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A Liver-High-Density Lipoprotein-Ovarian Axis of Fertility

Human plasma transports about 90% of its cholesterol on low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles. LDL delivers its cholesterol to cells primarily through receptor-mediated endocytosis via the LDL receptor pathway discovered by Goldstein and Brown (1) more than 30 yr ago. HDL is somewhat more complicated because cholesterol traffic between HDL and cells occurs in a two-way direction (2, 3). Moreover, lipoproteins carry two forms of cholesterol—cholesterol itself and cholesterol esters. These two molecules have distinct solubility properties and are therefore transported through different mechanisms.

Unlike LDL, HDL delivers cholesterol and cholesterol esters to cells through a process not involving classical receptor-mediated endocytosis. Rather, certain cells (hepatocytes and steroidogenic cells) take up cholesterol esters from HDL particles without taking in the entire particle (4, 5). This selective uptake pathway, first identified by the Pittman and Stein groups (4, 6), was shown by Krieger (7) to be mediated by the scavenger receptor B-1 (SR-BI). In contrast to cholesterol ester traffic, cholesterol traffic between cells and HDL is bidirectional and largely depends on the magnitude of the concentration gradient. Hence, a cholesterol-loaded cell will spontaneously release cholesterol to an HDL particle. This process is in part mediated by SR-BI (8, 9).

Early studies on dynamics of HDL-mediated cholesterol delivery *in vivo* showed that steroidogenic tissues take up substantial amounts of cholesterol from HDL, leading to the inference that this cholesterol is necessary for steroid production (10). This was further supported by the findings that SR-BI is regulated in steroidogenic tissues (11, 12), cholesterol delivered via SR-BI is a substrate for steroidogenesis (11, 12), and steroidogenic tissues are cholesterol ester depleted in the SR-BI−/− mice (12, 13). Thus, the discovery by Krieger's team that SR-BI-deficient female mice are not fertile suggested that they might not be able to supply themselves with sufficient cholesterol ester. But, Krieger's group (14) showed with ovary transplant experiments that in fact the ovaries function normally when placed in wild-type mice. Hence, SR-BI deficiency in a tissue other than the ovary had to be the culprit.

In this issue, Yesilaltay *et al.* (15) show that adenovirus-mediated or stable transgenic expression of SR-BI in the livers of SR-BI knockout mice is sufficient to restore fertility. SR-BI deficiency leads to an accumulation of abnormally large HDL particles with an unusually high content of unesterified cholesterol, apparently because these particles are poor substrates for the plasma enzyme responsible for esterifying cholesterol, lecithin:cholesterol acyl transferase. The rescue by ectopic SR-BI normalizes the HDL size and composition. A mutant form of SR-BI that interacts with LDL but not HDL, normalizes the abnormal HDL of the SR-BI knockout mice and restores fertility, pointing to the abnormal HDL (or the absence of normal HDL) as the basis for infertility.

HDL levels are affected by the ability of cells to secrete its protein components, primarily apolipoprotein A1. Its stability requires a requisite supply of phospholipids and cholesterol, which are delivered by ABC transporters. In the bloodstream, HDL lipids and proteins exchange with other lipoproteins and are modified through the action of lipases, esterases, and lecithin:cholesterol acyl transferase (16). Krieger hypothesizes that there are specific structural requirements for HDL to properly support ovarian function. Given the range of dietary and genetic factors that affect HDL structure, this hypothesis supplies several new categories of candidates to explain the high frequency of human female infertility.

In addition to the major phospholipids and neutral lipids, HDL transports many other hydrophobic molecules; *e.g.* fat-soluble vitamins, dolichol, and other isoprenoids. Thus, it is possible that the abnormal lipoproteins in the SR-BI knockout mice carry inappropriate amounts of essential molecules for proper oocyte maturation or an excess of detrimental molecules. New analytical methods may be able to sort this out.

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Abbreviations: HDL, High-density lipoprotein; LDL, HDL, low-density lipoprotein; SR-BI; scavenger receptor B-1.

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