Open Access Journal of Surgery

Juniper Publishers key to the Researchers

Mini Review
Volume 1 Issue 4 – November 2016

Open Access J Surg

Spermatogonial Stem Cell Technology and Regenerative Medicine

Leila Salari Asl, Sadegh Ghorbani and Hossein Eyni*

Department of Anatomical Sciences, Faculty of Medicine, Tarbiat Modares University, Iran

Submission: October 18, 2016; **Published:** November 28, 2016

First author: Leila SalariAsl, Department of Anatomical Sciences, Faculty of Medicine, Tarbiat Modares University, Tehran, Iran

***Corresponding author**: Hossein Eyni, Department of Anatomical Sciences, Faculty of Medicine, Tarbiat Modares University, Tehran, Iran

Abstract

The biologic activities of spermatogonial stem cells (SSCs) are the base for spermatogenesis and thus sustained male fertility. Therefore, comprehending the mechanisms governing their ability to both self- renew and differentiate is necessary. Moreover, because SSCs are the just adult stem cell to contribute genetic information to the next generation, they are a good target for genetic change. Some researchers have reported the derivation of multipotent cells from mouse and human spermatogonial stem cells. These spermatogonial stem cells demonstrate similarities with embryonic stem cells for phenotype and functionality, showing that these cells may be a promising alternative origin for stem-cell based therapies in regenerative medicine.

Keywords: Spermatogonial stem cell; Regenerative medicine; Transplantation

Introduction

Spermatogonial stem cell

Germ cell development begins with the characteristics of the primordial germ cells (PGCs) early in human fetal life. PGCs arise from the proximal epiblast and will replace to the extra embryonic mesoderm during the fourth and fifth week of embryonic development. By the finish of the fifth week to early sixth week, PGCs will embark for a second immigration via the dorsal mesenterium of the gut to the gonadal ridge. During their immigration, PGCs proliferate but once they has arrived the gonadal ridge, they enter into a mitotic arrest while differentiating into gonocytes. Shortly after birth these gonocytes put on the basal membrane of the seminiferous tubules where mitosis is reinitiated. From then on, they are called spermatogonial stem cells or SSCs [1]. Spermatogonial stem cells (SSCs) are a subpopulation of unspecialized stem cells that lie along the basement membrane of the seminiferous tubules of the testis and give rise to the germ line lineage in males. In the adult testis, only 0.03% of all germ cells are spermatogonial stem cells [2]. Testicular SSCs are typically unipotent and are only capable of giving rise to the germ cell lineage and ultimately spermatozoa.

This ability of SSCs, the only adult stem cell population that transmits genetic information to the next generation [3-5], to generate spermatozoa is critically dependent on the micro environment or niche that surrounds these cells [6-10]. Daily, 45-207 million spermatids are generated in the normal adult testis. This coining of germ cells is not regulated by the stem cells themselves but by the microenvironment environs the stem cells, i.e. the stem cell ''niche''. The niche is described as ''the microenvironment around stem cells that provides support and generates signals regulating self-renewal and differentiation'' [11]. The niche can action on a stem cell through various mechanisms: niche cells can make straight contact with the stem cell, niche cells can disguise paracrine factors acting on the stem cell or intermediate cells can ''communicate'' among the niche and the stem cells. When removed from their normal stem cell niche and cultured *in vitro*, SSCs display a broader developmental potential than they normally manifest *in vivo*. This has led to interest in their potential suitability for human regenerative medicine.

