Stem cells in human reproduction

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Human stem cell research has moved at a rapid pace since pluripotent human embryonic stem cells (hESC) were first derived from the inner cell mass of IVF preimplantation embryos (Thomson *et al.* 1998). This breakthrough generated much excitement amongst the scientific, medical, and general communities as the potential of hESC and their derivatives for novel cell-based therapies was anticipated. Immune rejection, teratoma formation, and ethical issues associated with hESC concurrently fuelled adult stem cell research, despite the more restricted differentiation repertoire of the latter. The recent discovery that mature tissue cells can be induced to a pluripotent state (induced pluripotent cells, iPS cells) with the introduction of up to four transcription factors (Takahashi *et al.* 2007) was heralded as a major step forward in stem cell research as iPS cells offer an endless supply of compatible cells for regenerative medicine purposes.

Stem cells are defined by three main properties that distinguish them from their more differentiated progeny; self-renewal or ability to replace themselves, differentiation into one or more lineages, and high proliferative potential. Other features of adult stem cells are their rarity in tissues and their relative proliferative quiescence compared to their daughter transit amplifying cells. The microenvironment or stem cell niche is a crucial regulator of adult stem cell function in maintaining tissue homeostasis and initiating stem cell proliferation in response to tissue damage (Li & Xie 2005).

Much research has focused on directing the differentiation of hESC into desired cell types for the study of developmental processes that cannot otherwise be studied in early human development. Protocols for deriving somatic lineages, cardiomyocytes, pancreatic, neuronal, and hematopoietic lineages, hepatocytes, and germ cells to name a few, have been developed. In this Focus Issue, Golos *et al.* (2010) summarize current knowledge on differentiating hESC into extraembryonic lineages, in particular trophoblast and the various trophoblast lineages, as models for the study of early human placental development. This important advance overcomes ethical restrictions on the use of human embryos for *in vitro* studies and the limitations of studying mouse trophoblast differentiation which differs

from human. Early observations during the initial derivation of hESC noted spontaneous differentiation into extraembryonic lineages through the detection of chorionic gonadotropin secretion (Thomson *et al.* 1998). Further development of these *in vitro* models has taken into account the role of non-trophoblastic cells. Composite embryoid bodies combining differentiating hESC and fibroblasts have been developed to study trophoblast differentiation in a model more closely simulating the cellular complexity and spatial arrangement of cells during the very earliest stages of placental morphogenesis (Golos *et al.* 2010). Other models are being developed to study trophoblast interactions with endothelial cells to examine mechanisms of blood vessel invasion and to explore leukocyte trophoblast interactions during implantation. These models are likely to enhance our understanding of the fundamental processes involved in early trophoblast differentiation, villous morphogenesis and placental formation, and extravillous trophoblast invasion, which is essential for the development of therapeutic options for preventing and treating pregnancy disorders related to inadequate implantation and placentation.

Adult stem cells have now been identified in most tissues and organs of the body. The best characterized are those found in organs undergoing rapid cellular turnover, such as hematopoietic tissue of the bone marrow, lining of the gut, and the epidermis. Despite the fact that female reproductive tract tissues undergo major remodeling events as part of the reproductive cycle, adult stem cells in these tissues had been overlooked and understudied for many years. A notable exception is the mammary stem cell which has been investigated for more than three decades in mouse and more recently isolated and characterized in human mammary gland (Lim *et al.* 2009). Of the tissues and organs encompassing the reproductive tract, the endometrium is the most regenerative, undergoing cycles of growth, differentiation, and shedding (Gargett 2007). In contrast to the characterization of adult stem cells in other highly regenerative tissues, most endometrial studies have focused on the human rather than mouse. This is likely related to the level of endometrial shedding since

menstruation is limited to humans and old world primates. Further, human endometrial tissue is readily available for study, given the large number of hysterectomies performed (Garry 2005) and the ease with which biopsy material can be obtained. In this Focus Issue, Maruyama *et al.* (2010) summarize the *in vitro* and *in vivo* evidence for epithelial, stromal, and endothelial stem/progenitor cells in human and mouse endometrium, and explores the possibility that these adult stem cells may originate from the bone marrow. A model is proposed which links the shedding of endometrial functional mesenchymal stem-like cells within menstrual debris to a possible role in repairing the ragged basalis surface for those endometrial fragments remaining in the uterine cavity (Gaide Chevronnay *et al.* 2009), and the establishment of ectopic endometriosis lesions for those shed into the peritoneal cavity. Mutations or epigenetic alterations of endometrial epithelial stem/progenitor cells may also play a role in the development of other endometrial proliferative disorders such as endometrial hyperplasia and endometrial cancer (Gargett 2007).

The concept that tumors contain two populations of cells, the cancer stem cells (CSCs) and the derived tumor cells, explains many features of cancers, but is still considered controversial (Maenhaut *et al.* 2010). The defining properties of CSCs are their ability to self-renew and generate tumors *in vivo* that recapitulate the full repertoire of cancer cells in the parent tumor (Clarke *et al.* 2006). The relative quiescence of CSCs spares them from the cytotoxic effects of chemo- and radiotherapy, making them responsible for tumor recurrence, tumor progression, and eventual tumor resistance. CSC interactions with tumor stroma recapitulate the adult stem cell niche; however, the niche no longer regulates CSC cell fate decisions limiting cell production. CSC activity is classically identified as serially transplantable tumor initiating cells using immunocompromised mouse xenograft models. Recently, however, CSCs have been identified in a range of human tumors through the use of various surface markers that bear no relation to CSC function (Maenhaut *et al.* 2010), but provide a convenient method for sorting CSCs for further characterization. In this Focus Issue, evidence for both endometrial CSCs (Hubbard & Gargett 2010) and ovarian CSCs (Bapat 2010) is reviewed. Markers are currently being identified which enable the prospective isolation of ovarian and endometrial CSCs, of which CD133 and the CD44/CD117 combination appear to hold some promise.

The identification of adult stem cells and CSCs in reproductive tract tissues has progressed significantly since the first publication appeared in 2004 (Chan *et al.* 2004). It is likely that the emerging issues raised by the reviews in this Focus Issue of *Reproduction* will be

addressed in the coming years as it is anticipated that progress will be more rapid. It is also possible that endometrial stem/progenitor cells will be used for regenerative medicine purposes for repair both within and beyond the female reproductive tract.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this editorial.

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