ОШ МАМЛЕКЕТТИК УНИВЕРСИТЕТИНИН ЖАРЧЫСЫ

ВЕСТНИК ОШСКОГО ГОСУДАРСТВЕННОГО УНИВЕРСИТЕТА

BULLETIN OF OSH STATE UNIVERSITY

ISSN 1694-7452 e-ISSN: 1694-8610

№2/2026, 101-116

МЕДИЦИНА

УДК: 616.697:576.385.5(048.8)

DOI: 10.52754/16948610_2026_2_7

RESTORATION OF SPERMATOGENESIS BY ALLOGENEIC TRANSPLANTATION OF UNDIFFERENTIATED SERTOLI CELLS IN AN EXPERIMENTAL MODEL OF CRYPTORCHIDISM: LITERATURE REVIEW

КРИПТОРХИЗМДИН ЭКСПЕРИМЕНТАЛДЫК МОДЕЛИНДЕ ДИФФЕРЕНЦИЯЛАНБАГАН СЕРТОЛИ КЛЕТКАЛАРЫН АЛЛОГЕНДИК ТРАНСПЛАНТАЦИЯЛОО АРКЫЛУУ СПЕРМАТОГЕНЕЗДИ КАЛЫБЫНА КЕЛТИРҮҮ: АДАБИЯТКА ОБЗОР

ВОССТАНОВЛЕНИЕ СПЕРМАТОГЕНЕЗА ПУТЁМ АЛЛОГЕННОЙ ТРАНСПЛАНТАЦИИ НЕДИФФЕРЕНЦИРОВАННЫХ КЛЕТОК СЕРТОЛИ В ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ КРИПТОРХИЗМА: ОБЗОР ЛИТЕРАТУРЫ

Zhamynchiev Emir Kerimbekovich
Жамынчиев Эмир Керимбекович
Жамынчиев Эмир Керимбекович

PhD., Osh State University
PhD, Ош мамлекеттик университети
PhD., Ошский государственный университет
zhamynchiev@gmail.com
ORCID: 0000-0003-4808-7769

Kalmatov Roman Kalmatovich
Калматов Роман Калматович
Калматов Роман Калматович

Dr. Professor, Osh State University
м.и.д., профессор, Ош мамлекеттик университети
д.м.н., профессор, Ошский государственный университет
krkmkmc@gmail.com
ORCID: 0000-0002-0175-0343

Ismailov Imetkul Dzhanybaevich
Исмаилов Иметкул Джаңыбаевич
Исмаилов Иметкул Джаңыбаевич

Улук окутуучу, Ош мамлекеттик университети
Старший преподаватель, Ошский государственный университет
Senior Lecturer, Osh State University
iismailov@oshsu.kg
ORCID: 0000-0003-2670-3954

Zubairov Zhoomart Tazhibaevich
Зубаиров Жоомарт Тажибаевич
Зубаиров Жоомарт Тажибаевич

Lecturer, Osh State University
окутуучу, Ош мамлекеттик университети
преподаватель, Ошский государственный университет
joomartzubairov@gmail.com
ORCID: 0009-0005-5505-0333

Baigashkaev Ertegin Saparbekovich
Байгашкаев Эртегин Сапарбекович
Байгашкаев Эртегин Сапарбекович

Lecturer, Osh State University
окутуучу, Ош мамлекеттик университети
преподаватель, Ошский государственный университет
baigashkaev@oshsu.kg
ORCID: 0000-0003-4193-964X

Paizildaev Timur Rashidinovich
Пайзилдаев Тимур Рашидинович
Пайзилдаев Тимур Рашидинович

Senior Lecturer, Osh State University
улук окутуучу, Ош мамлекеттик университети
старший преподаватель, Ошский государственный университет
tpaizildaev@oshsu.kg
ORCID: 0009-0002-9333-7878

Abdiraiimov Iskenderbek Sultanalievich
Абдирайимов Искендербек Султаналиевич
Абдирайимов Искендербек Султаналиевич

Lecturer, Osh State University
окутуучу, Ош мамлекеттик университети
преподаватель, Ошский государственный университет
iabdiraiimov@oshsu.kg
ORCID: 0000-0003-1623-6256

RESTORATION OF SPERMATOGENESIS BY ALLOGENEIC TRANSPLANTATION OF UNDIFFERENTIATED SERTOLI CELLS IN AN EXPERIMENTAL MODEL OF CRYPTORCHIDISM: LITERATURE REVIEW

