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Impact of maternal cholesterol metabolism on ovarian follicle development and fertility

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ABSTRACT

The relationship among maternal lipid metabolism, fetal development, and adult disease of the offspring represents an emerging topic of high epidemiological relevance. The present review highlights the very early aspects of this process. Recent data suggest a link between lipid metabolism and reproduction/fertility, not only on the systemic level, but also locally on the level of the ovary that maintains its own sterol metabolism, likely in a self-regulated fashion. Follicular fluid – which surrounds oocytes in a developing follicle – contains all relevant lipoprotein subclasses that reach the follicular fluid either by diffusion, in the case of high-density lipoproteins (HDL), or by local production within the granulosa cells, in the case of very low-density lipoproteins (VLDL). Here, we summarize current knowledge on lipoprotein metabolism in the ovary in the context of fertility, and hypothesize that lipoproteins within follicular fluid are relevant to the development of the early embryo and thereby putatively also to the programming of metabolic disease later in life.

1. Introduction

Cholesterol metabolism is a tightly regulated process that is subjected to very sensitive feedback inhibition (Ye and Debose-Boyd, 2011). For later stages of fetal development it has already been shown that, after placentation, the placenta has an important function in cholesterol transport to the fetus (see Woollett, 2011; Baardman et al., 2013, for a recent overview). However, less is known about the very early regulation of cholesterol metabolism in the follicle that surrounds the oocyte. We will briefly discuss the current concepts of cholesterol handling in the ovarian follicle and the possible clinical implications. Mainly human data will be discussed, unless otherwise stated.

2. Anatomical structure of the ovarian follicle

Ovarian follicular maturation encompasses enlargement of the oocyte, multiplication of follicular granulosa cells surrounding the oocyte, the formation of a fluid-filled antrum between the follicular cells, and differentiation of the surrounding interstitial cells in a thecal cell layer. The follicular fluid (FF) (source of oxygen, buffering molecules, carbohydrates, amino acids, lipids, growth factors, hormones and other molecules, Sutton et al., 2003) and its components are derived by diffusion from the thecal capillaries that surround the follicle, as well as by local production in the theca and follicular granulosa cells. The vascularized outer thecal cell layer is separated from the inner granulosa cells by a basement membrane.

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The capillary endothelium, subendothelial basement membrane, theca interna, follicular basement membrane, and the membrana granulosa form, from the outside to the inside, the blood–follicle barrier that serves as a complex molecular sieve for the transport of components from blood to follicular fluid. Small components pass unimpeded, while larger components pass selectively, or are completely excluded (Siu and Cheng, 2012). Therefore, an altered maternal serum metabolome likely has an impact on the microenvironment of the developing oocyte.

3. Lipoprotein metabolism

Cholesterol is of crucial importance for early mammalian development. First, it determines membrane fluidity, and therefore all proliferating cells require large quantities of cholesterol for membrane synthesis (Willnow et al., 2007; Woollett, 2008). Second, cholesterol, as a precursor of steroid hormones, is pivotal for ovarian follicular maturation (Stouffer et al., 2007). Therefore, substantial quantities of cholesterol need to be either transported to the follicular cells and ultimately the oocyte or synthesized locally by the theca and granulosa cells.