Spermatogonial stem cells as a source for fertility restoration

Spermatogonial stem cell disservice is an important reason of male infertility. Stem cell loss can happen after chemo- and radiotherapy [12-15] or due to a genetic disease, e.g. 47, XXY

Klinefelter's syndrome or AZF deletion [16,17]. Because children do not have the feasibility to bank spermatozoa, the preservation and transplantation of SSCs may become an important and main strategy to treat reproductive stem cell loss disturbances. In the last decade, most of research has been done on human SSC protection and transplantation [18]. Spermatogonial stem cell transplantation was first presented in the mouse in 1994 by Brinster and Zimmermann [19]. Spermatogenesis could be reinitiated in infertile receiver mice after transplantation of testicular cell suspensions from fertile donors. Shortly later, this technology was done in other mammalian species, including primates [20-24]. Even the transplantation between various species was proven successful [25,26].

These results, particular those from primate studies, propose a possibility of banking and transplanting human spermatogonial stem cells to barricade sterility caused by SSC loss. In mice and rat, the efferent duct has been shown to be an affective site for reintroducing SSCs by injection. However, compared to mouse and rat testis, human testis are bigger than and more fibrous. Thus, the injection technique has to be rectified. By using excised human testis donated by orchidectomy patients, different injection sites have been checked: the seminiferous tubules, the rete testis, the epididymis and the deferent duct. Schlatt et al. [21] have demonstrated that ultrasound-guided intratesticular rete testis injection was the better and least invasive injection technique with maximal infusion efficiency for larger testis. Tagged cells could be found in tubules near to the rete testis but not in tubules far away the rete testis. Brook et al. [27] evaluated the performance of single and multiple injections through the rete testis of isolated human testis.

Nevertheless, the hole into the testis was not monitored and it was unclear whether the injected hue had been injected in the seminiferous tubules or in the interstitial tissue or both. If spermatogonial stem cell transplantation has been demonstrated to be a successful procedure to produce live offspring in a mouse model [28], genetic and epigenetic changes due to the procedure should be taken into attention. Goossens et al. [29,30] observed that after *in vivo* and *in vitro* conception, transplanted males generated smaller litter sizes compared to normal fertile control mouse. However, the offspring demonstrated normal karyotypes and methylation patterns [31,32]. In another study, a detailed analysis of the motility kinematics and attentions of spermatozoa acquired after transplantation was performed demonstrating a less sperm concentration and sperm motility after transplantation [33]. The latter results may explain the reduced litter size as watched in the *in vivo* mating studies.

Taking into account the significance of the spermatogonial stem niche in spermatogenesis, grafting testicular tissue may be another to obtain functional sperm that is able to fertilize oocytes. In rodents and rabbits, perfect spermatogenesis has been seen and fertile offspring could be acquired through assisted reproductive techniques after grafting immature testicular tissue [34,35]. Grafting testicular tissue of human, however, did not produce spermatozoa. In prepubertal xenografts, this period was even lengthy (9 months) [36]. Lately, differentiation up to primary spermatocytes and the attendance of a few secondary spermatocytes was showed in testicular tissue from a peripubertal boy after xenotransplantation to mouse [37].

Spermatogonial stem cells as pluripotent cells

Newly, the pluripotency of SSCs from neonatal and adult mouse testis has been reported by various research teams. Kanatsu-Shinohara et al. [38] demonstrated the derivation of ES-like cells from neonatal mouse testis in culture. In their researches, ES-like cells were shown to be phenotypically alike to embryonic stem cells and to have the ability to differentiate *in vitro* into different types of somatic cells and to generate teratomas after injection into nude mice. In addition to, these ES-like cells formed germ line chimeras when injected into blastocysts, which proves the pluripotency of the spermatogonial stem cells derived from neonatal testis.

Afterwards, Guan et al. [39] demonstrated that SSCs from adult mouse testis could produce multipotent cells in vitro that were able to differentiate into various cell types of all three germ layers and to produce teratoma in immune deficient mice. These multipotent adult germ line stem cells donated to the development of different organs after injection into blastocysts. Similar phenomena could be showed in human spermatogonial stem cells. Conrad et al. [40] created an ES-like cell line derived from spermatogonial stem cells of adult human testis. The cells acquired cellular and molecular characteristics of human embryonic stem cells, but additionally these germ line derived stem cells differentiated into different types of somatic cells of all three germ layers when grown under situations used to induce the differentiation of human embryonic stem cells.

