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Estrogen reduces LDL transcytosis: A new mechanism of cardioprotection ?

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Editorial

Epidemiological data has documented that women are relatively protected from heart disease prior to menopause while the risk of heart disease is similar in postmenopausal woman and in men. This important finding has stimulated cardiovascular researchers to pursue the gender specific actions of the hormone estrogen. Physiologically, estrogen levels are higher prior to menopause and are reduced in postmenopausal women and this difference correlates with increased cardiovascular risk. Whether the difference in estrogen levels, per se, or the testosterone/estrogen ratio or other hormonal changes that occur during menopause is causal in promoting increased risk is a focal point of intense research.

The movement of blood borne low-density lipoprotein (LDL) across the endothelium and its sub-endothelial retention is critical for the initiation of atherosclerosis. Indeed, atherosclerosis prone segments of vessels accumulate more LDL than do atherosclerosis protected regions suggesting that the increased uptake and reduced transit of LDL provides the kindling for the subsequent bonfire of atherosclerosis. Mechanistically, LDL uptake into the endothelium largely occurs via transcytosis (i.e. luminal endocytosis followed by abluminal exocytosis) and this pathway is non-degradative for ApoB100, unlike the LDL receptor pathway found in all cells. However, the precise receptors and mechanisms critical for endothelial transcytosis are not known, and the effects of estrogen on these pathways have not been explored.

In this issue of ATVB, Ghaffari et al. provide striking evidence that estrogen reduces the transcytosis of LDL in endothelial cells. The first evidence supporting a sex difference in transcytosis derived from experiments in primary cultures of male and female coronary artery endothelial cells. Indeed, the transcytosis rate of LDL, quantified using a novel total

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internal reflectance microscopy method, was greater in coronary endothelial cells isolated from male versus premenopausal, female patients. The reduction in LDL transcytosis in female cells was diminished in cells from a single post-menopausal donor implying that this pathway may contribute to gender biased cardiovascular disease. Remarkably, treatment of arterial endothelial cells with physiological levels of estrogen, reduced LDL transcytosis in male, but not female, endothelial cells.

In order to glean mechanistic insights into how estrogen reduces LDL transcytosis in male cells, the authors focused on three known pathways that mediate LDL transcytosis; SR-B1, ALK1 and caveolin-1. Genetic manipulation or RNAi silencing of these three pathways reduce LDL uptake and transcytosis in vitro and in vivo[–]. Estrogen treatment of male endothelial cells reduced the levels of SR-B1 mRNA and protein, as well as LDL receptor mRNA, but had no effect on the mRNA levels of ALK1 or caveolin-1 protein. Importantly, rescue experiments documented that over-expression of SR-B1 could increase LDL transcytosis in estrogen treated cells and estrogen did not reduce transcytosis further in cells depleted of SR-B1 providing excellent evidence that SR-B1 is the major pathway affected by estrogen. Next the authors delved further into the cellular autonomy of estrogen actions. SR-BI is the main hepatic receptor for HDL mediated reverse cholesterol transport. Treatment of hepatocytes with estrogen had no effect on SR-BI levels but increased LDLR levels and subsequent LDL uptake demonstrating that the unique repressive actions of estrogen on SR-B1 levels in endothelium would reduce LDL uptake by the endothelium but increase hepatic cholesterol clearance.

In order to examine how estrogen impacts SR-B1 levels, the role of canonical estrogen receptors, alpha (ERα) and beta (ERβ), and a more recently described G protein coupled estrogen receptor (GPER) were manipulated. Antagonism of ERα and ERβ did not impair estrogen suppression of SR-B1 and transcytosis, whereas antagonism of GPER pharmacologically or with siRNA did. Therefore, estrogen binding to GPER is necessary for SR-B1 repression and reduced LDL transcytosis. Finally, the levels of SR-B1 were examined in male and female endothelial cells and the levels of SR-B1 protein were elevated in male cells. To determine causality of SR-B1 as an estrogen target, over-expression of SR-B1 in female coronary arterial endothelial cells recapitulated the inhibitory action of estrogen on LDL transcytosis previously seen only in male endothelial cells. Collectively, this innovative, high quality study has uncovered an exciting, unexplored action of estrogen regulating LDL transcytosis.

As with any new discovery, there are a number of interesting questions yet to be explored. For example, how does signaling through GPER repress of SR-B1 and what epigenetic determinants are critical for the cell autonomous actions of estrogen on endothelial cells versus hepatocytes? Why is the GPER-SR-B1 axis repressed or less responsive in cells from presumably premenopausal woman if it is estrogen responsive in male cells? More broadly, how does SR-B1 promote LDL transcytosis if it does not directly bind to LDL? Is it possible that SR-B1, localized in caveolae, is in complex with ALK1 since this protein directly binds LDL? The paper by Ghaffari et al. provides tantalizing new evidence supporting that idea that estrogen may reduce cardiovascular risk by reducing an initiating event in the pathogenesis of atherogenesis namely LDL transcytosis.

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