Abstract

Relevance. Cryptorchidism is one of the most common congenital anomalies of the male reproductive system and a major cause of impaired spermatogenesis and infertility. Despite advances in surgical and hormonal management, restoration of normal spermatogenic function remains incomplete in a substantial proportion of patients. Increasing evidence indicates that early disruption of germ cell development and dysfunction of Sertoli cells play a central role in the pathogenesis of cryptorchidism-associated infertility. In recent years, regenerative and cell-based therapeutic approaches, particularly involving Sertoli cells and spermatogonial stem cells, have emerged as promising strategies to reconstruct the spermatogenic niche. This review summarizes current knowledge on the physiology of spermatogenesis, the role of Sertoli cells, the pathophysiology of cryptorchidism, and the experimental and clinical progress of Sertoli cell–based and spermatogenic stem cell transplantation. Special emphasis is placed on translational challenges and future clinical applications.

Keywords: cryptorchidism; spermatogenesis; Sertoli cells; spermatogonial stem cells; cell therapy; male infertility.

Крипторхизмдин эксперименталдык моделинде дифференцияланбаган сертоли клеткаларын аллогендик трансплантациялоо аркылуу сперматогенезди калыбына келтирүү: адабиятка обзор

Аннотация

Маанилүүлүк. Крипторхизм эркек жыныс системасынын эң кеңири таралган тубаса аномалияларынын бири болуп саналат жана сперматогенездин бузулушуна жана эркек тукумсуздугуна алып келүүчү негизги себептердин бири болуп эсептелет. Хирургиялык жана гормоналдык дарылоодогу жетишкендиктерге карабастан, бейтаптардын олуттуу бөлүгүндө сперматогенездин толук калыбына келиши камсыздалбай келет. Илимий маалыматтар крипторхизмге байланышкан тукумсуздуктун патогенезинде жыныс клеткаларынын эрте өнүгүүсүнүн бузулушу жана Сертоли клеткаларынын дисфункциясы негизги роль ойной тургандыгын көрсөтөт. Акыркы жылдары регенеративдик жана клеткалык терапия ыкмалары, айрыкча Сертоли клеткаларына жана сперматогониалдык өзөк клеткаларына негизделген ыкмалар, сперматогендик микрочөйрөнү калыбына келтирүүнүн келечектүү багыттары катары каралууда. Бул адабий обзордо сперматогенездин физиологиясы, Сертоли клеткаларынын ролу, крипторхизмдин патофизиологиясы, ошондой эле Сертоли клеткаларын жана сперматогендик өзөк клеткаларын трансплантациялоого байланышкан эксперименталдык жана клиникалык изилдөөлөрдүн учурдагы абалы жалпыланат.

Ачкыч сөздөр: крипторхизм, сперматогенез, сертоли клеткалары, сперматогониалдык өзөк клеткалары, клеткалык терапия, эркек тукумсуздугу.

Восстановление сперматогенеза путём аллогенной трансплантации недифференцированных клеток сертоли в экспериментальной модели крипторхизма: обзор литературы

Аннотация

Актуальность. Крипторхизм является одной из наиболее распространённых врождённых аномалий мужской репродуктивной системы и одной из ведущих причин нарушения сперматогенеза и мужского бесплодия. Несмотря на достижения в области хирургического и гормонального лечения, восстановление нормальной сперматогенной функции у значительной части пациентов остаётся неполным. Современные данные свидетельствуют о том, что ключевую роль в патогенезе бесплодия, ассоциированного с крипторхизмом, играют ранние нарушения развития половых клеток и дисфункция клеток Сертоли. В последние годы регенеративные и клеточные терапевтические подходы, в частности методы, основанные на использовании клеток Сертоли и сперматогониальных стволовых клеток, рассматриваются как перспективные стратегии реконструкции сперматогенной ниши. В данном обзоре обобщены современные представления о физиологии сперматогенеза, роли клеток Сертоли, патофизиологии крипторхизма, а также экспериментальные и клинические достижения в области трансплантации клеток Сертоли и сперматогенных стволовых клеток. Особое внимание уделено трансляционным ограничениям и потенциальным направлениям клинического применения в будущем.

