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Review Article

Ever-changing cell interactions during the life span of the corpus luteum: Relevance to luteal regression☆

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ARTICLE INFO

Article history:
Received 29 June 2013
Accepted 17 December 2013
Available online 4 January 2014

Keywords:
Luteolysis
Prostaglandin F2α
Angiogenesis
Endothelial cells
Immune cells

ABSTRACT

The corpus luteum (CL) undergoes dramatic morphological and functional changes throughout its lifespan. It initially develops from cells that remain in the follicle following ovulation. Eventually the mature CL is composed of multiple, distinctive cell types including steroidogenic cells (small and large luteal cells) and other cell types (endothelial cells, pericytes, fibroblasts, and immune cells). Robust angiogenesis accompanies CL formation, establishing an elaborate blood vessel network at mid cycle. In the absence of embryonic signals, the CL will regress in a process triggered by prostaglandin F2α (PG). Luteal demise in the responsive gland is characterized by cessation of steroid production, angio-regression, and apoptotic cell death, brought about by leukocyte infiltration, inflammatory responses, and diminished angiogenic support. However, the young immature CL is resistant or refractory to the luteolytic actions of PG. Evidence based on functional genomics and other studies highlight the roles played by endothelial, immune, and steroidogenic luteal cells and their interactions in the PG-responsive *vs.* PG-refractory CL.

1. Introduction

The new corpus luteum (CL) develops from cells that remain in the follicle following ovulation. Ovulation that triggers CL formation is an inflammatory-like process [1], characterized by increased blood vessel permeability, formation of capillary sprouts, and leukocyte recruitment [1,2]. For instance, the appearance of eosinophils in early CL parallels angiogenesis and luteinization, thus supporting the notion that eosinophils may influence both events [3]. Eventually, the CL is composed of multiple, distinctive cell types including steroidogenic cells

☆ The material described in this review article was presented as an invited lecture at Ludwig Fraenkel Symposium "Endocrine Control of Corpus Luteum Function" in Wrocław, Poland (5–6 September, 2013).

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1642-431X/$ – see front matter
http://dx.doi.org/10.1016/j.repbio.2013.12.004

(small and large luteal cells) and non-steroidogenic cells (endothelial cells, pericytes, fibroblasts, and immune cells) [4–6]. The different phases of the CL lifecycle are accompanied by dynamic changes in vasculature, the luteal cell populations, and the cell–cell interactions. During its development, the CL undergoes a period of extremely rapid growth that involves hypertrophy, proliferation, and differentiation of the steroidogenic cells, as well as extensive angiogenesis [7,8]. Progesterone production reaches a maximal plateau phase in the mature CL. This is facilitated by an extensive network of blood vessels established at this stage of CL development. The luteal vascular tree is composed of arterioles and venules in the periphery of the CL; however, most of its area is composed of capillaries. Luteal steroidogenic cells differentiate in the presence of a growing capillary network, thus allowing the supply of needed nutrients and hormones and the intimate cellular crosstalk that supports its proper function. More recently, it was shown in rats that CD11c-positive cells, presumably ovarian dendritic cells, accumulate massively in the ovary in response to an ovulatory LH stimulus [9,10]. Furthermore, ovulation was impaired in the absence of these cells [9,10]. Immune cells, specifically neutrophils and macrophages are involved in luteal development and angiogenesis, as reviewed recently by Shirasuna et al. [11]. Later in the cycle, luteal demise is characterized by cessation of steroid production, angio-regression, and apoptotic cell death. These characteristic events are brought about by leukocyte infiltration, inflammatory responses, and diminished angiogenic support [12–16]. This current review describes recent significant advances on the cascade of processes that culminate in luteolysis highlighting the roles of immune and endothelial cells.

