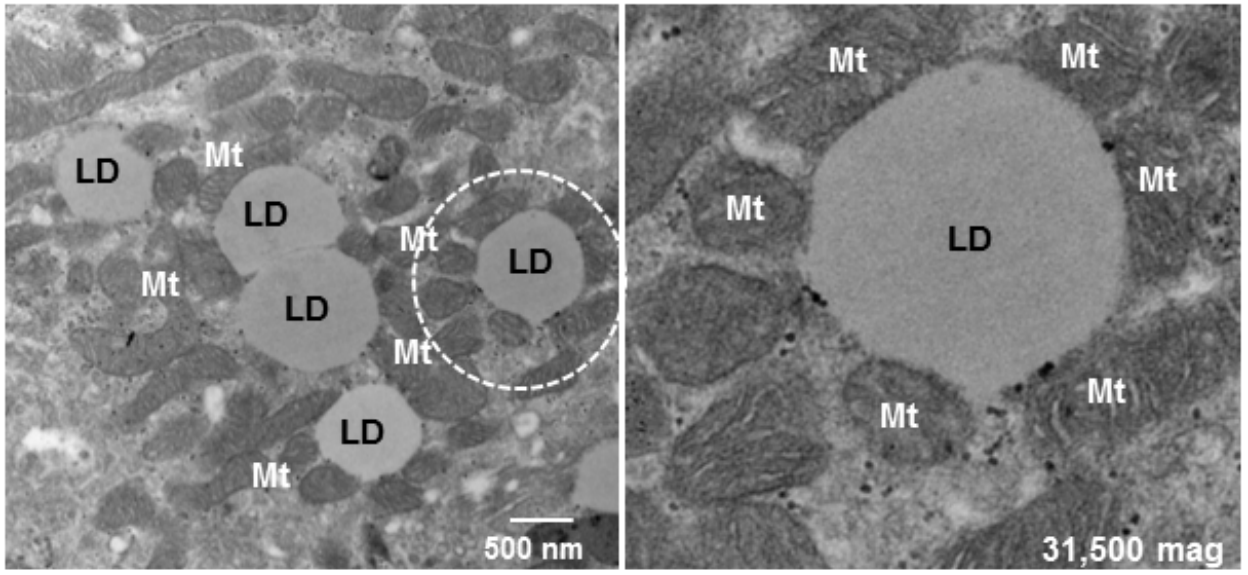
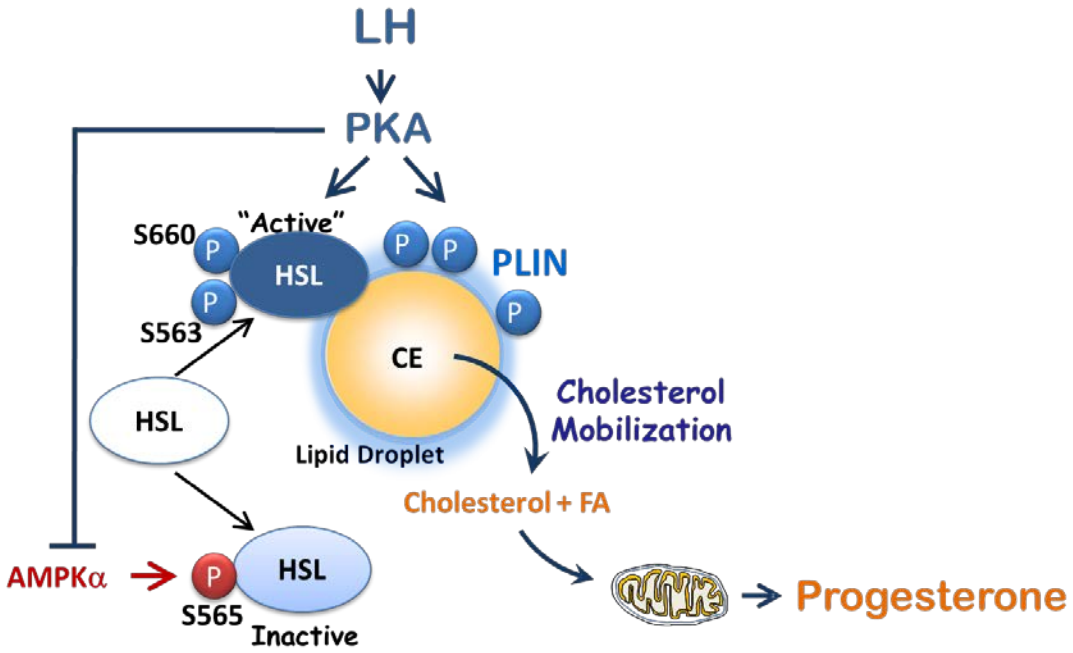
Lipid Droplets (LDs). Recent reviews point to LDs not as simple storage organelles but as critical mediators of health and disease. Lipid droplets store fatty acids and cholesterol esters as reservoirs for energetic substrates (fatty acids) or cholesterol for membrane biosynthesis or sterol production. They also serve to protect cells from lipotoxicity. Key to understanding LD size and activity is the presence or absence of specific LD coat proteins. A family of PLIN proteins (PLIN1-5) serves as LD organizing centers for enzymes and transporters in lipid metabolism. The PLIN family of proteins is composed of PLIN1 (perilipin), PLIN2 (adipophilin or ADRP), PLIN3 (previously Tip47), PLIN4 (previously S3-12) and PLIN5 (previously OXPAT). PLIN1 and PLIN4 are highly expressed in white adipose; PLIN 2, PLIN3 and PLIN 4 are widely expressed, although PLIN2 is abundant in liver, while PLIN5 is found in oxidative tissues like heart and brown adipose. The CIDE (Cell Death-Inducing DFFA-Like Effector) family of proteins also plays a key role in LD formation, in addition to their role in apoptosis. CIDEA is mainly expressed in brown adipose, CIDEB in liver and CIDEC (Fsp27) in white adipocytes. CIDE family members bind to LDs and regulate LD enlargement, thereby restricting lipolysis and favoring storage. CIDEC promotes directional lipid transfer from the smaller to larger lipid droplets. Plin1- and Cidec-null mice have similar phenotypes; reduced fat mass, increased lipolysis and increased β-oxidation. Cidea-null mice have increased lipolysis in brown adipose and are resistant to high-fat diet induced obesity and diabetes. It seems, therefore, that the level of PLINs and/or CIDE proteins in specific cell types can control basal and stimulated rates of lipolysis in target tissues. We will explore the expression of these proteins and how these proteins impact ovarian LDs and ovarian steroidogenesis.