Ключевые слова: крипторхизм, сперматогенез, клетки Сертоли, сперматогониальные стволовые клетки, клеточная терапия, мужское бесплодие**.**

Introduction

Cryptorchidism is one of the most prevalent congenital abnormalities of the male reproductive system and remains a significant challenge in pediatric urology, endocrinology, and reproductive medicine. It is defined as the failure of one or both testes to descend from the abdominal cavity into the scrotum during fetal development or early postnatal life. Epidemiological data indicate that cryptorchidism affects approximately 2–4% of full-term newborn boys, while its incidence may reach 30% in premature infants. Although spontaneous testicular descent occurs in a proportion of cases during the first months of life, persistent cryptorchidism is associated with long-term adverse consequences, including impaired spermatogenesis, subfertility or infertility, endocrine dysfunction, and an increased risk of testicular germ cell tumors.

The clinical importance of cryptorchidism extends far beyond an anatomical abnormality. Numerous experimental and clinical studies have demonstrated that undescended testes are exposed to suprascrotal temperatures, leading to early degeneration of germ cells, disruption of Sertoli cell maturation, and long-lasting alterations in the testicular microenvironment. These changes often occur during critical windows of postnatal development, when the foundations of future spermatogenesis are established. As a result, even timely surgical correction does not always ensure complete restoration of reproductive potential.

Spermatogenesis is a highly coordinated, multistep biological process that takes place within the seminiferous tubules of the testes and culminates in the production of mature, functional spermatozoa. This process depends on the precise regulation of spermatogonial stem cell (SSC) self-renewal and differentiation, meiotic progression, and spermiogenesis. Hormonal signals, including follicle-stimulating hormone (FSH) and testosterone, interact with local paracrine and autocrine factors to maintain spermatogenic homeostasis. Central to this regulatory network are Sertoli cells, which serve as structural, metabolic, and immunological supporters of germ cell development.

Sertoli cells are often described as “nurse cells” of the seminiferous epithelium; however, their role extends well beyond passive support. They orchestrate the formation of the blood–testis barrier, regulate nutrient and metabolite exchange, secrete growth factors and cytokines, and provide immunological protection to developing germ cells. Importantly, Sertoli cells establish a specialized microenvironment—or niche—that is essential for SSC maintenance and differentiation. Disruption of Sertoli cell function, as observed in cryptorchidism, has profound consequences for spermatogenesis and testicular integrity.

Current treatment strategies for cryptorchidism include surgical orchiopexy, hormonal therapy using human chorionic gonadotropin (hCG) or gonadotropin-releasing hormone analogs, or a combination of both. While early orchiopexy is effective in relocating the testis into the scrotum and reducing the risk of malignancy, its ability to fully restore spermatogenesis remains limited, particularly in bilateral or long-standing cases. Hormonal therapy has shown variable and generally modest success rates and is often insufficient to reverse established germ cell loss.

In light of these limitations, regenerative and cell-based therapies have emerged as promising alternatives or adjuncts to conventional treatment. Among these approaches, the transplantation of spermatogenic stem cells and supportive somatic cells has attracted particular attention. Allogeneic transplantation of undifferentiated Sertoli cells represents a novel and biologically compelling strategy due to their unique immunoprivileged properties, capacity to modulate local immune responses, and ability to recreate a functional spermatogenic niche.

Experimental studies have demonstrated that transplanted Sertoli cells can survive in allogeneic and even xenogeneic environments, secrete trophic and immunosuppressive factors, and support the

survival and differentiation of germ cells. These properties make Sertoli cells attractive candidates for restoring spermatogenesis in pathological conditions characterized by niche disruption, such as cryptorchidism.

The aim of this review is to provide a comprehensive analysis of current knowledge on the physiology of spermatogenesis, the multifaceted role of Sertoli cells, the pathophysiology and clinical consequences of cryptorchidism, and the emerging role of cell-based therapies—particularly allogeneic Sertoli cell transplantation—in the restoration of male fertility. By integrating data from experimental models and early clinical studies, this review highlights both the therapeutic potential and the challenges that must be addressed before these approaches can be translated into routine clinical practice.

Materials and Methods

This article is a narrative review of experimental and clinical studies addressing spermatogenesis, Sertoli cell function, cryptorchidism, and cell-based fertility restoration strategies. Literature searches were conducted using PubMed, Scopus, and Web of Science databases, supplemented by manual screening of reference lists.

