Cholesterol Enters the Fetal Circulation in Humans via ATP-binding Cassette Transporters A1 and G1

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While maternal-fetal cholesterol transfer may serve to compensate for insufficient fetal cholesterol biosynthesis under pathological conditions, it may have detrimental consequences under conditions of maternal hypercholesterolemia leading to pre-atherosclerotic lesion development in fetal aortas. Maternal cholesterol may enter fetal circulation by traversing syncytiotrophoblast and endothelial layers of the placental barrier. We hypothesized, that endothelial cells (EC) of the feto-placental vasculature display a high and tightly regulated capacity for cholesterol release. Using primary EC isolated from human term placenta (HPEC), we investigated cholesterol release capacity and examined transporters involved in cholesterol efflux pathways controlled by liver-X-receptors (LXRs), key regulators of cholesterol metabolism. HPEC demonstrated 2.5-fold higher cholesterol release to lipid-free apolipoprotein (apo)A-I than human umbilical vein EC (HUVEC), while both cell types showed similar cholesterol efflux to high-density lipoproteins (HDL). Interestingly, treatment of HPEC with LXR activators increased cholesterol efflux to both types of acceptors, while no such response could be observed for HUVEC. In line with enhanced cholesterol efflux, LXR activation in HPEC increased expression of ATP-binding cassette transporters ABCA1 and ABCG1, while not altering expression levels of ABCG4 and scavenger receptor class B, type I (SR-BI). Pharmacological inhibition of ABCA1 or silencing of ABCG1 by RNAi decreased cholesterol efflux to HDL_3 (-57%) and apoA-I (-70%), respectively. Thus, EC of the placental barrier exhibit unique, efficient and LXR-regulated cholesterol efflux mechanisms when compared to vascular bed EC (HUVEC). We propose a sequential pathway mediated by ABCA1 and ABCG1, respectively, by which HPEC participate in forming mature HDL particles in the fetal blood.