Journal of Steroid Biochemistry, Vol. 11, pp. 799 to 800
Pergamon Press Ltd 1979. Printed in Great Britain

GRANULOSA–THECAL CELL INTERACTION IN OVARIAN STEROIDOGENESIS

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SUMMARY

1. It is clear from all studies of follicles in many species that the theca under LH control favors androgen production and the granulosa stimulated by FSH favors aromatization. This is consonant with synergism of FSH and LH in follicle development and the synergism of the two cells in oestrogen production.
2. While granulosa and theca from all species have a qualitatively similar production pattern, they differ quantitatively and the human deviates the most with more thecal aromatization and granulosa androgen production than other species.
3. The spectrum of cell steroid production appears to change after luteinization, especially after the acquisition of LH receptors by the granulosa.
4. While the theca may be the sole major source of preovulatory ovarian vein oestrogen in the primate, its limited aromatization in other species precludes this as an absolute phenomenon.
5. Two-cell interaction must be viewed as a species variable dynamic process with changes occurring as each follicle develops during the ovarian cycle.

The interdependence of granulosa and thecal cells for *rat* ovarian follicular oestrogen production was clearly demonstrated by Falck in 1959 [1]. While neither cell type could synthesize oestrogens alone, Falck suggested from a pilot study in a footnote of his paper that progesterone produced by the granulosa might be processed further into oestrogens by the theca.

In 1962, Short, based upon assays of endogenous steroid levels in the *mare* follicle and corpus luteum, introduced a "two-cell theory" which attributed complete oestrogen production to the theca and only progesterone production to the luteinized granulosa cell [2].

Bjersing and Carstensen demonstrated that *porcine* granulosa cells could convert *tracer levels* of androstenedione to testosterone and could aromatize both androgens to oestrogens. Conversion of pregnenolone and progesterone to androgens was limited in the granulosa cell fraction. The theca was less effective in converting androstenedione to testosterone than the granulosa, but more active in aromatization [3, 4]. However, aromatization of *radioactive tracer* testosterone to oestrogen by the mare follicular cells was demonstrated by Ryan and Short[5] with the granulosa cell more active than the theca.

In 1966, Ryan and Petro reported that both the granulosa and theca of the FSH–LH-stimulated preovulatory human ovarian follicle could convert tracer progesterone and pregnenolone to 17-OH progesterone and oestrogens [6]. The theca accumulated androstenedione while the granulosa did not. Subsequently Ryan *et al.* [7] reported that both granulosa and theca from FSH–LH-stimulated human ovarian follicles could each synthesize oestrogens and their steroid intermediates from radioactive acetate, but that both cell types were more effective together in producing oestrogens than either cell type alone. Channing in 1969 [8], using a tissue culture system of human follicular cells, suggested that the theca produced more oestrogen from radioactive pregnenolone than did granulosa and that there was no apparent synergism of the two cell types in oestrogen production. Endogenous production of oestrogen was also greater with human theca than with granulosa cells in culture.

There was obviously no concensus of the true picture of granulosa–theca cell function, and the referenced studies varied in terms of species (rat, porcine, equine, human), steroid measurement (tracer, endogenous precursors) and experimental system (bioassay, endogenous steroid levels, surviving cell incubations, normal and stimulated ovaries and tissue culture).

In 1975, using a hamster ovarian model, Makris and Ryan[9] established a clear-cut synergism of granulosa and thecal cells for oestrogen production from endogenous substrates in tissue culture. Furthermore, the theca favored androgen production and the granulosa aromatization. A new "two-cell theory" involving thecal contribution of androgen for granulosa cell conversion to oestrogen was suggested. This was accompanied by work in the rabbit, rat and sheep [10–14] with the further demonstration that LH-stimulated thecal production of androgen- and FSH-stimulated granulosa aromatase [12, 13].

Channing and Coudert, however, found that in the monkey the *in vivo* removal of follicular fluid and granulosa cells from the major preovulatory follicle did not impede ovarian venous oestrogen output [15].

These disparate data are not in as much conflict as the theories derived from their interpretation and the diverse experimental systems upon which they depend.

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