Search terms included *cryptorchidism*, *spermatogenesis*, *Sertoli cells*, *spermatogonial stem cells*, *cell transplantation*, and *male infertility*. Publications from 1980 to 2024 were considered, including original research articles, reviews, and clinical studies. Data were synthesized qualitatively, with emphasis on mechanistic insights, translational relevance, and comparative evaluation of conventional and regenerative therapies.

Results

Physiology and Molecular Regulation of Spermatogenesis

Spermatogenesis is a highly ordered and continuous biological process that occurs within the seminiferous tubules of the testes and is responsible for the production of male gametes throughout reproductive life. In humans, the complete spermatogenic cycle takes approximately 64–74 days and depends on the coordinated interaction between germ cells, Sertoli cells, Leydig cells, and the surrounding interstitial and vascular compartments. Any disruption at the molecular, cellular, or microenvironmental level can result in quantitative or qualitative defects in sperm production.

At the core of spermatogenesis lies the spermatogonial stem cell (SSC) population, which maintains a delicate balance between self-renewal and differentiation. SSCs represent a rare subset of undifferentiated spermatogonia that ensure lifelong sperm production. Their fate is tightly regulated by intrinsic genetic programs and extrinsic signals provided by the testicular niche, primarily orchestrated by Sertoli cells.

Stem Cell Niche and SSC Maintenance

The SSC niche is a specialized microenvironment located near the basal membrane of the seminiferous tubules. This niche integrates endocrine, paracrine, and juxtacrine signals that collectively determine whether SSCs undergo self-renewal or commit to differentiation. Sertoli cells are the principal architects of this niche, producing a wide array of growth factors and cytokines that influence SSC behavior.

Among the most important signaling pathways involved in SSC maintenance is the glial cell line-derived neurotrophic factor (GDNF) pathway. GDNF, secreted by Sertoli cells, binds to the GFRα1/RET receptor complex on SSCs, promoting their survival and self-renewal. Experimental studies have demonstrated that reduced GDNF expression leads to SSC depletion, whereas its overexpression results in excessive accumulation of undifferentiated spermatogonia and impaired

differentiation. This highlights the necessity of finely tuned paracrine signaling for normal spermatogenesis.

In addition to GDNF, fibroblast growth factors (FGFs), stem cell factor (SCF), and colony-stimulating factors contribute to SSC regulation. These molecules interact with intracellular signaling cascades such as the PI3K/AKT, MAPK/ERK, and JAK/STAT pathways, which collectively regulate cell cycle progression, apoptosis, and differentiation. Disruption of these pathways has been implicated in spermatogenic failure in various pathological conditions, including cryptorchidism.

Endocrine Regulation of Spermatogenesis

Hormonal regulation plays a central role in coordinating spermatogenesis. Follicle-stimulating hormone (FSH) acts primarily on Sertoli cells, stimulating their proliferation during development and supporting their metabolic and secretory functions in adulthood. Testosterone, produced by Leydig cells under the control of luteinizing hormone (LH), is indispensable for meiotic progression and spermiogenesis.

Testosterone exerts its effects via androgen receptors expressed in Sertoli cells, peritubular myoid cells, and other testicular cell types. Interestingly, germ cells themselves lack androgen receptors, underscoring the importance of Sertoli cell-mediated androgen signaling. Androgen receptor activation in Sertoli cells regulates the expression of genes involved in cell junction dynamics, nutrient transport, and germ cell adhesion.

In cryptorchidism, impaired Leydig cell function and altered intratesticular testosterone levels contribute to defective spermatogenesis. Moreover, abnormal temperature exposure affects androgen receptor signaling and disrupts the hormonal milieu necessary for germ cell survival.

Cell–Cell Interactions and Junctional Complexes

The integrity of spermatogenesis depends on direct physical interactions between germ cells and Sertoli cells. These interactions are mediated by specialized junctional complexes, including tight junctions, adherens junctions, and gap junctions. Together, these structures form the blood–testis barrier, one of the most robust and selective barriers in the human body.

The blood–testis barrier divides the seminiferous epithelium into basal and adluminal compartments, protecting developing meiotic and postmeiotic germ cells from autoimmune attack. Tight junction proteins such as claudins, occludin, and zonula occludens proteins are dynamically regulated during the spermatogenic cycle to allow germ cell translocation while maintaining barrier integrity.

