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Letter to the Editor

One Hundred Years but they do not Show them

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After a long period of controversy dating from the second half of the 20th century, it is now generally accepted that in mammals adult gametes derive from a relatively small number of precursors termed the primordial germ cells (PGCs). PGCs are the first germ cell population established during embryo development and are the direct precursors for both the oocytes and spermatogonia. They are lineage determined in the mesoderm of the yolk sac early in embryogenesis and subsequently move into the developing gonads. About one hundred years ago, in 1911, two German scientists Felix W. [1] and Fuss A. [2], on the basis of morphological criteria, independently described for the first time PGCs in extragonadal sites of the human embryo. Until the beginning of the eighties, the molecular bases of PGC formation, migration, proliferation and sex differentiation and the secret of their unique capability to maintain the genome status potentially pluripotent and able to regain totipotency following sperm and oocyte fusion at fertilization, have remained basically a mystery.

We now know that the processes by which gametes are formed are surprisingly similar across the animal kingdom. Future germ cells arise outside the somatic gonads early in development as a small population of PGCs. Subsequently they move to the future gonadal tissues (gonadal ridges in the Vertebrates), before the gonads have formed, where they invade the somatic cells and begin the differentiation steps that will produce the adult gametes. PGCs are sexually determined only after they enter the gonadal ridges [3]. Although extragonadal PGC formation and migration are similar in many organisms, the particulars of how, when and where PGCs are formed differ greatly. Basically, PGCs can form either as a result of interactions between tissues through inductive mechanisms or in a cell autonomous fashion by inheritance of cytoplasmic determinants. Along the years, the development of methods for the isolation and culture of mouse PGCs, for gene expression analysis in a single cell and the use of genetic modified mouse, have allowed to unravel some of the PGC secrets. But how the study of PGC biology is today a so hot topic?

Actually these studies have given and continue to give fundamental contributions for understanding crucial aspects of germ cell formation and stem cell biology as well that is the essence of the origin of a new life and the basis of homeostasis of most tissues. Studies on nuclear reprogramming and epigenesis, gene imprinting, the molecular basis of the pluripotency and even on the origin of tumour stem cells, meet soon or later with the PGC biology. Moreover, the recent revival of an old view that in Mammals like in some other species, oocytes can be formed in the postnatal ovary from oogonia stem cells (OSCs) located within the ovary surface epithelium, raises the challenging question if really all adult gametes derive from PGCs and the old dogma of reproduction in Mammals that the number of oocytes is already fixed in fetal or neonatal ovaries. Whether OSCs participating to the normal physiological dynamics of the adult ovary really exist and whether they originate from PGCs or give rise to PGCs or represent an independent stem cell line is not known [4]. Actually, a number of works showed that PGC-like and oocyte-like cells can be obtained *in vitro* from different types of stem cells. Since for obvious ethical reason PGCs are difficult to be studied in the human embryo, the possibility to obtain bona fide PGCs from human stem cell lines *in vitro* paved the way to unravel the mysteries of such fascinating never grow old cells also in our species.

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