The Corpus luteum: Control and functions

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Introduction. The primate corpus luteum is a transient endocrine gland that differentiates from the ovulatory follicle midway through the ovarian/menstrual cycle (Stouffer, RL et al. Reprod Biol 13:259-271, 2013). Its formation and limited lifespan is critical for fertility, as luteal-derived progesterone is the essential steroid hormone for embryo implantation and maintenance of intra-uterine pregnancy until the placenta usurps this steroidogenic function. The pituitary gonadotropin, luteinizing hormone (LH), and the LH-like hormone, chorionic gonadotropin (CG), are vital luteotropic hormones during the menstrual cycle and early pregnancy, respectively. However, it is increasingly recognized that local factors, including angiogenic factors (e.g., vascular endothelial growth factor, VEGF), prostaglandins (e.g., PGE2 and PGF2α), and steroids (e.g., progesterone) act in an autocrine or paracrine manner to mediate or counteract the luteotropic effects of LH/CG**.**

Methods and Results. Recent advances from this research group identify the critical local role of progesterone and its receptor-signaling pathways in the formation and regression of the monkey (macaque) corpus luteum during the menstrual cycle. First, to examine the role of the genomic progesterone receptor (PGR) in ovulation and luteinization of the dominant follicle, adenoviral vectors (AdV) expressing short-hairpin (*sh*) RNA that recognizes the rhesus macaque PGR or a non-targeted scrambled *sh*RNA (control) were injected into the preovulatory follicle 20 hours before administering an hCG bolus to induce periovulatory events. Follicles injected with the control AdV-scrambled *sh*RNA ovulated in a timely manner, and serum P levels increased to typical (ng/ml) levels in a functional luteal phase. In contrast, intrafollicular injection of AdV-PGR *sh*RNA typically blocked follicle rupture (except one animal) and prevented the rise in circulating P levels. Ovarian samples confirmed the presence of a trapped oocyte in the AdV-PGR *sh*RNA treated follicles and the absence of intense nuclear staining for PGR. In contrast, intense immunohistochemical staining for PGR was evident in the luteinizing follicle wall of control follicles. Second, to determine if the numbers of immune cells or their activity in the primate corpus luteum are regulated by the loss of LH support or indirectly via loss of LH-dependent P production/action, female monkeys received no treatment (controls), a GnRH antagonist (Antide) or Antide plus a progestin (R5020). Antide treatment markedly increased the numbers of CD11b (primarily granulocytes, as well as monocytes and activated lymphocytes) and CD14 (monocytes/macrophages)-positive immune cells in luteal tissue, but not CD16 (natural killer cells)-positive cells. Adding R5020 with Antide reduced the numbers of CD11b- and CD14-positive cells to those of controls. Further studies established that progesterone levels must decline to baseline (0.3 < ng/ml) for 3-4 days at the end of the menstrual cycle for the increase in immune cells to occur. Moreover, these cells produced 16 cytokines during acute incubation in vitro, including chemokines such as MCP-1 and MDC, as well as several interleukins.

Conclusions. The data support the concepts that: (1) induction of P and its receptor in response to the mid-cycle gonadotropin surge is critical for ovulation and luteal development, whereas (2) the decline in P and P-receptor signaling during functional luteal regression is required for subsequent structural luteolysis involving immune cell attraction and activation.

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