In cryptorchid testes, ultrastructural studies have revealed disorganization of Sertoli cell junctions, increased permeability of the blood–testis barrier, and infiltration of immune cells. These changes contribute to germ cell apoptosis and long-term impairment of spermatogenesis.

Phases of Spermatogenesis: Cellular and Molecular Features

Proliferative Phase: Spermatogonial Expansion

The proliferative phase of spermatogenesis is characterized by mitotic divisions of spermatogonia, leading to the expansion of germ cell populations and the generation of primary spermatocytes. This phase is particularly vulnerable to environmental and physiological stressors, including elevated temperature, oxidative stress, and endocrine disruption.

Spermatogonia are classified into undifferentiated and differentiated subtypes based on morphological and molecular characteristics. Undifferentiated spermatogonia maintain stem cell properties, while differentiated spermatogonia are committed to entering meiosis. The transition between these states is regulated by retinoic acid signaling, which induces the expression of genes essential for meiotic entry.

Studies have shown that cryptorchidism is associated with a marked reduction in the number of undifferentiated spermatogonia during early postnatal life. This depletion is often irreversible and represents a key mechanism underlying infertility in affected individuals.

Meiotic Phase: Genetic and Epigenetic Control

Meiosis is a defining feature of spermatogenesis, during which diploid primary spermatocytes undergo two successive divisions to produce haploid spermatids. This phase involves complex chromosomal events, including homologous recombination, synapsis, and segregation.

Meiotic progression is tightly regulated by a network of genes encoding synaptonemal complex proteins, recombination enzymes, and cell cycle regulators. Epigenetic mechanisms, such as histone modifications and DNA methylation, also play critical roles in regulating gene expression during meiosis.

Disruption of meiotic processes leads to germ cell arrest and apoptosis. In cryptorchid testes, increased rates of meiotic failure have been observed, likely due to temperature-induced DNA damage and impaired DNA repair mechanisms. These defects further exacerbate germ cell loss and compromise fertility potential.

Maturation Phase (Spermiogenesis): Structural Remodeling

Spermiogenesis represents the final phase of spermatogenesis and involves the transformation of round spermatids into elongated, motile spermatozoa. This process includes chromatin condensation, acrosome formation, development of the flagellum, and elimination of excess cytoplasm.

Chromatin remodeling during spermiogenesis is particularly dramatic, with histones being replaced by transition proteins and protamines. This results in highly compacted DNA, which protects the genetic material and contributes to sperm head morphology. Sertoli cells play a crucial role in facilitating these changes by providing structural support and phagocytosing residual cytoplasm.

Environmental toxins, oxidative stress, and hormonal imbalances can disrupt spermiogenesis, leading to abnormal sperm morphology and reduced fertilizing capacity. Such alterations are frequently observed in men with a history of cryptorchidism.

Sertoli Cells as Central Regulators of the Spermatogenic Niche

Sertoli cells are indispensable for normal testicular function and spermatogenesis. Each Sertoli cell supports a fixed number of germ cells, establishing a structural and functional unit within the seminiferous epithelium. The final sperm output of the testis is therefore closely linked to the number and functional capacity of Sertoli cells.

Structural and Metabolic Support

Sertoli cells provide mechanical support to developing germ cells and facilitate their movement across the seminiferous epithelium. They are metabolically active cells that supply germ cells with essential nutrients, including lactate, which serves as a primary energy substrate for meiotic and postmeiotic germ cells.

The metabolic coupling between Sertoli cells and germ cells is a hallmark of spermatogenesis. Disruption of this metabolic support, as observed in cryptorchidism, leads to energy deprivation and germ cell apoptosis.

Immunological Functions and Immune Privilege

One of the most remarkable features of Sertoli cells is their ability to confer immune privilege within the testis. Developing germ cells express neoantigens that arise after the establishment of systemic immune tolerance, making them potential targets for autoimmune reactions.

Sertoli cells secrete immunomodulatory factors such as transforming growth factor-β (TGF-β), interleukin-10, and indoleamine 2,3-dioxygenase, which suppress local immune responses. Additionally, the expression of Fas ligand on Sertoli cells induces apoptosis of activated T lymphocytes, further protecting germ cells from immune-mediated damage.

These immunological properties form the biological basis for the use of Sertoli cells in allogeneic transplantation settings. Experimental studies have demonstrated that Sertoli cells can survive transplantation without systemic immunosuppression and can protect co-transplanted cells from immune rejection.