Conclusion

Transplantation of SSCs may become a promising procedure to keep the fertility of prepubertal patients. Their testicular tissue could be removed and cryopreserved before treatment. After recuperation, the tissue/cells could be grafted or transplanted into the patient's own testis and fortunately spermatogenesis will be reinitiated. For cancer patients, additional methods would be essential for the isolation of SSCs and the removal of malignant cells. Other future choice would be *in vitro* maturation of SSCs after isolation and malignant cell removal. By this means, functional spermatozoa could be derived from mouse SSCs [41]. These *in vitro* generated spermatozoa could be used to fertilize oocytes by assisted reproductive techniques. These above indicated strategies could also be appropriate for adult patients with non-obstructive azoospermia. After seclusion and *in vitro* maturation, SSCs from these donors may have the capacity to generate functional spermatozoa. Although, before using these methods in patients, more research is required.

How to cite this article: Leila S A, Sadegh G, Hossein E. Spermatogonial Stem Cell Technology and Regenerative Medicine. Open Access J Surg. 2016; 1(4): 555570.

The potential of human spermatogonial stem cells to differentiate into pluripotent cells or transdifferentiate into other cell types is interesting and may create an additional function for spermatogonial stem cell banking. Apart from fertility preservation, the banked cells could potentially be used as a provenance for stem cell therapy targeting other diseased organs. SSCs could be induced into pluripotent cells *in vitro*, by adding sure growth factors or inductive mesenchymes before their induction into the target cell type. Other strategy may be the straight injection into the human body at the location of injury or disease, e.g. bone marrow, myocardium. However, a number of problems abide before SSCs can be used as an alternative origin for pluripotent stem cells. The main challenge is to acquire sufficient numbers of purified SSCs from a small part of testicular biopsy.

A large part (about 1 g) of testicular biopsy includes less than 5 million cells with only 1500 being right stem cells. This is far from the number required for cell therapy besides mentioning the low de- and transdifferentiation rates. Therefore, an efficient procedure for SSC isolation and in vitro enlarging has to be developed. Several researches on the *in vitro* amplification of human adult SSCs has been reported [42]; an important challenge for any clinical application is to eschew the risk of teratoma formation after transplantation. The development of an effective induction protocol and the regulation of the recipient's immunology system may be essential to remove the risk of teratoma formation. Although there is not yet an obvious clinical prospect for SSC-based cell therapy in the clinic, SSC banking may become an encouraging and applicable strategy in the future.

