Male germ cell transplantation

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In November 1994, Ralph Brinster and coworkers published two papers that should be regarded as the start of a paradigm shift in reproductive biology. The authors reported on the successful transplantation of germ cells to sterile mouse testes. The donor cells not only survived and proliferated in the recipient testes but they also entered the long and complex process of spermatogenesis, and differentiated into fully functional spermatozoa able to fertilize eggs and give rise to normal offspring (1, 2). The potentials of these novel discoveries were clearly evident to Martin Dym as expressed by his commentary in the same issue of the Proceedings of the National Academy of Sciences of the USA where the original papers were published (3). More recently, these initial findings in the mouse have been partially reproduced in a rat model using a somewhat different technical approach for the transplantation (4). This year, Brinster and coworkers have extended their original findings by showing that frozen and stored murine male germ cells are equally successful as transplantation donor cells when compared with freshly prepared testicular cells (5). Further, and most exciting, they were also able to show that xenogenic donor germ cells (from rats) could survive and give rise to apparently normal rat spermatozoa when transplanted into sterile mouse testes (6).

Basically, what Brinster and coworkers have developed is a technique to microinject testicular germ cells into the seminiferous tubules of mouse testes that were sterile due to a genetic defect or as a result of aggressive cytostatic treatments. The instrumentation and procedures employed were adopted and were not very different from those routinely used in clinical in vitro fertilisation programmes involving intracytoplasmic sperm injection to the egg. In most of the cited studies, fairly crude populations of early postnatal or prepubertal testicular germ cells were used as donor cells for transplantation. However, it was found that germ cell preparations from adult testes could also be used as donors cells (5), an observation that might have wide implications in reproductive biology including human reproduction (see below). Attempts to purify the donor cells or to use more immature cells, such as embryonic stem cells, either failed or gave poorer results. Paternity of donor cell origin was verified by genetic marker analysis of the offspring. Although the fertility rate of the transplanted testes was very low, the cited studies demonstrated clearly that spermatogonial stem cells which are present in low numbers in the crude donor cell preparation could be functionally rescued in a favourable testicular environment outside the donor animal. Surprisingly, it was also found that host testes which were not totally sterile but were still harbouring some endogenous spermatogenesis also accepted transplanted germ cells, thus resulting in two separate fertile populations of spermatozoa of either donor or host haplotype. It must be stressed, however, that none of Brinster’s experiments employed transplantation across immunological barriers, as the donors and hosts were either syngeneic with respect to major histocompatibility complex antigens or lacked immunoreactivity due to host animal immunodeficiency. In fact, all attempts to transplant rat testicular germ cells to testes of immunocompetent mice failed (6). Further, it must be pointed out that the number of donor spermatozoa that were recovered from the epididymes of the xenogeneic hosts was very low (at best a ratio of 1/40 donor vs host spermatozoa) and it remains to be proven whether these xenogenic spermatozoa are fertile and capable of producing normal offspring. Nevertheless, as there are as yet no methods available for long-term culture of spermatogonial stem cells, the model envisaged by Brinster and coworkers using murine testes of immunodeficient animals to host spermatogenesis of another species might be a useful tool to rescue and propagate functional germ cells from donors with a threatened gonadal function.

The implications of the above findings are, of course, enormous for reproductive biology in general. It is also obvious that the described techniques could have wide applications in transgenic animal technology although the issue of genetic modification of germ line cells is still a topic of deep ethical concern. There is no reason to believe that the described rat–mouse xenogeneic model would not apply also to other combinations of species including man. One might, therefore, speculate that in the future it would be possible to cryopreserve human germ line stem cells and/or to rescue them in a xenogeneic immunodeficient mouse model. This may contribute to treatment of male infertility in humans (or rather preservation of fertility) e.g. in cases of malignancies treated with gonadotoxic chemotherapy resulting in sterility.
References