Electron micrograph of lipid droplets (LD) surrounded by mitochondria (Mt) in steroidogenic cells isolated from the bovine corpus luteum.

Hormone-sensitive lipase (HSL) is a key cytosolic enzyme in the regulation of lipid stores that translocates to LDs in response to catecholamine stimulation. A current view of the mechanisms regulating lipolysis suggests that the LD-associated PLIN1 coats the LD and functions as a scaffold in the regulation of lipolysis. Under basal conditions, perilipin acts as a barrier to the hydrolysis of lipids within the LD by preventing access to adipocyte triglyceride lipase and HSL, the major lipases in adipose cells. Following hormonal stimulation of PKA, perilipin and HSL are phosphorylated, which leads to the movement of HSL from the cytosolic compartment to the LD. Once associated with the LD the phosphorylation of HSL may also facilitate its binding to lipid substrates permitting triglyceride hydrolysis to proceed. The presence of both perilipin and HSL in the ovary suggests that LH via a cAMP/PKA signaling pathway may regulate the phosphorylation of perilipin and HSL to hydrolyze cholesterol esters to produce substrate for progesterone synthesis. Studies with HSL-null mice revealed that inhibition of HSL resulted in decreased steroidogenesis in the adrenals and inhibited sperm production in the testis. These findings suggest that HSL is involved in the intracellular processing and availability of cholesterol for adrenal steroidogenesis. Of interest is a report demonstrating an interaction between StAR and HSL in the rat adrenal following treatment with ACTH. Furthermore, the co-expression of StAR and HSL resulted in elevated HSL activity and mitochondrial cholesterol content. While the evidence

points to an important role for HSL in steroidogenesis, there is little information concerning the LD and the events that control this early step in ovarian steroidogenesis.



Proposed mechanism for the activation of hormone sensitive lipase and cholesterol mobilization for the production of progesterone.

Lipidomics: Links to analysis of lipids present in ovarian lipid droplets.

Metabolomics: Links to gonadotropin-induced alterations in cellular metabolites in steroidogenic cells.

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