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Stem cell roles in reproduction: what is the basic science?

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Welcome to this thematic MHR issue on 'Stem cell roles in reproduction: what is the basic science?' The aim of this Special Issue is to emphasize the emerging role(s) of stem cells in reproduction. We are pleased to showcase five original research articles and three New Research Horizon reviews, which integrate the exciting fields of reproduction and stem cells. These papers will contribute new insights into the functions of reproductive stem cells, challenge dogmas and create new paradigms for reproductive biology research.

Virtually all post-natal organs, including those of the reproductive system, contain small populations of stem cells that have the capacity for growth, homeostasis and repair of many tissues after damage or ageing. MicroRNAs have emerging roles in the control of virtually all biological processes, including the biology of stem cells. In reproduction, germ-line stem cells (GSCs) serve as a source for gamete production and also give rise to cells with embryonic stem cell (ESC) properties when cultured under specialized conditions. In this issue, Zovoilis *et al.* (p. 793) demonstrate that multipotent adult GSCs (maGSCs) derived from adult mouse testis express germ cell markers characteristic for primordial germ cells and display a specific microRNA expression profile that shows a connection to their germ cell origin but also influences their differentiation potential when compared with the microRNA expression pattern of differentiating ESCs. Jung *et al.* (p. 804) presents an original research article on distinct microRNA signatures in various testes-derived male GSCs and suggests that differential expression could serve as a screening tool to distinguish between GSCs and maGSCs to avoid teratoma formation after clinical transplantation for male infertility. As a way to confirm diagnosis in azoospermic patients, Medrano *et al.* (p. 811) compare the expression profiles of germ cell markers c-KIT, stage-specific embryonic antigen-1 and VASA and found different expression profiles depending on the azoospermic aetiology suggesting that such a screen could be a complementary tool to discriminate between mosaic and non-mosaic Sertoli-cell only patients.

Following menstruation endometrial regeneration is thought to involve small populations of resident multipotent stem cells, or stem cells originating from the bone marrow. The discovery of these uterine stem cells supports a new theory for the cause of endometriosis, which may arise after ectopic stem cell transdifferentiation.

Garett and Masuda (p. 818) review the accumulating evidence for endometrial stem cells, identify their likely sources and discuss their potential roles in endometrial proliferative disorders. Stem cells reside within fixed tissue compartments (niches). These specialized highly regulated microenvironments (surrounding cells, extracellular matrices and factors/signals) control the normal rate of stem cell proliferation, survival and fate. Alterations to this intricate control could result in stem cell transformation. Evidence that stem cell transformation could be the underlying cause in reproductive cancer is presented and the exciting potential for future stem cell studies to lead to new reproductive cancer therapies is discussed.

Stem cells from the human placenta, cord blood, amniotic fluid and menstrual blood (among other reproductive tissues) are a rich, non-invasive and ethically acceptable source of stem cells. These stem cells can be used for regenerative medicine and are potentially amenable to reprogramming for use in various patient-specific cell therapies. Many of these reproductive stem cells express known pluripotency factors such as Octamer 4 (OCT4) and SRY (sex determining region Y)-box 2. David Kristensen *et al.* (p. 835) demonstrate for the first time that OCT4 and its downstream factors are expressed in human somatic epithelial cells from the urogenital tract and that these cells can form spheres, a general characteristic of stem cell behaviour. Meyer *et al.* (p. 846) show through DNA microarray analysis that maGSCs and ESCs exhibit comparable transcriptomes, including genes associated with pluripotency and that both cell types spontaneously differentiate in a similar manner. Masip *et al.* (p. 856) summarizes the cellular reprogramming field and compares the procedures and efficiency of induced pluripotent stem cell (iPSC) generated from various somatic cell types including those from reproductive tissues. The current limitations of induced pluripotency are presented and innovative strategies for iPSC generation such as small molecule iPSC generation and non-integrated transgenic methods are discussed. The hot research topic of direct transdifferentiation, which has considerable implications for cellular therapy, is also reviewed.

Despite decades of research, the biological role(s) of fetal microchimerism (FMC) remain obscure. Several recent studies have demonstrated that fetal stem cells are the likely source of these cells.

Once fetal stem cells enter the maternal circulation early in pregnancy, they have the potential for a beneficial contribution to tissue repair, or a malevolent contribution to disease, depending on the tissue (niche) they eventually reside in. Lee *et al.* (p. 869) provide an extensive review on fetal stem cell microchimerism, which examines the methods used for FMC detection, the origin prevalence and ‘stemness’ of stem cells implicated in FMC, the possible contribution of FMC to various illnesses such as autoimmune diseases and cancer, and finally the potential utility of fetal stem cells for therapies.

Overall, these articles sum up the current focal points of stem cell research in reproductive medicine and encapsulate the essence of MHR, which seeks to publish and disseminate fundamental knowledge on the molecular aspects of human reproduction. Unravelling the functions of various stem cells in reproduction will increase our fundamental knowledge of the normal process of reproduction, provide insight into their role in disease and help develop strategies to harness their therapeutic potential. Enjoy the issue.