Middle East Fertility Society Journal xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Middle East Fertility Society Journal

journal homepage: www.sciencedirect.com

Review

The applications and recovery outcome of spermatogonia stem cells in regenerative medicine

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ARTICLE INFO

Article history:
Received 3 April 2017
Revised 19 May 2017
Accepted 23 May 2017
Available online xxxx

Keywords:
Spermatogonial stem cells
Regenerative medicine
Cell transplantation
Embryonic stem like cell
Pluripotency

ABSTRACT

Spermatogonial stem cells are unique cells that line the basal lamina of seminiferous tubules in the testis and have the potential of self-renewal and differentiation.

These cells pass on genetic information to the next generation via the process of spermatogenesis and have an important role in the maintenance of male fertility. Recent reports have shown the pluripotency characteristics of spermatogonial stem cells at the cellular and molecular level. These cells can convert into Embryonic stem like cells that exhibit similar phenotype with embryonic stem cells and the capacity to differentiate into all three germ layers: Ectoderm, endoderm and mesoderm.

These properties make spermatogonial stem cells an appropriate source for use in regenerative medicine.

Spermatogonial stem cells considered as an alternative and novel cell source that limits the technical and ethical problems accompanied with the other pluripotent stem cells. Patient-specific cell lineages without limitations of immunological rejection and specific auto transplantation are the beneficial's associated with these cell population.

Also, cell therapy based on spermatogonial stem cells engraftment, promises for preservation of fertility and induces the reproductive potential in infertile patients.

Here, we discuss the applications of spermatogonial stem cells in regenerative medicine with focus on all important aspects, including: cell isolation, propagation, differentiation and especially cell transplantation.

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Funding . . . 00
Acknowledgements . . . 00
References . . . 00

Peer review under responsibility of Middle East Fertility Society.

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http://dx.doi.org/10.1016/j.mefs.2017.05.008
1110-5690/

Please cite this article in press as: M. Nazm Bojnordi, The applications and recovery outcome of spermatogonia stem cells in regenerative medicine, Middle East Fertil Soc J (2017), http://dx.doi.org/10.1016/j.mefs.2017.05.008

1. Introduction

Recently, therapeutic strategies for treatment of diseases have been developed based on cell transplantation which offer alternative choices for some severe disorders. Regenerative medicine has been developed to reconstruct and restore damaged organ function via cell therapy [47,49]. In contrast to chemical drugs or mechanical devices, cell therapy can facilitate the repair of tissues via natural biochemical processes within the organs. Regenerative medicine includes all aspects of a cellular technique including cell isolation, propagation, differentiation and finally transplantation [20,41].

Scientists in the field of regenerative medicine have investigated a wide range of stem cells for their differentiation potential and therapeutic efficiency [29]. New studies showed the pluripotency characteristics of Spermatogonial stem cells (SSCs) derived from the testis showing that SSCs possibly are an appropriate source for regenerative medicine [30].

In this review we discuss main aspects that must be considered about the applications of SSCs in regenerative medicine and discus about SSCs isolation with focus on recent studies, their propagation and differential properties and finally, transplantation to animal models.

2. SSCs isolation and propagation

Isolation of SSCs is the first step in cellular techniques on regenerative strategies. Purification of SSCs can solve the problem of their limited number in the testis [31,35].

At the start of the spermatogenesis there is a category of undifferentiated spermatogonia, consisting of singles, pairs and chains of up to 16 spermatogonia. The SSCs are among the single spermatogonia [40]. Until now, widely different approaches to purify SSC have been reported by various groups.

Kanatsu-Shinohara et al. could isolate SSCs from mouse neonatal testes that only contain spermatogonia [22]. Purification of SSCs from adult testis [16] was achieved via cell sorting based on expression of STRA8, a premeiotic marker. GFRα1, a membrane marker was used by Hofmann et al. for SSC purification [18].

