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## **Are HDL receptors really located where we think they are in the liver?**

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The central role played by high density lipoproteins (HDLs) in reverse cholesterol transport has been studied in details over the past years. One of the many functions of HDLs is to facilitate the uptake of cholesterol from cells of peripheral organs and to deliver it to the liver where it is transferred to the bile for excretion. Scavenger receptor class B type 1 (SRB1), which is abundantly expressed in the liver, participates in the selective hepatic cholesterol uptake from mature HDL particles [1]. A second recently discovered pathway involves HDL particle uptake by the P2Y13 purinergic receptor [2]. How SRB1 binds to HDLs and unload its cholesterol cargo remains to be precisely determined, as different mechanisms have been proposed, implicating or not HDL particle endocytosis [3, 4].

The experiments studying the implication of SRB1 in reverse cholesterol transport have so far always considered that this occurs in hepatocytes. In our current understanding of reverse cholesterol transport, liver sinusoidal endothelial cells (LSECs) act as a hedgerow separating blood circulation from the space of Disse (the extracellular space located between endothelial cells and hepatocytes), allowing HDLs to passively move from the circulation to the hepatocytes where their cholesterol cargo is processed [5]. Given the known high capacity of LSECs to scavenge many different particles, Ganesan and colleagues evaluated the participation of these cells in HDL metabolism in a study recently published in Scientific Reports [6]. Using two different approaches (high-resolution confocal microscopy of ultrathin section of mouse liver and flow cytometry of purified cell populations), they convincingly conclude that LSECs express substantially more SRB1 than hepatocytes. They explain the discrepancy between their findings and what has been described so far in the literature by technical limitations of earlier approaches.

If hepatocytes really express almost no SRB1, how do HDLs enter hepatocytes to be metabolized and how is cholesterol eventually secreted into the bile? Different routes are possible. Ganesan and colleagues do not exclude that a very small amount of

SRB1, not detectable with current technologies, is present on hepatocytes and mediates the interaction with HDLs. Alternatively, other HDL receptors might mediate the uptake of HDLs in hepatocytes, such as CD36 or P2Y13 [2, 7]. Another possibility is that HDLs captured by the SRB1-bearing LSECs is made available to the hepatocytes by a mechanism involving transcytosis. Similar mechanisms have been observed in other endothelial cells [8, 9]. Whether HDLs that bind to SRB1 expressed on LSECs transcytose as intact molecules or whether unloading of cholesterol already happens in LSECs and only cholesterol is then transferred to hepatocytes remains to be investigated.

Mice and humans are quite different in their lipoprotein metabolism [10]. In mice, cholesterol is mainly transported by HDLs whereas in humans LDLs fulfil this function. This difference comes from the presence of the cholesterol ester transfer protein, present in humans and absent in mice, which allows the transfer of cholesterol from HDLs to LDLs. These species differences highlight the importance of conducting a study on human samples similar to the one mentioned here on SRB1 expression in hepatocytes and LSECs.

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### **Conflicts of interest**

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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The authors of this study provide compelling evidence that SRB1 is more abundantly expressed in liver sinusoidal endothelial cells than in hepatocytes, challenging the current view of how HDL particles are captured by the liver.

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This review provides a detailed up-to-date comparison and critical analysis of the various steps of reverse cholesterol transport in mouse and man.