Title: The retroendocytosis pathway of ABCA1/apoA-I contributes to HDL formation
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Abstract: ATP-binding cassette protein A1 (ABCA1) mediates transfer of cellular free cholesterol and phospholipids to apolipoprotein A-I (apoA-I), an extracellular acceptor in plasma, to form high-density lipoprotein (HDL). It is currently unknown to what extent ABCA1 endocytosis and recycling contribute to the HDL formation. To address this issue, we expressed human ABCA1 constructs with either an extracellular HA tag or an intracellular GFP tag in cells, and used this system to characterize endocytosis and recycling of ABCA1 and apoA-I. Under basal conditions, ABCA1 and apoA-I are endocytosed via a clathrin- and Rab5-mediated pathway and recycled rapidly back to the cell surface, at least in part via a Rab4-mediated route; approximately 30% of the endocytosed ABCA1 is recycled back to the cell surface. When receptor-mediated endocytosis is inhibited, the level of ABCA1 at the cell surface increases and apoA-I internalization is blocked. Under these conditions, apoA-I mediated cholesterol efflux from cells that have accumulated lipoprotein-derived cholesterol is decreased, whereas efflux from cells without excess cholesterol is increased. These results suggest that the retroendocytosis pathway of ABCA1/apoA-I contributes to HDL formation when excess lipoprotein-derived cholesterol has accumulated in cells.