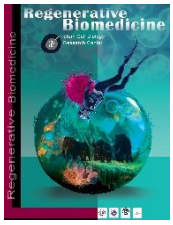

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Mini-Review Article

Releasing Scaffold Can Improve Spermatogenesis

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Abstract

Testicular tissue and cell transplantation have been suggested as a feasible therapeutic alternative for patients whose testicular tissue was cryopreserved before beginning gonadotoxic treatments. There have been no studies that show sperm production following the transplantation of human immature testicular tissue or spermatogonial stem cells. The main obstacles to human immature testicular tissue transplantation include the maintenance of early spermatogonial populations, hypoxia and reperfusion damage, and insufficient or delayed testicular graft neovascularization. The design and development of bioengineered scaffolding that can enhance ITT grafting in several animals and support testicular cells appears to be a potential strategy for maintaining human fertility. Original and review papers were gathered by searching the PubMed and Google Scholar databases. The search terms used were 'drug delivery', 'immature testicular tissue', 'in vivo spermatogenesis', 'scaffold', 'transplantation', and a combination of words using the AND and OR functions, as well as their corresponding equivalents in Mesh. This paper summarizes the advancements achieved in animal models of fertility restoration through the release of scaffolds.

Keywords: Drug delivery, Scaffold, Spermatogonial Stem Cells, Tissue engineering, Transplantation

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Introduction

Spermatozoa cryopreservation is a common method of preserving fertility for adult patients undergoing gonadotoxic therapies, including radiotherapy and chemotherapy. For prepubescent males with cancer, spermatogenic arrest, or Klinefelter syndrome, this operation is not feasible because spermatogenesis occurs after puberty. In prepubertal patients, a small piece of the testicular biopsy, including the germ cells, should be cryopreserved before beginning gonadotoxic therapies (1). Although this approach is still considered experimental, strong research and developing technologies may eventually enable its standard use (2). To restore fertility after treatment, a variety of methods have been proposed that use the patient's own frozen-thawed immature testicular tissue (ITT). These methods include in vitro maturation, autotransplantation of testicular tissue fragments or spermatogonial stem cells (SSCs), and the generation of testicular organoids for use in vivo or in vitro (3). Transplanting stem cells into seminiferous tubules is a well-researched technique that is beneficial to a variety of animals (4). Studies demonstrate that SSC transplantation is feasible in a primate species, enhancing the possibility that this method will be applied in clinical practice in the future (5). Some restrictions exist on SSC transplantation in humans due to the unestablished domain of human SSC culture and the inadequate co-transplanted microenvironment for SSC maintenance (6).

Testicular tissue pieces can be implanted into the recipient as a replacement for SSC suspensions. By keeping the SSC in their natural environment, this method maintains the response between germ cells and somatic cells. (7). In a number of investigations, immunodeficient mice underwent orthotopic or heterotopic grafting of ITT from different animal species, which led to tissue maturation and complete spermatogenesis (8-11). No evidence of sperm production has been shown following the xenotransplantation of human ITT derived from prepubertal boys or human fetuses (12-14). The preservation of early spermatogonial populations, hypoxia and reperfusion damage, and inadequate or delayed testicular graft neovascularization are the key obstacles to human immature testicular tissue transplantation (15).

Because biodegradable polymeric scaffolds offer a temporal and spatial environment conducive to cellular proliferation and tissue in-growth, they have drawn a lot of attention in the field of tissue engineering (16). To promote tissue regeneration and repair, proteins and growth factors, with or without cells, may be delivered locally via synthetic polymer scaffolds (17). Sustained delivery of growth factors encapsulated or embedded within porous matrices can promote cell growth and morphogenesis, resulting in functionally organized tissues (18).

This review provides a summary of the development of a transplantable releasing scaffold that facilitates the development and differentiation of isolated testicular tissues.

Releasing scaffold

With novel perspectives on the issue of male fertility, regenerative medicine and tissue engineering provide a rare chance to propose practical treatments in this field (19). By

adding growth factors, polymeric scaffolds can be engineered to enhance their functionality in tissue remodeling and regeneration. Tissue remodeling or organogenesis may be significantly improved by localized, sustained delivery of paracrine factors, either by stimulating or inhibiting cell proliferation, survival, migration, and/or differentiation (18). Several researchers have reported the effect of releasing scaffold on testicular tissue grafts in preclinical experiments (3, 20, 21).

Poels et al. (20) conducted a study where they transplanted testicular tissue from mice into the scrotum using an alginate hydrogel that contained VEGF-nanoparticles. They found that VEGF-NP significantly increased the formation of new blood vessels, but it did not have any impact on the survival of spermatogenic cells. On the other hand, the use of alginate alone improved the survival of spermatogonia cells.

In testicular tissue grafts, alginate hydrogels supplemented with platelet-derived growth factor delivery nanoparticles improved vascularization and vascular development compared to VEGF-only supplementation; however, potential interactions with NECINH should be further explored (21). Therefore, enhancing or expediting the formation of a fully developed vascular network in grafts could enhance the survival of both tissue and spermatogonia. Several studies using testicular tissue transplantation have aimed to enhance tissue vascularization using vascular growth factors (20, 21).

