Oogonial Stem Cells: Should we be considering and preparing for clinical application?

It is premature

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Advances in reproductive biology and medicine over the past 40 years have materially impacted human and animal health and set the stage for the promising field of regenerative medicine. While progress has been made in the use of embryonic (ES) and induced pluripotent stem cells (iPSCs) (1) for reproductive organ replacement(2), attention has been mainly directed at the potential use of stem cells to generate germ cells in males and females. With regard to spermatogenesis, progress has been considerable in animal models where the challenge of defining an appropriate niche to support germ cell development from ES-derived primordial-germ-cell-like cells (PLCs)(3, 4). With respect to the female germline, the conversation regarding clinical utility remains focused not so much on the ability of ES or iPSCs to be converted into mature oocytes, as shown in mice (5), but rather on whether an endogenous stem cell exists in the mammalian ovary that could under as yet ill-defined conditions proceed throughout the complex and protracted series of events known as oogenesis. It will be argued that (a) the data provided for the existence of ovarian germline stem cells remain ambiguous and subject to multiple interpretations, (b) while an operational niche has been defined supporting oogenesis from ES and iPS cells in the mouse(6), differences in ovarian development between rodents and primates may require alternative strategies and (c) inherent genetic instability due to meiotic recombination is likely to thwart the generation of healthy oocytes from various stem cell sources currently under investigation.

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Evelyn E Telfer

Prepare now

For many years Scientists have been attempting to develop oocytes from stem cells. The source of cells have been Embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and Oogonial stem cell (OSCs) (ovarian derived). Controversy aside, a major hurdle in developing these cells into functioning oocytes has been the development of an *in vitro* system that supports oocyte development from the earliest stages through to maturity. This has now been achieved in mice with the production of live young from *in vitro* grown primordial germ cells (Morohaku et al., 2016) and from ESCs and iPSCs obtained from skin cells (Hikabe et al., 2016). Whilst there are major differences between human and mouse oocyte development the mouse work provides proof of concept and has driven the development of systems that could be applied to human. Given the moral and ethical issues surrounding ES cells and iPSCs a more suitable source of germline starting material could be ovarian derived germ line stem cells or Oogonial Stem Cells that have been isolated from the ovaries of adult women (White at al., 2012). There has been much controversy surrounding these cells which has hampered progress but OSCs are currently being used clinically as a source to harvest autologous mitochondria (Woods and Tilly, 2015; Cagnone et al., 2016). Given the potential utility of these cells and particularly their application to fertility preservation the time is now to prepare for clinical application. Clinicians and Scientists in this field should be engaging in a process whereby the pre-clinical and clinical development requirements are defined and the ethical, moral and legal implications considered in order to establish the pathway for human studies that will lead to safe and ethical uses.

Cagnone, G., Tsai, T-S., Makanji, Y., Matthews, P. M., Gould, J. A., Bonkowski, M. S., Elgass, K., Wong, A. S. A., Wu, L. E., McKenzie, M., Sinclair, D. A. & St John, J. C. 2016 In : Scientific Reports. 6, p. 1 - 15 15 p., 23229 wide range of organ systems.

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