The biologic features of high-density lipoprotein (HDL) cholesterol delivery to the cell have mostly been investigated in hepatocytes, the consensus termination point of the reverse cholesterol transport pathway. It has long been known that the delivery of HDL cholesterol to the hepatocyte does not involve the internalization and degradation of the lipoprotein particle, as is the case for the apolipoprotein (apo)B-containing lipoproteins, but rather it is based on the selective unloading of the cholesterol cargo from the particle into the cell. With the discovery that the scavenger receptor type BI (SR-BI) acts as the hepatic HDL receptor, the final events of HDL cholesterol delivery have been well characterized: HDL binds to SR-BI through apolipoprotein AI (apoAI), the cholesteryl ester (CE) cargo of HDL is selectively unloaded into the cell where it is trafficked back into forming lipoproteins or into the bile, and the lipid-poor apoAI returns in the circulation for another round of peripheral cholesterol collection. Even though this appears to be a systemic mechanism for redistribution of peripheral cholesterol to a central organ in charge of cholesterol disposal, it is possible that alternative processes might have developed so that particular non-hepatic cell types can acquire needed cholesterol from the HDL.

See page 1669

Adipocytes might be unique in their need of acquiring cholesterol, because of their limited ability to synthesize their own. This can be caused by a preferential utilization of acetate for fatty acid synthesis or reduced efficiency of enzymes downstream of squalene synthase in the pathway of cholesterol synthesis. In addition, the membrane pool of fat cells might need large amounts of cholesterol at times of rapidly expanding adipocyte size, both to maintain cellular integrity and to regulate cellular hypertrophy. For this reason, the adipocyte may have developed multiple and partially redundant ways to extract cholesterol from circulating lipoproteins such as the HDL. Because SR-BI is abundantly expressed by adipocytes, it is likely that significant amounts of cholesterol are taken in by these cells through the classic HDL delivery mechanism. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, an article from Drs Vassiliou and McPherson reports on the detailed mechanism of an alternative unique pathway for selective uptake of HDL-derived CE in fat cells. Previous work done in the authors’ laboratory had shown that the uptake of HDL cholesterol in adipocytes occurs in part through noncanonical pathways. For example, they showed that CE transfer protein (CETP) expressed by the adipocyte is involved in the selective extraction of CE from the HDL, and that the transfer of CE can be increased by the use of additional CETP and reduced by the use of an inhibitory antibody against CETP. In other studies, they showed that the low-density lipoprotein (LDL) receptor related protein (LRP) is involved in this process as well, a surprising notion given that LRP is an internalizing receptor fully capable of driving apoB-containing remnant lipoproteins through the endocytic pathway to a destiny of complete lysosomal degradation. Interestingly, LRP needs the presence of a mediator to perform its function in HDL cholesterol extraction from the cell. This mediator, which is present in adipocytes but absent in skin fibroblasts, appears to be apoE, a well-recognized apoprotein that influences the processing and clearance of plasma lipoprotein cholesterol and also influences intracellular cholesterol homeostasis in several cell types.

In the current study, the authors have painstakingly defined the mechanisms for this SR-BI–independent CE selective uptake from HDL in adipocytes. Using both primary adipocytes as well as immortalized liposarcoma cells (SW872), the authors show that this process, responsible for one third of the selective uptake of CE from HDL in fat cells, is fully dependent on the cooperation between apoE and LRP. Indeed, this process: (1) does not normally occur in skin fibroblasts but can be induced by incubating cells with extracellular apoE; (2) is abolished in adipocytes from apoE-null mice; and (3) is abrogated by the effect of the receptor associated protein (RAP) in skin fibroblasts only in the presence of exogenous apoE. It is intriguing that several other interventions affecting LRP-mediated internalization reduced the selective uptake of CE HDL from adipocytes to the level seen in apoE-deficient conditions. The fact that extracellular apoE is able to activate the LRP-dependent pathway indicates that apoE probably works through its positioning on the cell membrane. The authors also show that the CE that transfers from the HDL to the adipocyte through this pathway follow a dual destiny; first they are distributed throughout the cell membrane in a reversible compartment that can be extracted by the presence of extracellular HDL, and then eventually they are positioned in an intracellular compartment not amenable to exchange with HDL in the media. Most of the CE in the reversible compartment are redirected into the extracellular space by a process involving apoE. It is the newly formed particle of apoE and HDL-derived CE that is finally captured by the LRP for a more committed internal-
In the adipocyte, delivery of HDL cholesterol occurs through both SR-BI-dependent and SR-BI-independent mechanisms. The former, likely responsible for the majority of cholesterol acquisition by the cell, is based on the docking of the HDL to the SR-BI and transfer of CE to the cytoplasm. The SR-BI-independent mechanism starts with CE transfer, probably mediated by CETP, from the HDL to the plasma membrane, and continues with the apoE-mediated resecretion (efflux) of the HDL CE followed by its final uptake (recapture) by LRP. This mechanism may be responsible for ~one third of cholesterol acquisition by the adipocyte.

In the near future, influence the distribution of cholesterol to the adipocytes and ultimately affect cellular plasticity and function? (4) Does the cholesterol content of the adipocyte play a role in the development of the insulin resistance syndrome?

In summary, it seems that fat cells consider cholesterol more as treasure than as trash, because they have developed a dual mechanism to extract CE from HDL; one is based on the typical HDL receptor SR-BI, the other is based on a novel “efflux recapture” process that needs apoE and the LRP. Because apoE and LRP are linked in secretion recapture loops also in hepatocytes and macrophages, there may be a biological advantage for the LRP-mediated entry of cholesterol into the cell.

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References

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