Recently, great progress in SSCs purification has been made. The results of Aloisio et al. in 2014, indicated PAX7 as a marker of SSCs in mice [2]. Spermatogonia cells that were positive for this marker, exhibited proliferation activity and colony formation leading to lineage differentiation and derivation of mature sperm. Chan et al. selected Id4-Gfp marker for isolation of SSCs from adult mice testes. Their findings proved that the Id4-Gfp + cell population fulfills the defining criteria of SSCs able to form colonies after transplantation into donor testes [6]. Komai et al. introduced Bmi1 as a specific marker for SSCs in comparison to other markers like GFRα1. Bmi1 marker is expressed in SSCs and their proliferation is dependent on seminiferous stages and BMI positive SSCs can provide long-term regeneration of SSCs [24]. Melissa in 2014 showed expression of the transcriptional repressor ID4 in undifferentiated mouse spermatogonia cells which mediates cell proliferation and is up-regulated, following stimulation with GDNF [19,40,46].

The in vitro culture and propagation of SSCs makes a good model for investigation of spermatogenesis, studies of male infertility as well as genetic manipulation for species preservation [11,44,27].

During recent years, the appropriate techniques to SSCs maintain in vitro have been developed including: culture of SSCs in the presence of serum or serum free medium and special stem pro media and co culture systems [10,26,32].

3. Induction of embryonic stem–like cells from SSCs

Despite the unipotency of SSCs to generate male gamete, recent reports have indicated the pluripotency potential of cultured SSCs in vitro. New studies have shown that SSCs are not only unipotent stem cells, but can also attain pluripotency characteristics in culture conditions and convert to embryonic stemlike cells (ES like cells). The generation of pluripotent stem cells from primordial germ cells (PGCs) as well as from SSCs in culture that are called Embryonic germ cells (EG cells) and ES like cells, respectively has been reported [13,22].

ES like cells resemble embryonic stem cells at the cellular and molecular level and these cells can differentiate into all three germ layers properties including ectodermal, mesodermal and endodermal germ layers [22,16].

The procedures to obtain ES like cells from testis are very different between various groups. Pioneering studies on the pluripotency of SSCs were carried out by Shinohara et al. who transformed SSCs of neonatal mouse testis into ES like cells using a hematopoietic stem cell medium, containing growth factors like GDNF and testicular somatic cells as a feeder layer, which is replaced by mitomycin-treated mouse embryonic fibroblasts (MEFs). ES cell colonies appeared within one to two months and were cultured under standard ES cell culture conditions. In this study, ES like cells were similar to Embryonic stem cells (ESCs) in potential with a differentiation capacity to all three germ layers [22].

Later, the Shinohara group announced the generation of ES like cells from adult mouse testis cells. The pluripotent cells derived from adult mouse SSCs showed the specific characteristics of pluripotency e.g.: expression of molecular and cellular levels of specific markers, the capacity to differentiation into the three germ layers and the formation of teratomas [23].

Guan et al. induced ES like cells from the adult mouse testis in a different approach. They initially, cultured spermatogonia cells in Dulbecco's Modified Eagle's Medium (DMEM) with serum and GDNF. After sorting, STRA8 positive cells were cultured in DMEM medium without GDNF and then ES-like cells formed following the addition of LIF and MEFs as a feeder layer. Guan et al. [16] and Seandel et al. [42] reported generation of ES-like colonies in a prolonged procedure, in which a mixture of testicular cells were cultured. Despite previous complex and time consuming methods, we have induced ES like cells in neonatal mouse testis using a co-culture system of SSCs with Sertoli cells [37]. However the origin of ES-like cells and the dedifferentiation mechanism are still not understood. Based on previous studies, generation of ES like cells from testis needs no defined approach or very specific protocol. ES like cells are generated using various feeder layers and feeder free culture systems. When we compare different researches, it is concluded that the kind of culture medium (for example; specific stem cells medium, DMEM medium) isn't a definitive factor for induction of ES like cells. It seems the surrounding environment of SSCs has the determinative role in the determination of the final step of SSCs to become either precursors of male gametes or transform into another lineage [12].

Further progress was reported in the generation of ESlike cells from human testis. Induction of a sufficient ES-like cell population from human SSCs was achieved via a specific culture system of SSCs in the presence of laminin and collagen. ES-like cells derived from human testis expressed pluripotency markers and were differentiated to ectodermal, mesodermal and endodermal layer derivatives [9,33].

The generation of ES like cells from human testis opens a new window for the therapeutic application of SSCs in human regenerative medicine.

Please cite this article in press as: M. Nazm Bojnordi, The applications and recovery outcome of spermatogonia stem cells in regenerative medicine, Middle East Fertil Soc J (2017), http://dx.doi.org/10.1016/j.mefs.2017.05.008