Del Vento et al. (3) demonstrated that testicular tissue incorporated into NECINH-NPs-loaded alginate hydrogel enhanced spermatogonial survival and maintained tissue integrity significantly more effectively than encapsulation in alginate alone; this finding contributes to the advancement of ITT transplantation as a viable method for restoring fertility. In contrast to encapsulation in alginate alone, Del Vento et al. (3) demonstrated that testicular tissue incorporated into NECINH-NPs-loaded alginate hydrogel enhanced spermatogonial survival and maintained tissue integrity significantly more effectively than encapsulation in alginate alone; this finding contributes to the advancement of ITT transplantation as a viable method for restoring fertility.

An important step in restoring male fertility would undoubtedly be the successful production of bioengineered scaffolds containing drug delivery systems.

Material and method

We used the PRISMA flowchart (Fig. 1) to search the keywords in two databases, including the Google Scholar and PubMed databases. Our objective was to extract information regarding the therapeutic function of releasing scaffolds in male infertility. We discovered 241 studies related to our keywords. Following that, 122 studies were found to be duplicates. We found 103 potentially relevant papers after screening the experimental study. Finally, 21 studies were considered in this review.

Conclusion

The survival and expansion of the cells depend on scaffolds, which give them enough signals and keep them in the proper differentiation stage. Therefore, it is crucial to

devote special attention to techniques for integrating adhesion peptides and growth factors into scaffolds in order to impact cell behavior. Our study's findings marked a major advancement in the production of ideal releasing scaffolds, which are required before cryobanked ITT from prepubertal males is autotransplanted in the hopes of restoring fertility in the future. It appears that the development of bioengineered scaffolds with DDS that can support testicular cells and enhance ITT transplantation in various species may be a promising approach to preserving fertility in humans.

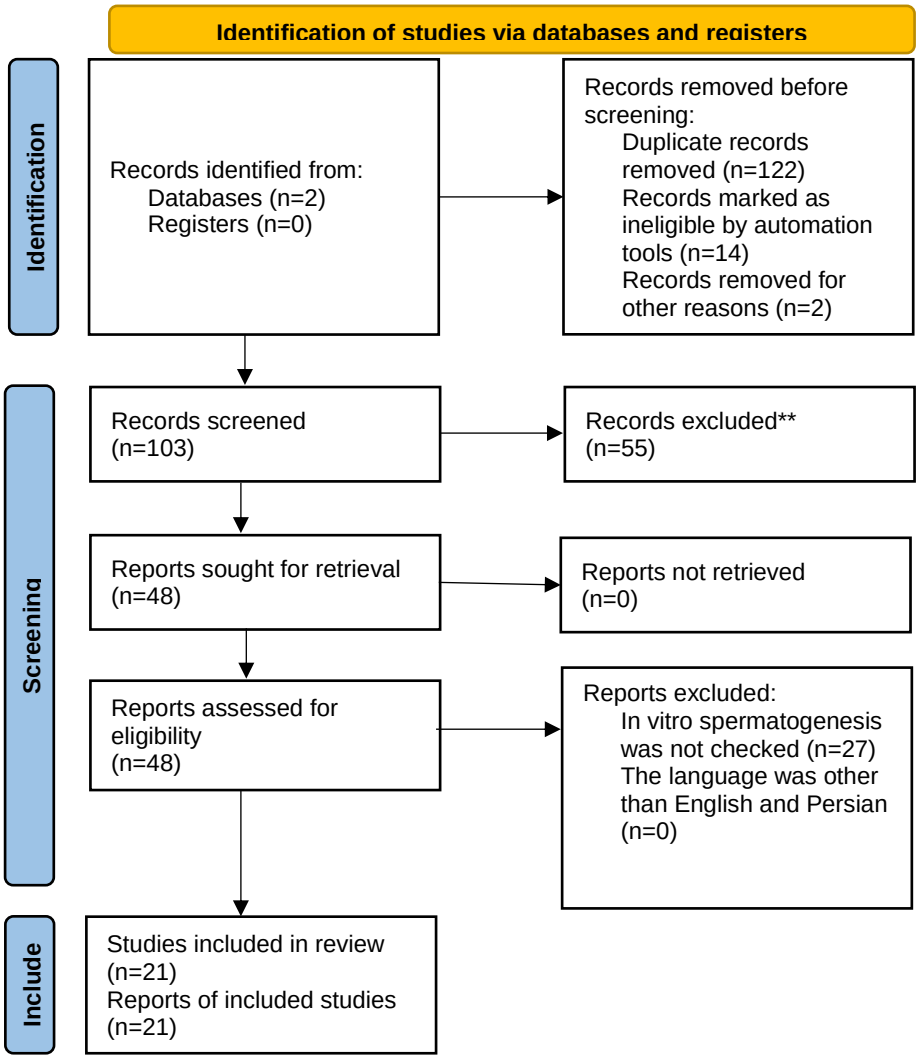

Figure 1. PRISMA flowchart of screened papers including the numbers of identified references, the numbers and reasons for exclusion, and final total number of included studies.

Conflict of interest

The authors have no conflict of interest to declare.

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