Since cholesterol and even more so, cholesteryl esters, the storage form of cholesterol, are practically insoluble in water, specialized transport systems exist, lipoproteins, to facilitate the exchange of cholesterol between different body compartments via the aqueous phase of the blood or body fluids (Annema and Tietge, 2012). In the systemic metabolism of lipoproteins the liver plays a central role (Dikkers and Tietge, 2010; Annema and Tietge, 2012). In the forward pathway of cholesterol transport, hepatocytes package cholesterol that is either derived from the diet or synthesized within the liver, into large very low-density lipoprotein (VLDL) particles, which are secreted into the blood stream (Dikkers and Tietge, 2010; Annema and Tietge, 2012). VLDLs contains as major structural component, apolipoprotein (apo) B, and are enriched in triglycerides (Shelness and Ledford, 2005). Hydrolysis of the triglyceride component of VLDL by the action of lipoprotein lipase (LPL) remodels VLDL into the smaller and denser low-density lipoproteins (LDL), which can be taken up into virtually any cell of the body in a receptor-mediated fashion (Dallinga-Thie et al., 2010). Besides hepatocytes, enterocytes are a relevant cell type assembling and secreting apoB-containing lipoproteins (Pan and Hussain, 2012), but also other organs such as heart (Boren et al., 1998; Nielsen et al., 1998), placenta (Madsen et al., 2004) or ovary possess this capacity (Gautier et al., 2010; Hussain et al., 2012). Apart from these tissues, microsomal triacylglycerol transfer protein (MTP) can also be detected in the kidney (Krzystanek et al., 2010), in natural killer T cells (Dougan et al., 2005), and in scarce amounts in skeletal muscle (Bartels et al., 2014). In the reverse cholesterol transport pathway, cholesterol is effluxed by specific transporters onto high-density lipoproteins (HDLs) (Annema and Tietge, 2012). HDLs are considerably smaller and more heterogeneous than VLDLs and LDLs, and are formed mainly by hepatocytes (around 70%) and enterocytes (around 30%) (Triolo et al., 2013). HDLs transport cholesterol back to the liver, where, after receptor-mediated uptake, the cholesterol can be either stored or directly secreted into the bile or metabolically converted into bile acids (Dikkers and Tietge, 2010; Annema and Tietge, 2012).

4. Cholesterol transport to and de novo synthesis within the ovarian follicle

In FF HDL is mainly present and only smaller amounts of LDL/VLDL are found (Gautier et al., 2010). Most of the HDL particles present in FF are thought to be derived from the plasma compartment via diffusion through the basement membrane (Jaspard et al., 1997), although formally a contribution of local HDL formation in the ovary has not been excluded. Of note, passive unselected diffusion as a mode of entry of HDL into FF appears unlikely, since in the case of the vascular endothelium it has now been established that directed transcytosis events play a role in the transport of HDL through the endothelial layer (Von Eckardstein and Rohrer, 2009). The precise mechanism of HDL transport through the endothelial cell layer is largely unclear, e.g., the nature of the vesicles involved in this process. However, it is established that from the side of the blood compartment SR-BI and ABCG1 (but not ABCA1) as well as the ecto-F1-ATPase- and P_2Y_{13}-dependent holoparticle uptake are involved. Furthermore, available data indicate that during transcytosis remodeling of HDL occurs, resulting in changes in size and composition (Von Eckardstein and Rohrer, 2009). A similar mode of regulation appears likely in the case of the ovary, as human FF HDL particles contain less cholesterol, but are richer in phospholipids compared with serum HDL particles (Jaspard et al., 1997). Regarding the substantially larger apoB-containing lipoproteins VLDL and LDL, entry into the follicle by diffusion seems even less probable. Rather, VLDLs are locally assembled and secreted by granulosa cells into the FF (Gautier et al., 2010), where they are likely to be remodeled by the hydrolysis of triglycerides through lipoprotein lipase (Camps et al., 1990).

5. Indications for the role of cholesterol in folliculogenesis, steroidogenesis, and immune cell function

Cholesterol is a major constituent for steroidogenesis in theca and granulosa cells. Theca cells surrounding the follicle convert plasma-derived cholesterol into androstenedione under the control of luteinizing hormone (LH). The androstenedione is transported through the basal membrane to the granulosa cells, where it is converted into estrogen by follicle-stimulating hormone (FSH)-induced aromatase. This is called the two cell-two gonadotropin model for hormone synthesis. Estrogen, in turn, is necessary to prevent follicle atresia. In this way cholesterol is indispensable for folliculogenesis (Erickson and Schreiber, 2001).

After ovulation, the granulosa and theca cells differentiate into the luteinized cells of the corpus luteum. Again cholesterol is needed, this time for the production of estrogens and progesterone, which are important for the maintenance of early pregnancy. The source of cholesterol for the highly vascularized corpus luteum is species-specific, e.g. HDL in ruminants and LDL in humans