

<FURTHER DEVELOPMENT 14.1>

Completing the first meiotic division

Oocytes are maintained in the dictyate stage by their outer layer of follicle cells. As early as 1935, Pincus and Enzmann discovered that removing mouse oocytes from the follicle caused the re-initiation of meiosis. The fully grown oocytes within antral follicles are maintained in this first meiotic prophase stage through the action of cyclic GMP (cGMP). This cGMP has two routes from the mural cells to the cumulus cells surrounding the egg. First, cGMP is transported through gap junctions from the outer granulosa cells of the follicle through the cumulus cells of follicle and into the oocyte (Gilula et al 1978; Norris et al. 2009); (**FIGURE 14.4A**). Second, a paracrine factor, C-type natriuretic protein (CNP), is secreted from the mural granulosa cells into the antrum, causing cGMP to be made in the cumulus granulosa cells (Kawamura et al. 2011) from which it is transmitted to the oocyte via gap junctions. Thus, just as the oocyte helped induce a cloud of follicle cells around it, so these follicle cells induce the continued growth of the oocyte.

Once cGMP has accumulated in the oocyte, it blocks phosphodiesterase enzymes from degrading cyclic AMP (cAMP). The resulting increase in cAMP blocks meiosis by maintaining protein kinase A (PKA) in an active state. Active PKA has two ways of blocking meiosis. Both prevent the activity of Maturation Promoting Factor (MPF), the enzyme complex that re-initiates the cell cycle. First, PKA phosphorylates the Cdc25 protein, thus inactivating the activator of MPF. Second, PKA phosphorylates Wee1, thereby activating this inhibitor of MPF (see **Figure 14.4C**; Mehlmann et al. 2004; Han and Conti 2006). Therefore, the mural follicle cells keep the oocyte in meiotic prophase (dictyate stage) until hormones allow division to continue.

Oocyte maturation and ovulation is initiated when LH from the pituitary gland binds to the

mural granulosa cells, and their activated LH receptors lower the concentration of cGMP in the follicle cells, primarily by inhibiting the enzyme that produces cGMP. Because the follicle cells are connected by gap junctions to the oocyte, cGMP in the oocyte diffuses outwards into the large volume of the follicle, lowering the cGMP concentration in the oocyte (Norris et al. 2009; Shuhaibar et al. 2015; Jaffe and Egbert 2017). As a result of the cGMP decrease in the oocyte, cAMP in the oocyte is degraded. In the relative absence of cAMP, two critical events can now occur. First, MPF is reactivated in the oocyte, and this kinase can then phosphorylate the proteins that lead to the resumption of meiosis. Within the follicle, meiosis proceeds to second metaphase, where it pauses again until fertilization (see Section 7.XX). Second, the cAMP decrease activates the myosin that interacts with actin to place the meiotic division near the cortex of the oocyte (Chen et al. 2012). Thus, the first meiotic division is completed and the oocyte nucleus proceeds to the second meiotic division.

References

- Norris R. P., Ratzan W. J., Freudzon M, Mehlmann L. M., Krall J, Movsesian M. A., Wang H, Ke H, Nikolaev V. O., Jaffe L. A. 2009. Cyclic G. M.P from the surrounding somatic cells regulates cyclic A. M.P and meiosis in the mouse oocyte. *Development* 136: 1869–1878.
- Jaffe L. A., Egbert J. R. 2017. Regulation of mammalian oocyte meiosis by intercellular communication within the ovarian follicle. *Annu Rev Physiol* 79: 237–260.
- Han S. J., Conti M. 2006. New pathways from P. K.A to the Cdc2/cyclin B complex in oocytes: Wee1B as a potential P. K.A substrate. *Cell Cycle* 5: 227–231.

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