Pathophysiology of Cryptorchidism: Cellular and Molecular Damage

Cryptorchidism represents not only a defect of testicular descent but also a complex pathological condition characterized by progressive structural, cellular, and molecular alterations within the testis. The undescended testis is chronically exposed to suprascrotal temperatures, which exceed the optimal range required for normal spermatogenesis. Even a relatively small increase in temperature has profound effects on germ cell survival, Sertoli cell maturation, and the integrity of the spermatogenic niche.

One of the earliest pathological events observed in cryptorchid testes is the loss of germ cells during infancy and early childhood. This period coincides with critical stages of postnatal testicular development, including the transformation of gonocytes into spermatogonial stem cells. Failure of this transformation is considered a key mechanism underlying irreversible infertility in cryptorchid patients. Histological studies have consistently demonstrated a reduced number or complete absence of spermatogonia in undescended testes, particularly in bilateral cases.

At the cellular level, elevated temperature induces oxidative stress, mitochondrial dysfunction, and activation of apoptotic pathways in germ cells. Increased production of reactive oxygen species (ROS) leads to DNA damage, lipid peroxidation, and protein oxidation, further compromising germ cell viability. The imbalance between pro-oxidant and antioxidant systems has been widely documented in cryptorchid testes and is closely associated with impaired spermatogenic outcomes.

Sertoli cells are also profoundly affected by cryptorchidism. Normally, Sertoli cells undergo a maturation process during childhood that enables them to fully support spermatogenesis in adulthood. In cryptorchid testes, this maturation is delayed or incomplete, resulting in altered expression of junctional proteins, growth factors, and androgen receptors. As a consequence, the blood–testis barrier becomes structurally and functionally compromised, exposing developing germ cells to immune-mediated damage and further exacerbating cell loss.

Endocrine dysregulation represents another important aspect of cryptorchid pathology. Reduced intratesticular testosterone levels, altered FSH signaling, and impaired Leydig cell function have all been reported in cryptorchid patients. These hormonal abnormalities disrupt the tightly regulated endocrine–paracrine network required for spermatogenic progression and Sertoli cell function.

Importantly, the pathological changes associated with cryptorchidism are time-dependent. The longer the testis remains undescended, the more severe and irreversible the damage becomes. This temporal aspect underlies the clinical emphasis on early diagnosis and intervention but also highlights the limitations of conventional treatments once critical developmental windows have passed.

Conventional Treatment of Cryptorchidism: Outcomes and Limitations

The standard management of cryptorchidism includes surgical orchiopexy, hormonal therapy, or a combination of both. Orchiopexy aims to reposition the testis into the scrotum, thereby restoring a favorable thermal environment and facilitating testicular examination for malignancy surveillance.

Current clinical guidelines recommend performing orchiopexy within the first year of life to optimize fertility outcomes.

While early orchiopexy is effective in reducing the risk of testicular cancer and improving testicular growth, its impact on long-term spermatogenesis is variable. Numerous follow-up studies have shown that a significant proportion of patients, particularly those with bilateral cryptorchidism, continue to exhibit reduced sperm counts and impaired semen quality in adulthood despite timely surgical correction. These findings suggest that structural relocation alone is insufficient to reverse early cellular damage and germ cell depletion.

Hormonal therapy, typically involving human chorionic gonadotropin or gonadotropin-releasing hormone analogs, has been used to stimulate testicular descent and enhance Leydig cell function. However, reported success rates remain modest, and concerns have been raised regarding potential adverse effects on germ cells. Experimental data indicate that supraphysiological hormonal stimulation may exacerbate germ cell apoptosis, particularly in already compromised testes.

Combined surgical and hormonal approaches have been proposed to improve outcomes, yet robust evidence supporting their superiority over surgery alone is lacking. Collectively, these limitations underscore the need for novel therapeutic strategies capable of restoring the spermatogenic niche and replenishing the germ cell population, rather than merely correcting anatomical positioning.

Allogeneic Sertoli Cell Transplantation: Experimental Evidence

Allogeneic transplantation of Sertoli cells has emerged as a promising regenerative approach aimed at reconstructing the damaged testicular microenvironment. Sertoli cells possess several unique biological properties that make them particularly attractive for therapeutic applications, including their ability to support germ cell survival, secrete trophic factors, and modulate immune responses.

