Twists and turns in the business of gonadal stem cells

David F. Albertini

Published online: 25 July 2014
© Springer Science+Business Media New York 2014

It has now been over a decade since the curative potential of stem cells was first offered for public consumption. The making of human embryonic stem cells had been established by a handful of centers around the world, and the dawning of regenerative medicine was formally announced by the likes of media coverage rivalling that associated with the birth of Dolly the sheep. What has driven the mindset for this heralded branch of contemporary biomedical research?

Tracing the roots of stem cell research seems not to be a matter academic tradition and discovery-based direction. Even though the history of this field is prepubescent in years, it is rarely analyzed in a historical context given the self-ascribed urgency that rests firmly in the hands of institutions and/or commercial ventures intent on bringing to market products that in the end—and in the beginning—may provide a quantitative and qualitative dimension of lifespan extension. Anyone interested in the origins of this mindset would do well to pick up a copy of Stephen Hall's "Merchants of Immortality: Chasing the Dream of Human Life Extension." (ISBN 0-618-09524-1, 2003, Houghton Mifflin, New York, NY).

This prescient and authoritative account of stem cell science circa 2003 weaves the interests of scientists, venture capitalists, politicians, and ethicists into a macrocosm of attitudes that has shaped and influenced the course of research in the field of regenerative medicine. And, it is safe to say that a decade ago, when the state of affairs was reduced to the matter of how to prevent age-related deterioration of our brains,

kidneys, livers, hearts and assorted sensory organs, nowhere in sight was the subject of gonadal regeneration and the prospect of the ultimate example of the fountain of youth! But within two years, reports appeared in prominent journals touting the generation of germ cells of male or female varieties from—you guessed it—stem cells. As we have reviewed in JARG, the topic of germ cell derivation from embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) remains alive and well thanks in no small way to the elegant studies from Japan in 2012 and 2013 based on work with mice. To recapitulate ever so briefly, the take-home message from these was that stem cells of various kinds can be re-programmed into a gametogenic pathway if, and only if, the correct sequence of growth factors is presented in a developmentally appropriate niche consistent with the stages of oogenesis or spermatogenesis evidenced prior to or during the reproductive lifespan. Like real estate, then, location drives opportunity as apparently the gonadal neighborhood does for our gametes.

It is fair to ask then whether the past decade of stem cell research has brought the dream of reversing the accoutrements of our aging bodies any closer to reality? And, more to the purview of JARG, what reproductive disorders might lend themselves to intervention with stem cell therapies?

Timely and relevant for future prospects of stem cell therapy is the condition in women known as diminished ovarian reserve, or DOR. Whether confronting the diminishing returns on the ovarian follicle stores that attend the natural aging process in humans, or facing the alarming realities associated with premature ovarian failure and the spectrum for onset patients variably present with, DOR continues to dominate the landscape of human ARTs. In particular, the evolving and contemporaneous theme of fertility preservation aiming to protect or restore gonadal function receives regular attention from the press because of the palatable link between germ cells and stem cells. In this issue, we bring our readership to

---

Capsule Prospects for bringing human reproduction into the field of regenerative medicine have emphasized gametocentric approaches and stem cell plasticity. Why attention should be redirected to the somatic cell lineages of gonads is discussed in relation to the discovery of multipotent mesenchymal stem cells in the human ovary.

D. F. Albertini (✉)
University of Kansas Medical Center, Kansas, KS, USA
e-mail: dalbertini@kumc.edu

the forefront of twists and turns in stem cell science as it pertains to the subject of gonadal stem cells.

