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Role of mitochondria in steroidogenesis

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Adrenal gonadal, placental and brain mitochondria contain several steroidogenic enzymes, notably the cholesterol side chain cleavage enzyme, P450scc, which is the enzymatic rate-limiting step in steroidogenesis which determines cellular steroidogenic capacity. Even before this step, the access of cholesterol to this enzyme system is both rate-limiting and the site of acute regulation via the steroidogenic acute regulatory protein (StAR) which interacts with a complex multi-component 'transduceosome' on the outer mitochondrial membrane (OMM). The components of the transduceosome include the 18 kDa translocator protein (TSPO), the voltage-dependent anion channel (VDAC-1), TSPO-associated protein 7 (PAP7, ACBD3 for acyl-CoA-binding-domain 3), and protein kinase A regulatory subunit 1α (PKAR1A). The precise fashion in which these proteins interact and move cholesterol from the OMM to P450scc, and the means by which cholesterol is loaded into the OMM, remain unclear. Human deficiency diseases have been described for StAR and for P450scc. Mitochondria also contain several 'downstream' steroidogenic enzymes.

Movement of cholesterol to mitochondria

Mitochondria play highly specialized, indispensable roles in the production of steroid hormones, which are necessary for life-sustaining homeostasis and reproduction in all vertebrates. All steroid hormones (glucocorticoids, mineralocorticoids, estrogens, progestins, androgens, and neurosteroids) are made from cholesterol. The enzymology of steroid biosynthesis from cholesterol has been reviewed

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in detail recently.[1] Steroidogenic cells can employ two potential sources of cholesterol for steroidogenesis. First, cells may synthesize cholesterol *de novo* from acetate via a complex pathway primarily found in the endoplasmic reticulum (ER). However, the robust cholesterol requirements of steroidogenic cells are largely met by importing cholesterol bound to circulating lipoproteins. There are two principal mechanisms for this: uptake of circulating high density lipoproteins (HDL) via scavenger receptor B1 (SR-B1), and uptake of low-density lipoproteins (LDL), which are primarily derived from dietary sources. LDL can suppress the rate-limiting enzyme in cholesterol synthesis, 3-hydroxy-3-methylglutaryl co-enzyme A (HMGCoA) reductase. Cholesterol associated with LDL is taken up by the LDL receptors on the cell surface through receptor-mediated endocytosis. Although receptor-mediated endocytosis of LDL is the principal human source of steroidogenic cholesterol, endogenous synthesis can suffice, as patients with congenital abetalipoproteinemia and low LDL cholesterol have normal basal cortisol concentrations and mildly impaired cortisol secretion in response to adrenocorticotropic hormone (ACTH), and those treated with high doses of statins have no impairment of cortisol secretion. Rodents differ from most other mammals in using HDL cholesterol taken up by SR-B1 as their principal source of steroidogenic cholesterol; HDL and SR-B1 play relatively minor roles in human steroidogenesis. Thus steroidogenesis requires coordinated regulation of the cellular uptake, transport, and utilization of cholesterol followed by a series of unique biosynthetic steps. These processes are coordinated by the sterol regulatory element binding proteins (SREBPs), a family of basic helix–loop–helix transcriptional regulators that are also involved in lipid metabolism and adipocyte differentiation. The biochemistry and cell biology of intracellular cholesterol trafficking have been reviewed recently[2] (Fig. 1).

Irrespective of source, steroidogenic cholesterol is stored in lipid droplets as cholesteryl esters. After circulating LDL particles are internalized by endocytosis, the resulting endocytic vesicles fuse with

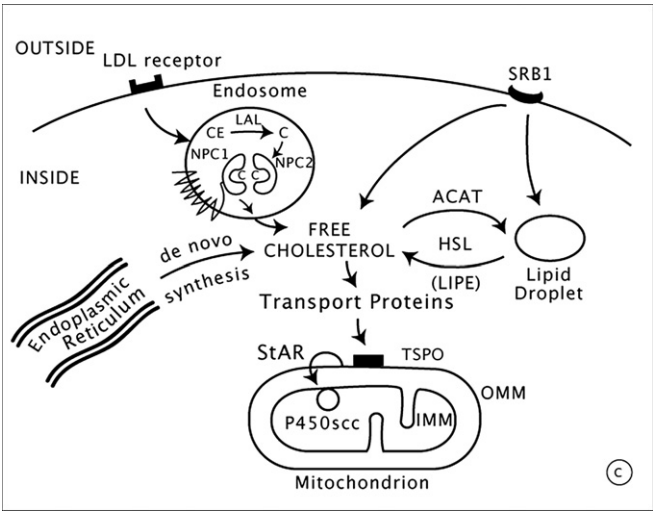

Fig. 1. Intracellular cholesterol economy. Human steroidogenic cells take up circulating low-density lipoproteins (LDL) by receptor-mediated endocytosis, directing the cholesterol to endosomes; rodent cells principally utilize cholesterol from high-density lipoproteins (HDL) via scavenger receptor B1 (SRB1). Cholesterol can also be synthesized *de novo* in the ER. Cholesteryl esters are cleaved in endo-lysosomes by lysosomal acid lipase (LAL); free cholesterol is then bound by NPC1, transferred to NPC2, and exported. The MLN64/MENTHO system resides in the same endosomes as the NPC system, but its role in cholesterol trafficking remains unproven. Cholesterol can be re-esterified by acyl-CoA: cholesterol transferase (ACAT) and stored in lipid droplets as cholesteryl esters. Free cholesterol may be produced by hormone-sensitive lipase (HSL). Cholesterol may reach the outer mitochondrial membrane (OMM) by non-vesicular means by utilizing cholesterol transport proteins such as those with START domains. Movement of cholesterol from the OMM to the inner mitochondrial membrane (IMM) requires the multi-protein 'transduceosome' on the OMM, as shown in detail in Fig. 3. In the adrenal glands and gonads, the hormone-induced steroidogenic acute regulatory protein, StAR, is responsible for the rapid movement of cholesterol from the OMM to the IMM, where it can be converted to pregnenolone by P450scc (CYP11A1). (© W.L. Miller).