Editorial

Apoptosis in reproductive biology

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Recent studies aimed at a greater understanding of the occurrence and regulation of cell death in reproductive biology provide a promising new direction for novel approaches to understanding normal and pathological aspects of reproduction. Several instances of physiologically occurring cell death (programmed cell death, PCD), associated with reproduction and described 40 or 100 years ago (i.e. germ cell degeneration, follicle atresia and luteolysis, embryo implantation, homeostatic maintenance and cyclicity of non-gonadal reproductive tissues), are now being re-examined by novel morphological, biochemical and molecular biology methods. The majority of these processes appear to display the features of apoptosis and some of them have turned out to be useful models to investigate the molecular mechanisms of this phenomenon. Two of the most interesting models deal with cell death in the ovary and testis and are separately reviewed in this issue of *Cell Death and Differentiation* (Tilly and Tilly, 1997; Dunkel and Erkkilä, 1997).

The earliest description of PCD within the ovary was made in 1885 during a detailed morphological analysis of rabbit follicle atresia (Flemming, 1885). Only recently, however, using sensitive biochemical assays to detect apoptotic markers (that is, formation of DNA ladders), has it been clearly established that the induction of apoptosis in granulosa cells is the trigger for atresia in a variety of animal species (Tilly *et al*, 1991; Hughes and Gorospe, 1991). In addition, it is now recognized that gonadotropins are the primary endocrine factors responsible for inhibiting apoptosis and atresia in developing mammalian follicles (Tilly *et al*, 1992, 1995). On the basis mainly of results of *in vitro* culture of isolated rat or mouse follicles, the ability of FSH and LH to suppress apoptosis and atresia have been shown to interact with signals activated by intrafollicular growth factors. Moreover, gonadotropin-independent pathways probably contribute to the maintenance of granulosa cell survival whereas activation of Fas receptor plays a role in the negative selection of developing follicles. References on these arguments and a model of the hormonal mechanisms and cell-to-cell interactions required to maintain survival or to induce apoptosis in granulosa cells can be found in the Educational Corner of this issue (De Felici, 1997). It is important to note that apoptosis is involved in two other instances of cell death in the ovary: the massive degeneration of oogonia and oocytes during the fetal period (up to 90% of the female gametes are lost during this period) (Pesce *et al*, 1993; Coucouvanis *et al*, 1993) and the regression of the corpus luteum (Orlicky *et al*, 1992). It is now known that several pro- and anti-apoptosis genes, including *p53*, *c-myc* and members of the *bcl-2* and *Ice* gene families, are expressed in germ cells or

in somatic cells of the ovary. Current perspectives on the intriguing relationship between the regulation of apoptosis by hormonal and growth factors and death gene expression are extensively discussed in the review by Tilly and Tilly.

Spontaneous death of certain classes of germ cells has been shown to be a constant feature of normal spermatogenesis in many mammalian species (for a review, see Roosen-Runge, 1962). Morphological and quantitative studies indicate that germ cell demise is most commonly found in differentiating spermatogonia throughout testis development and that only 25% of the theoretically possible number of preleptotene spermatocytes is produced from the original population of spermatogonia (Huckins, 1978). Recent biochemical evidence links testicular cell death to increased internucleosomal apoptotic DNA fragmentation and shows that under pathological or experimental conditions, besides spermatogonia, spermatocytes and spermatides can also undergo apoptosis (Tapaninen *et al*, 1993; Shikone *et al*, 1994; Billing *et al*, 1995; Sinha Hikim *et al*, 1995; Callard *et al*, 1995). At least three cell death genes are expressed in the testes: *bcl-2*, *bax* and *p53* (for references see the review of Dunkel and Erkkilä in this issue); However, the exact role of these genes has not been established. Interestingly, Fas ligand is expressed in Sertoli cells (Bellgrau, 1995), but whether it has a role in germ cell apoptosis is unknown. In their review, Dunkel and Erkkilä point out that three main factors play a role in determining the onset of apoptosis of the male germ cells: (1) the developmental stage of the animal; (2) serum levels of gonadotropins as well as intratesticular androgens induced by LH; and (3) the stages of the seminiferous epithelial cycle. It should also be considered that, as in the ovary, gonadotropin-independent pathways probably contribute to the control of spermatogenic cell survival. For example, the c-Kit ligand expressed by Sertoli cells appears to be able to favour the survival of spermatogonia and spermatocytes (Packer *et al*, 1995).

On the wave of the renewed studies in cell death, apoptosis in reproduction is attracting interest in several broad fields of clinical investigation. Data reported in the present review by Dunkel and Erkkilä showing that cryptorchidism-induced testis degeneration is associated with increased germ cell apoptosis and that hGC treatment dramatically increases this phenomenon, demonstrate that apoptosis can be the mechanism of degenerative pathologies in reproduction. It is likely that characterization of the molecular basis of this process will provide new clues to explain some causes of infertility, to understand the pathological effects of chemotherapeutic compounds or

environmental toxic agents on reproduction and the genetic defects that predispose people to reproductive abnormalities.

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