References

1. Ohta H, Wakayama T, Nishimune Y (2004) Commitment of fetal male germ cells to spermatogonial stem cells during mouse embryonic development. Biol Reprod 70(5): 1286-1291.
2. Kubota H, Brinster RL (2006) Technology insight: In vitro culture of spermatogonial stem cells and their potential therapeutic uses. Nat Clin Pract Endocrinol Metab 2(2): 99-108.
3. Brinster RL (2002) Germline stem cell transplantation and transgenesis. Science 296(5576): 2174-2176.
4. Dym M (1994) Spermatogonial stem cells of the testis. Proc Natl Acad Sci USA 91(24): 11287-11289.
5. de Rooij DG, Russell LD (2000) All you wanted to know about spermatogonia but were afraid to ask. J Androl 21(6): 776-798.
6. de Rooij DG (2009) The spermatogonial stem cell niche. Microsc Res Tech 72(8): 580-585.
7. Hess RA, Cooke PS, Hofmann MC, Murphy KM (2006) Mechanistic insights into the regulation of the spermatogonial stem cell niche. Cell cycle 5(11): 1164-1170.
8. Kostereva N, Hofmann MC (2008) Regulation of the spermatogonial stem cell niche. Reprod Domest Anim 43(2): 386-392.
9. Hofmann MC (2008) Gdnf signaling pathways within the mammalian spermatogonial stem cell niche. Mol Cell Endocrinol 288(1-2): 95-103.
10. Jones DL, Wagers AJ (2008) No place like home: anatomy and function of the stem cell niche. Nat Rev Mol Cell Biol 9(1): 11-21.
11. Schofield R (1977) The relationship between the spleen colony-forming cell and the haemopoietic stem cell. Blood cells 4(1-2): 7-25.
12. Wallace WHB, Shalet SM, Crowne E, Morris-Jones P, Gattamaneni H, et al. (1989) Gonadal dysfunction due to cis-platinum. Med Pediatr Oncol 17(5-6): 409-413.
13. Wallace WHB, Shalet SM, Lendon M, Morris-Jones P (1991) Male fertility in long-term survivors of childhood acute lymphoblastic leukaemia. Int J Androl 14(5): 312-319.
14. Radford JA, Lieberman B, Brison DR, Smith A, Critchlow J, et al. (2001) Orthotopic reimplantation of cryopreserved ovarian cortical strips after high-dose chemotherapy for Hodgkin's lymphoma. Lancet 357(9263): 1172-1175.
15. Thomson AB, Campbell AJ, Irvine DS, Anderson RA, Kelnar CJ, et al. (2002) Semen quality and spermatozoal DNA integrity in survivors of childhood cancer: a case-control study. Lancet 360(9330): 361-367.
16. Paulo Navarro-Costa, Carlos E Plancha, João Gonçalves (2010) Genetic dissection of the AZF regions of the human Y chromosome: thriller or filler for male (in) fertility? Journal of Biomedicine and Biotechnology 2010: 1-18.
17. Giltay JC, Maiburg MC (2010) Klinefelter syndrome: clinical and molecular aspects. Expert Rev Mol Diagn 10(6):765-776.
18. Geens M, Goossens E, De Block G, Ning L, Van Saen D, et al. (2008) Autologous spermatogonial stem cell transplantation in man: current obstacles for a future clinical application. Hum Reprod Update 14(2): 121-130.
19. Ralph L Brinster, James W Zimmermann (1994) Spermatogenesis following male germ-cell transplantation. Proc Nati Acad Sci 91(24): 11298-11302.
20. Honaramooz A, Behboodi E, Megee SO, Overton SA, Galantino-Homer H, et al. (2003) Fertility and germline transmission of donor haplotype following germ cell transplantation in immunocompetent goats. Biol Reprod 69(4): 1260-1264.
21. Schlatt S, Rosiepen G, Weinbauer G, Rolf C, Brook P, et al. (1999) Germ cell transfer into rat, bovine, monkey and human testes. Hum Reprod 14(1): 144-150.
22. Mikkola M, Sironen A, Kopp C, Taponen J, Sukura A, et al. (2006) Transplantation of Normal Boar Testicular Cells Resulted in Complete Focal Spermatogenesis in a Boar Affected by the Immotile Short-tail Sperm Defect. Reproduction in Domestic Animals 41(2): 124-128.
23. Kim Y, Turner D, Nelson J, Dobrinski I, McEntee M, et al. (2008) Production of donor-derived sperm after spermatogonial stem cell transplantation in the dog. Reproduction 136(6): 823-831.
24. Hermann BP, Sukhwani M, Hansel MC, Orwig KE (2010) Spermatogonial stem cells in higher primates: are there differences from those in rodents? Reproduction 139(3): 479-493.
25. Dobrinski I, Avarbock MR, Brinster RL (1999) Transplantation of germ cells from rabbits and dogs into mouse testes. Biol Reprod 61(5): 1331-1339.

How to cite this article: Leila S A, Sadegh G, Hossein E. Spermatogonial Stem Cell Technology and Regenerative Medicine. Open Access J Surg. 2016; 1(4): 555570.

