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The regulation of ovarian follicle growth, demise and the ovulatory response

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The laboratory deals with basic questions of mammalian ovarian physiology and endocrinology, the control of follicular growth and when a mature preovulatory follicle has evolved, its ovulatory response culminating in the release of a fertilizable ovum.

Follicular growth and selection

Contrary to the naïve thought, degeneration rather than ovulation is the ultimate fate of the vast majority of oocytes. Of the approx. 2 million oocytes in the human ovary at birth only 400 reach ovulation during the fertile life. Each of these oocytes is in a "nest" of supporting cells forming the ovarian follicles. Thus, more than 99,9% of human follicles undergo degenerative changes, referred to as atresia, which involves apoptosis, or programmed cell death of follicular granulosa cells. Follicular atresia is currently examined in collaboration with Atan Gross (see there).

Ovulation

At the present the laboratory works mainly on the resumption of oocyte maturation, which is a component of the ovulatory response. We were the first to establish an *in vitro* system that enabled the discovery of the basic facts of the hormonal regulation of oocyte maturation. cyclic AMP (cAMP) plays a central role in the regulation of meiotic maturation of mammalian oocytes. High oocyte levels of cAMP were implicated in the maintenance of meiotic arrest, and a decrease in the oocyte cAMP is necessary for resumption of meiosis. On the contrary,

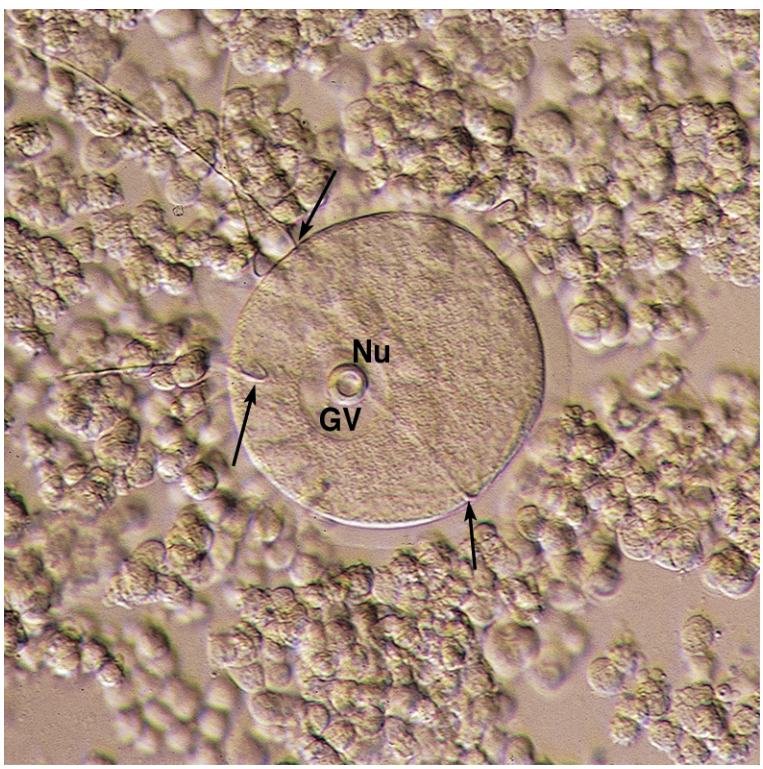

Fig. 1 *An ovulated immature oocyte obtained from the oviduct after treatment with PDE3 inhibitor. Note the several spermatozoa within the perivitelline space (arrows) unable to fertilize.GV-oocyte nucleus; Nu-nucleolus.*

the stimulation of the ovulatory process by luteinizing hormone (LH), including the resumption of meiosis, is clearly associated with a rise in cAMP levels in the somatic cells of the follicle. In collaboration with Professor Conti from Stanford, we have provided a solution to this paradox by invoking the selective regulation of specific phosphodiesterases in the somatic and germ cell compartments of the preovulatory follicle. Differential regulation of PDEs in the somatic (containing PDE4) and germ cell (containing PDE3) compartments of the follicle by gonadotropins seems to be involved in the regulation of their cAMP level. Stimulation of oocyte PDE may explain the paradoxical decline in cAMP levels in the oocyte, allowing resumption of meiosis, concomitantly with its rise in the somatic compartment of the follicle in response to stimulation of ovulation by LH. Furthermore, pharmacologic inhibition of oocyte PDE3 may allow the development of a specific, midcycle contraceptive that does not affect the menstrual cycle (Fig. 1).

The recently suggested role of a meiosis activating sterol (MAS) in the mediation of LH induction of meiosis is being assessed by a combination of pharmacological and molecular biology approaches. These studies did not provide evidence for such a physiological role of MAS. (i) Specific inhibitors of MAS synthesizing enzymes, including lanosterol demethylase (LDM), did not prevent spontaneous or LH-stimulated meiosis at doses that have previously been shown to effectively suppress LDM activity. At higher doses they caused degeneration of oocytes. (ii) The timing of LDM expression in the ovary was incompatible with a role for MAS in meiosis. (iii) The preferential localization of LDM protein in the oocytes (Fig. 2) suggests MAS production in oocytes, rather than its transport from the somatic compartment as expected by the suggested role of MAS in the regulation of meiosis as a putative cumulus-oocyte signal molecule. Finally, (iv) the time-course of resumption of meiosis by MAS revealed a significant delay as compared to oocytes maturing spontaneously or due to hormone-stimulated maturation.

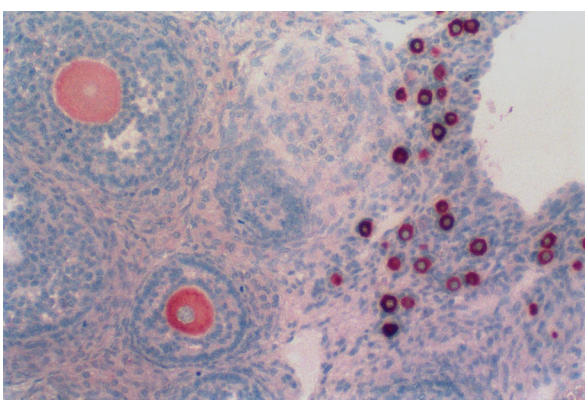

Fig. 2 *Histochemical localization of LDM protein in growing oocytes.*

Selected Publications

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