Setting the stage on the side of female reproductive physiology is the systematic review on the genetics of diminished ovarian reserve by Green and colleagues at the NIH. In addition to offering insight into the genetic associations that can be gleaned from the literature for humans and mice, a number of familiar and not-so-familiar genes emerged as possible candidates for deeper analysis in patient populations that would represent the spectrum of DOR as unrelated or contributory players. On returning to the matter of stem cell plasticity within the ovary, it is notable that papers subject to analysis did not uncover any of the genetic links that might be ascribable to ovarian stem cells of either germline or somatic lineages. And yet, the stem cell potential of the ovary, like that of the endometrium or fallopian tube, must be enormous given the physiological regenerative capability that is demonstrated in a repetitive fashion during the reproductive lifespan of ourselves and many other mammals. So has the search for stem cells in the ovary been misguided down the pathway of eternal bliss taking the form of de novo oocyte production? As noted above, the holy grail for rejuvenating gonadal function in animal model systems resides not in the germ cell but in the immediate niche that naive or contrived germ cells may find themselves. Much headway has been made in the direction of isolating and characterizing ovarian stem cells with a “gonial” persona. But is this line of research overlooking something even more fundamental to the maintenance of ovarian exocrine and endocrine function?

The new twist to the ongoing debate regarding ovarian immortality and regenerative medicine may have more to do with stem cell plasticity in the somatic lineages, much to the dismay of the oocentrics in the audience. As reported by Stimpfel and colleagues, human ovarian cortical tissue is populated by mesenchymal stem cells (MSCs) that bear transcriptional profiles not unlike those derived from human bone marrow (see Stimpfel et al. *Putative mesenchymal stem cells isolated from adult human ovaries* DOI [10.1007/s10815-014-0254-8](https://doi.org/10.1007/s10815-014-0254-8)). These cells can be readily isolated by standard techniques and when assayed under appropriate in vitro conditions for the expression of multipotentiality, like their bone marrow counterparts ovarian MSCs differentiated into neural, osteogenic, adipogenic, and pancreatic lineages. It is important for the reader to bear in mind that human MSCs from various tissue sources have a checkered past with respect to the demonstration of their intrinsic capacity for tissue repair and maintenance in vivo or in vitro. Moreover, the ovarian

tissues used in this work were from patients spanning a wide and “older” age range with no direct evidence in hand yet to substantiate their contribution to any of the many somatic cell types resident within the human ovary. Nevertheless, this work sets the stage for broadening our sights into the role of ovarian stem cells in normal and pathological states.

On the male side of the coin, things are a bit more fixed in time and space. Spermatogenic cycles transit the length of the seminiferous tubules and draw directly on an established population of spermatogonial stem cells known to interact proximally within the Sertoli cell niche. Hence, efforts have by necessity concentrated on the procurement and characterization of spermatogonial stem cells (SSCs) and towards this end two papers are featured this month that exemplify progress in both the culture of SSCs deploying a Sertoli cell feeder layer (In vitro culture and characterization of spermatogonial stem cells on Sertoli cell feeder layer in goat; DOI [10.1007/s10815-014-0276-2](https://doi.org/10.1007/s10815-014-0276-2)) and development of an enrichment technique for SSCs (Development of a high-yield technique to isolate spermatogonial stem cells from porcine testes, DOI [10.1007/s10815-014-0271-7](https://doi.org/10.1007/s10815-014-0271-7)) in two domesticated animal species. Respectively, these studies address the growing awareness of the critical role played by somatic cells in the maintenance of male germ cells as well as improving technology for isolation of a sufficient number of SSCs to meet what are already recognized as limitations in current technology for restoration of gametogenic gonadal function.

Whether stem cell science will be used to harness gonadal physiology for treatment of infertility remains questionable. More broadly speaking, regenerative medicine proponents themselves are recognizing that curative strategies will not be as straightforward as originally hoped during the first decade of stem cell research.

In closing, it is fitting to note that at the opening ceremony for the ESHRE meeting in Munich last month, Sir John Gurdon was interviewed by Dr. Anna Vieira on the occasion of receiving lifelong honorary membership. When asked what he thought about stem cell therapy becoming a reality, he replied “the most immediate benefit (for these cells) would be drug testing and over the long term they will be helpful for the treatment of age-related macular degeneration of the retina since stem cell generated retinal pigment epithelial cells could be implanted and possible arrest deterioration...” . Perhaps then the future for gonadal stem cells will lie not in the wide-scale extension of our reproductive lifespans but rather in offering patients with premature aging disorders the chance to have a biological child.