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Mini Review

Tissue Engineering for Reconstitution of Human Testicular Niche; One Step Closer to Fertility Preservation and Male Infertility Treatment

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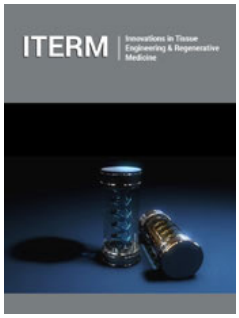

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Submission: May 20, 2019
Published: July 09, 2019

Volume 1 - Issue 3

How to cite this article: Mahdieh J, Jalal G, Fatemeh Hajizadeh T, Behrouz A. Tissue Engineering for Reconstitution of Human Testicular Niche; One Step Closer to Fertility Preservation and Male Infertility Treatment. Innovations Tissue Eng Regen Med. 1(3).ITERM.000513.2019.

Abstract

Using various sources of stem cells together with different types of scaffolds provides a new route to investigate developmental process of male gametes, which until now was difficult to investigate in the human. In the future tissue engineering may be used for new regenerative medicine application in male infertility. This brief review outlines the progressive insights of this novel biomedical technology and its capabilities, how tissue engineering can mimic developmental processes *in vitro* and generate a three-dimensional niche for spermatogenesis for research and potential therapies.

Keywords: *In vitro* gametogenesis; Male infertility; Stem cells; Tissue engineering; Reproductive medicine

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Although assisted reproductive techniques (ART) have facilitated infertility treatments still in some cases especially those with lack of gametogenesis these methods are not helpful. Gametes (sperm and egg: germ cells) which are originated from primordial germ cells (PGCs) play the most crucial role in the body which is transferring genetic information from a generation to the next generation. Therefore, understanding the molecular and cellular mechanisms controlling gametogenesis in human is critical to improve infertility treatments. Nevertheless, ethical and technical difficulties make it almost impossible to access human materials for such researches [1]. Tissue engineering is a multi-disciplinary biotechnological area which employing biomaterial and cell biology techniques for reconstitution of artificial tissues and organs *in vitro* to use in regenerative medicine [2]. Consequently, according to which tissue or organ is aimed be regenerated various types of biomaterials and different sources of cells using specific growth factors will be applied (Figure 1).

Male infertility is caused by failures in sperm production. Stem cells and biotechnology might be able to help for future treatments using *in vitro* gametogenesis (IVG). Studies have been started since 1983 by Professor McLaren on PGC culture in mouse [3]. Later, with the birth of embryonic stem cells (ESCs) in mouse [4] and human [5]; scientists have started to work on IVG from ESCs [6-8]. But the first successful report on actual sperm production from mouse ESCs was reported in 2006 with offspring in mouse [9]. Later using organ culture and germ-line stem cells (GSCs) Sato and colleagues were able to produce sperms *in vitro* [10]. In human, however, the story is different as explained by Surani's group. They

have shown that early primordial germ cell (PGC) development in human is depending on the expression of SOX17 whereas in mouse Blimp1 plays the critical role [11]. Nevertheless, there are debates regarding the pluripotency of the putative GSCs from human testis [12]. Recently, researchers worked on the reconstitution of human testis niche using porous [13] and nanofiber scaffolds [2]. The results of these works are making us one step closer to the actual understanding of the causes of male infertility which will lend it to the regenerative medicine treatments eventually. In the future, using artificial niches produced by testis derived cells seeded onto the scaffolds and IVG from hESCs, it might feasible to mimic testicle organoids as a human *in vitro* model.

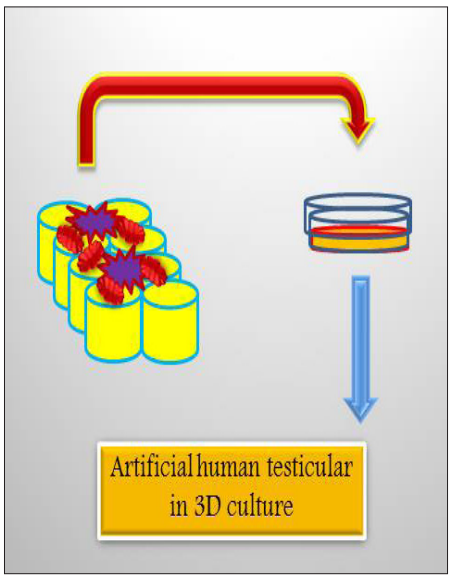

Figure 1: A schematic diagram showing how cells and scaffolds are plated into the dish to form an artificial niche for tissue engineering for sperm production. Testicular derived cells as stromal cells for male germ cells niche together with pluripotent stem cells-derived male germ cells can be cultured onto the scaffold made using testis specific ECM such as laminin and type IV collagen to reconstitute artificial human testis to mimic human male germ cell development for in vitro studies.

Conclusion

According to the recent reports [14,15] the path for the future could be using decellularized seminiferous tubules from different mammals as a natural biocompatible scaffold for reconstitution of human testicular organoids using either human testicular cells or their conditioned medium with hESCs or iPSCs [16].

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