2. Prostaglandin F2α-triggered luteal regression

Prolongation of CL life span and progesterone secretion are obligatory for pregnancy maintenance, but the mature CL will regress in the absence of appropriate embryonic signal. Therefore, CL regression is necessary for initiating a new reproductive cycle. Prostaglandin F2α (PG) is the principal hormone triggering luteolysis in species exhibiting an estrous cycle [17,18], including cattle. During a non-fertile cycle, PG is secreted from the uterus, which then triggers CL regression and starts a cascade of events leading to its demise [17,18]. Initially, luteal function is inhibited and plasma progesterone declines. This is followed by apoptosis and structural involution of the CL [19,20]. However, the young or developing CL is refractory to the luteolytic actions of PG [21–24]. Before the CL has acquired luteolytic capacity (earlier than day 5 of the bovine cycle), many of the above-described changes do not occur in response to PG administration. For example, progesterone secretion is not reduced, apoptotic cell death does not occur and the CL continues to develop [17,21,22]. However, multiple studies have demonstrated that refractoriness of early CL to the luteolytic actions of PG is not due to the absence of receptors for PG (PTGFR), which are present in young (PG refractory) and midcycle (PG responsive) CL [25], or due to the total lack of a PG-induced physiological response. A decrease in luteal mRNA for PTGFR and HSD3B1 and an increase in oxytocin production occur in response to PG administered both before and after acquisition of luteolytic capacity [26,27].

Several mechanisms of luteal regression have been suggested to explain the stage-specific response to PG, including indirect effects of nitric oxide [28], endothelin 1 (EDN-1) [27,29–31] and tumor necrosis factor α (TNFα) [32] and direct effects of PG on luteal cells. However, none of these mechanisms satisfactorily explain PG refractoriness of early CL or the luteolytic effects of PG. We hypothesized that differences in PG-induced transcriptional regulatory mechanisms between early *vs.* midcycle CL would reveal key PG-induced changes in gene expression associated with luteolysis and a means of distinguishing responsiveness from resistance to luteolysis. To this end, functional genomics technologies were used to compare PG-induced changes in mRNA transcript profiles for PG-refractory (collected on day 4 of the estrous cycle) *vs.* PG-responsive (collected on day 11 of the cycle) bovine CL [13].

2082 prostaglandin-regulated transcripts were detected in total in day 11 (mature) CL at 4 and 24 h after PG administration, but only 469 prostaglandin-regulated transcripts were detected in PG resistant day 4 CL. A more robust gene expression response to PG was demonstrated for day 11 than for day 4 bovine CL at both 4 and 24 h after PG injection [13] (Fig. 1). Changes in the luteal transcriptome accompanying luteolysis have also been examined in other species. Microarray studies of day 19 CL of pregnancy collected from *PTGFR* mutant and wild-type mice documented specific genes impacted by loss of function of the PG receptor [33]. In primates, transcriptome changes accompanying spontaneous CL regression [34], loss of luteotropic support induced *via* gonadotropin-releasing hormone (GnRH) antagonist administration [35,36] and luteolysis induced by exogenous PG administration [35,36] have also been demonstrated. In cows and monkeys, partial overlap in PG regulated genes was observed in above studies, including [13,35,36], 3 beta-hydroxysteroid dehydrogenase/delta $5 \rightarrow 4$-isomerase type 1 (*HSD3B1*), steroidogenic acute regulatory protein (*STAR*), and luteinizing hormone/choriogonadotropin receptor (*LHCGR*) – genes regulating steroidogenesis, and *SERPINE1* also known as plasminogen activator inhibitor-1. Pharmacological administration of PG can effectively induce luteolysis in all of above species [37,38] as well as other farm animals [17,18].

Day 11 CL (PG responsive) are characterized by a more robust and specific gene expression response to PG than are day 4 (PG refractory) CL. Abundance of only 52 of the 1421 mRNAs (3.7%) in day 11 CL regulated by PG at 24 h after injection was also changed at 24 h after PG injection in day 4 CL. In contrast similar PG-induced regulation of abundance of 23% of transcripts at 4 h after PG in day 11 CL was seen in day 4 CL (Fig. 1). These results demonstrated a significant, albeit transient gene expression response of day 4 CL to PG administration. In addition, <10% overlap in gene ontology categories enriched for PG-regulated genes specific to day 11 CL was observed at both 4 and 24 h after PG injection [13]. However, the receptor activity gene ontology category was enriched for PG-regulated genes encoding transcripts with increased abundance 4 h post PG in day 11 but not day 4 CL [13].