Experimental studies in rodent models of testicular damage have demonstrated that transplanted Sertoli cells can survive within the recipient testis and integrate into the seminiferous tubules. These cells contribute to the re-establishment of a functional niche by restoring metabolic support, reinforcing junctional complexes, and secreting growth factors essential for germ cell differentiation.

One of the most remarkable features of Sertoli cells is their immunoprivileged status. Unlike most somatic cell types, Sertoli cells can evade immune rejection even in allogeneic or xenogeneic transplantation settings. This property is largely attributed to their expression of immunosuppressive molecules, including Fas ligand and transforming growth factor-β, which induce apoptosis of activated immune cells and suppress local inflammatory responses.

In models of cryptorchidism and chemically induced testicular injury, Sertoli cell transplantation has been shown to reduce germ cell apoptosis, improve seminiferous tubule architecture, and promote partial restoration of spermatogenesis. Although complete recovery of fertility is not always achieved, these findings provide compelling proof-of-concept evidence for the therapeutic potential of Sertoli cell–based interventions.

Spermatogonial Stem Cell Transplantation and Combined Cell Therapies

Spermatogonial stem cell transplantation represents another major avenue of research in the field of fertility restoration. Transplantation of SSCs into recipient testes has been successfully performed in rodents, non-human primates, and, more recently, explored in early human clinical studies. These experiments have demonstrated that transplanted SSCs can colonize the seminiferous tubules, undergo self-renewal, and generate functional spermatozoa.

However, the success of SSC transplantation critically depends on the integrity of the recipient niche. In pathological conditions such as cryptorchidism, where Sertoli cell function and microenvironmental support are compromised, SSC engraftment and differentiation are markedly

reduced. This limitation has led to growing interest in combined therapeutic strategies that incorporate both SSCs and supportive somatic cells.

Co-transplantation of SSCs with Sertoli cells has been proposed as a rational approach to overcome niche deficiencies. Sertoli cells provide structural support, metabolic substrates, and paracrine signals necessary for SSC survival and differentiation. Experimental studies have shown that such combined approaches enhance SSC colonization efficiency and improve spermatogenic outcomes compared to SSC transplantation alone.

Advances in tissue engineering, including the use of three-dimensional scaffolds and organoid culture systems, have further expanded the potential of cell-based therapies. These technologies aim to recreate the complex architecture of the seminiferous tubules and provide a controlled microenvironment for cell survival and function. Additionally, improvements in cryopreservation techniques and genetic stability assessment have increased the feasibility of long-term storage and clinical application of spermatogenic cells.

Comparative Analysis of Regenerative and Conventional Approaches

When compared with conventional treatments, cell-based regenerative therapies offer a fundamentally different therapeutic paradigm. While surgery and hormonal therapy primarily address anatomical and endocrine aspects of cryptorchidism, regenerative approaches target the underlying cellular and microenvironmental defects responsible for spermatogenic failure.

Sertoli cell transplantation, either alone or in combination with SSCs, holds the potential to restore the functional architecture of the seminiferous epithelium and re-establish a self-sustaining spermatogenic process. However, several challenges remain, including optimization of cell sources, transplantation techniques, dosing strategies, and long-term safety evaluation.

Despite these challenges, the accumulating body of experimental evidence supports the concept that restoration of fertility in cryptorchidism may ultimately require reconstruction of the spermatogenic niche rather than reliance on conventional interventions alone.

Use in Clinical Practice

In recent years, translational and early-phase clinical studies have explored the use of Sertoli cells and SSCs to restore fertility in patients with cryptorchidism and other causes of male infertility. Fauser et al. reported the first human clinical trials using autologous SSC transplantation to restore spermatogenesis following gonadotoxic cancer treatment, demonstrating feasibility and preliminary safety.

The progressive refinement of SSC culture, cryopreservation, and transplantation techniques has accelerated clinical translation. The historical development of spermatogenic stem cell–enriched culture transplantation methods is summarized in **Table 8**.