26. Ogawa T, Dobrinski I, Avarbock MR, Brinster RL (1999) Xenogeneic spermatogenesis following transplantation of hamster germ cells to mouse testes. Biol Reprod 60(2): 515-521.

27. Brook PF, Radford JA, Shalet SM, Joyce AD, Gosden RG (2001) Isolation of germ cells from human testicular tissue for low temperature storage and autotransplantation. Fertil Steril 75(2): 269-274.

28. Brinster RL, Avarbock MR (1994) Germline transmission of donor haplotype following spermatogonial transplantation. Proc Natl Acad Sci USA 91(24): 11303-11307.

29. Goossens E, Frederickx V, De Block G, Van Steirteghem A, Tournaye H (2003) Reproductive capacity of sperm obtained after germ cell transplantation in a mouse model. Hum Reprod 18(9): 1874-1880.

30. Goossens E, Frederickx V, De Block G, Van Steirteghem A, Tournaye H (2006) Evaluation of in vivo conception after testicular stem cell transplantation in a mouse model shows altered post-implantation development. Hum Reprod 21(8): 2057-2060.

31. Goossens E, De Rycke M, Haentjens P, Tournaye H (2009) DNA methylation patterns of spermatozoa and two generations of offspring obtained after murine spermatogonial stem cell transplantation. Hum Reprod 24(9): 2255-2263.

32. Goossens E, de Vos P, Tournaye H (2010) Array comparative genomic hybridization analysis does not show genetic alterations in spermatozoa and offspring generated after spermatogonial stem cell transplantation in the mouse. Hum Reprod 25(7): 1836-1842.

33. Goossens E, De Block G, Tournaye H (2008) Computer-assisted motility analysis of spermatozoa obtained after spermatogonial stem cell transplantation in the mouse. Fertil Steril 90(4): 1411-1416.

34. Honaramooz A, Snedaker A, Boiani M, Schöler H, Dobrinski I, et al. (2002) Sperm from neonatal mammalian testes grafted in mice. Nature 418(6899): 778-781.

35. Schlatt S, Honaramooz A, Boiani M, Schöler HR, Dobrinski I (2003) Progeny from sperm obtained after ectopic grafting of neonatal mouse testes. Biol Reprod 68(6): 2331-2335.

36. Goossens E, Geens M, De Block G, Tournaye H (2008) Spermatogonial survival in long-term human prepubertal xenografts. Fertil Steril 90(5): 2019-2022.

37. Van Saen D, Goossens E, Bourgain C, Ferster A, Tournaye H (2011) Meiotic activity in orthotopic xenografts derived from human postpubertal testicular tissue. Hum Reprod 26(2): 282-293.

38. Kanatsu-Shinohara M, Inoue K, Lee J, Yoshimoto M, Ogonuki N, et al. (2004) Generation of pluripotent stem cells from neonatal mouse testis. Cell 119(7): 1001-1012.

39. Guan K, Nayernia K, Maier LS, Wagner S, Dressel R, et al. (2006) Pluripotency of spermatogonial stem cells from adult mouse testis. Nature 440(7088): 1199-1203.

40. Conrad S, Renninger M, Hennenlotter J, Wiesner T, Just L, et al. (2008) Generation of pluripotent stem cells from adult human testis. Nature 456(7220): 344-349.

41. Sato T, Katagiri K, Gohbara A, Inoue K, Ogonuki N, Ogura A, et al. (2011) In vitro production of functional sperm in cultured neonatal mouse testes. Nature 471(7339): 504-507.

42. Sadri-Ardekani H, Mizrak SC, van Daalen SK, Korver CM, Roepers-Gajadien HL, et al. (2009) Propagation of human spermatogonial stem cells in vitro. JAMA 302(19):2127-2134.

How to cite this article: Leila S A, Sadegh G, Hossein E. Spermatogonial Stem Cell Technology and Regenerative Medicine. Open Access J Surg. 2016; 1(4): 555570.