CSIRO PUBLISHING

www.publish.csiro.au/journals/rfd *Reproduction, Fertility and Development*, 2005, **17**, 1–2

Mouse oocytes control metabolic co-operativity between oocytes and cumulus cells

John Eppig

The Jackson Laboratory, 600 Main Street, Bar Harbor, ME 04609, USA. Email: jje@jax.org

Precise coordination between the development of the oocyte and the ovarian follicle is essential in order to provide an egg that is fully competent to undergo fertilisation and embryo development. A key component of this co-ordination is changing patterns of gene expression and protein synthesis by various populations of granulosa cells throughout follicular development. There are two populations of GCs in large antral (Graafian) follicles: mural granulosa cells (MGCs) that line the follicle wall, and cumulus cells (CCs) closely associated with the oocyte. The fully-grown oocytes of large antral follicles suppress the expression of some genes in CCs that are expressed more highly in MGCs; *Lhcgr* and *Kitl*, for example. To discover genes expressed more highly in CCs than in MGCs, we used subtraction hybridisation. Among the genes expressed more highly in CCs was one encoding an amino acid transporter (*Slc38a3*). *Slc38a3* mRNA was not detected in oocytes. Expression of *Slc38a3* mRNA was reduced in the CCs after removal of the oocyte and restored by co-culturing CCs with fully-grown oocytes. Alanine is one of the amino acids transported by *Slc38a3*. This amino acid is transported poorly across the oocyte plasma membrane, but gains access to the oocyte from the cumulus cells via gap-junctional communication. We found that alanine transport into cumulus cells is promoted by one or more paracrine factors secreted by fully-grown oocytes, but not by growing oocytes from pre-antral follicles. Thus fully-grown oocytes promote the transport of alanine into CCs, and this amino acid is then passed on to the oocyte via gap junctions.

Also among the genes expressed more highly in CCs than MGCs are genes encoding enzymes in the glycolytic pathway. Fully-grown oocytes, but not growing oocytes, promote elevated expression of some of these genes. Likewise, oocytes promote both glycolysis and oxidative phosphorylation by isolated CCs and MGCs. Classical studies by Biggers, Brinster, and others have shown that oocytes do not effectively utilise glucose as an energy source, and that oocytes require the presence of cumulus cells in order to resume meiosis when glucose is the only energy source present. In contrast, oocytes can resume meiosis in the absence of cumulus cells when pyruvate is the sole energy source. Thus oocytes apparently promote glycolysis by their companion granulosa cells to provide energy for their own development. In addition, this may be one way that oocytes coordinate their development with that of follicular somatic components.

These are remarkable examples of metabolic co-operativity between the oocyte and companion cumulus cells controlled by the oocyte. (Supported by Grants HD23839 and HD44416 from the NICHD.)

Bibliography

D'Alessandris, C., Canipari, R., Di Giacomo, M., Epifano, O., Camaioni, A., Siracusa, G., and Salustri, A. (2001). Control of mouse cumulus cell-oocyte complex integrity before and after ovulation: plasminogen activator synthesis and matrix degradation. *Endocrinology* **142**, 3033–3040. doi:10.1210/EN.142.7.3033

Elvin, J. A., Clark, A. T., Wang, P., Wolfman, N. M., and Matzuk, M. M. (1999). Paracrine actions of growth differentiation factor-9 in the mammalian ovary. *Mol. Endocrinol* **13**, 1035–1048. doi:10.1210/ME.13.6.1035

Eppig, J. J. (2001). Oocyte control of ovarian follicular development and function in mammals. *Reproduction* **122**, 829–838. doi:10.1530/REP.0.1220829

Eppig, J. J., Wigglesworth, K., and Pendola, F. L. (2002). The mammalian oocyte orchestrates the rate of ovarian follicular development. *Proc. Natl Acad. Sci. USA* **99**, 2890–2894. doi:10.1073/PNAS.052658699

Gilchrist, R. B., Ritter, L. J., and Armstrong, D. G. (2000). Growth-promoting activity of mouse oocytes is developmentally regulated. *Biol. Reprod.* **62**, 272.

Gilchrist, R. B., Ritter, L. J., and Armstrong, D. G. (2001). Mouse oocyte mitogenic activity is developmentally coordinated throughout folliculogenesis and meiotic maturation. *Dev. Biol.* **240**, 289–298. doi:10.1006/DBIO.2001.0451

Li, R., Norman, R. J., Armstrong, D. T., and Gilchrist, R. B. (2000). Oocyte-secreted factor(s) determine functional differences between bovine mural granulosa cells and cumulus cells. *Biol. Reprod.* **63**, 839–845.

Matzuk, M. M., Burns, K. H., Viveiros, M. M., and Eppig, J. J. (2002). Intercellular communication in the mammalian ovary: Oocytes carry the conversation. *Science* **296**, 2178–2180. doi:10.1126/SCIENCE.1071965

Pangas, S. A., Jorgez, C. J., and Matzuk, M. M. (2004). Growth differentiation factor 9 regulates expression of the bone morphogenetic protein antagonist, gremlin. *J. Biol. Chem.* **279**, 32 281–32 286. doi:10.1074/JBC.M403212200

Rajkovic, A., and Matzuk, M. M. (2002). Functional analysis of oocyte-expressed genes using transgenic models. *Mol. Cell. Endocrinol.* **187**, 5–9. doi:10.1016/S0303-7207(01)00710-9

© IETS 2005 10.1071/RDv17n2paperabs 1031-3613/05/020001

Salustri, A., Hascall, V. C., Camaioni, A., and Yanagishita, M. (1993). Oocyte-granulosa cell interactions. In 'The Ovary'. (Eds E. Y. Adashi and P. C. K. Leung.) pp. 209–225. (Raven Press: New York, NY, USA.)

Su, Y. Q., Denegre, J. M., Wigglesworth, K., Pendola, F. L., O'Brien, M. J., and Eppig, J. J. (2003). Oocyte-dependent activation of mitogen-activated protein kinase (ERK1/2) in cumulus cells is required for the maturation of the mouse oocyte-cumulus complex. *Dev. Biol.* **263**, 126–138. doi:10.1016/S0012-1606(03)00437-8

Sutton, M. L., Cetica, P. D., Beconi, M. T., Kind, K. L., Gilchrist, R. B., and Thompson, J. G. (2003). Influence of oocyte-secreted factors and culture duration on the metabolic activity of bovine cumulus cell complexes. *Reproduction* **126**, 27–34. doi:10.1530/REP.0.1260027

Wu, X., Chen, L., Brown, C. A., Yan, C., and Matzuk, M. M. (2004). Interrelationship of growth differentiation factor 9 and inhibin in early folliculogenesis and ovarian tumorigenesis in mice. *Mol. Endocrinol.* In press.

Yan, C., Wang, P., DeMayo, J., Elvin, J. A., Carino, C., *et al.* (2001). Synergistic roles of bone morphogenetic protein 15 and growth differentiation factor 9 in ovarian function. *Mol. Endocrinol.* **15**, 854–866. doi:10.1210/ME.15.6.854