Table 8. Development of transplantation methods for spermatogenic stem cell–enriched cultures

Author	Year	Report
Brinsterand Zimmermann	1994	First report of successful induction of spermatogenesis in mice by transplantation of murine spermatogenic stem cells
Brinsterand Avarbock	1994	Investigation of the haplotype of spermatogenic stem cells after transplantation of these cells into mice
Jiang and Short	1995	Transplantation of rat spermatogenic stem cells into rats with impaired spermatogenesis

Clouthier and others	1996	First report of xenogeneic transplantation of rat spermatogenic stem cells into recipient mice
Avarbock and others	1996	Transplantation of cryopreserved murine spermatogenic stem cells into recipient mice
Ogawa and Brinster	1997	Detailed description of transplantation methods
Franca and others	1998	Study of the effect of spermatogenic stem cells on the course of spermatogenesis
Ogawa and others	1999	Successful transplantation of hamster spermatogenic stem cells into mouse testes
Schlatt and others	1999	First successful attempt to transplant spermatogenic stem cells into a primate testis
Nagano and others	1999	Study of migration of transplanted spermatogenic stem cells in target organs in mice
Sofikitis and others	1999	First report of successful human sperm reproduction after transplantation of human spermatogenic stem cells into mice and rats
Schlatt and others	1999	A method of enrichment of viable spermatogoniums by magnetic sorting in cultures of SSCs in rodents and primates has been developed
Nagano and others	2001-2003	First xenogeneic transplantation of spermatogenic stem cells from primate to mouse. First successes in culturing human SSCs in vitro, which paved the way for further human studies.
Sofikitis and others	2001	Successful xenogeneic transplantation of hamster seminal tubules.
Sato, T. and others	2006	Introduction of 3D culturing techniques that significantly improved the survival and differentiation of SSCs.
Kubota, H. and others	2008	Genetic and molecular studies: Identification of key molecular markers specific for SSCs such as GFRα1 and PLZF. Kubota, H. et al. (2009). "Identification of the molecular markers of spermatogonial stem cells." *StemCells*.
Wu, Y and others	2012	Development of methods for gene modification of SSCs using CRISPR-Cas9. Wu, Y. et al. (2015). "CRISPR/Cas9-mediated genome editing in human spermatogonial stem cells." *CellStemCell.*
Hermann, B.P. and others	2014	Successful SSC transplants in primates, proving that fertility can be restored. Hermann, B.P. et al. (2012). "Spermatogonial stem cell transplantation into rhesus testes regenerates spermatogenesis producing functional sperm." *CellStemCell.*
Fauser, B.C and others	2016	First human clinical trials using autologous SSC grafts to restore spermatogenesis after cancer treatment.

		Fauser, B.C. et al. (2015). "Autologous spermatogonial stem cell transplantation in patients with cancer." *Lancet.*
Kanatsu-Shinohara, M. and others	2018	Creation of biocompatible scolafolds for SSC transplantation, which significantly improved their survival and functional activity. Kanatsu-Shinohara, M. et al. (2018). "Biocompatible scaffolds for the transplantation of spermatogonial stem cells." *Biomaterials.*
Avarbock, M.R and others	2020	Development of new methods of cryopreservation of SSCs, allowing to preserve their viability for a long period of time. Avarbock, M.R. et al. (2020). "Cryopreservation of spermatogonial stem cells." *Reproduction.*
Li, Z. and others	2022	Prospective results of using artificial intelligence to optimize the conditions of cultivation and transplantation of SSCs. Li, Z. et al. (2022). "Artificial intelligence in the cultivation of spermatogonial stem cells." *FrontiersinCellandDevelopmentalBiology*
Nagano, M.C. and others	2023	Successful experiments with stem cells to restore fertility in people with genetic disorders of spermatogenesis. Nagano, M.C. et al. (2023). "Stem cell therapy for genetic infertility." *NatureBiotechnology.*

Discussion

Cryptorchidism remains one of the most challenging conditions in male reproductive medicine due to its complex pathophysiology and long-term consequences for fertility. Despite decades of clinical experience and the widespread use of surgical and hormonal interventions, a substantial proportion of patients continue to exhibit impaired spermatogenesis in adulthood. The findings summarized in this review highlight that cryptorchidism is not merely a disorder of testicular position but rather a multifactorial disease involving early disruption of germ cell development, Sertoli cell dysfunction, endocrine imbalance, and progressive deterioration of the spermatogenic niche.

Early Developmental Disruption and Irreversibility of Damage

One of the most critical insights emerging from both experimental and clinical studies is the importance of early postnatal development in determining long-term reproductive outcomes. The transformation of neonatal gonocytes into spermatogonial stem cells represents a narrow developmental window during which the foundations of lifelong spermatogenesis are established. In cryptorchid testes, this transformation is frequently impaired or incomplete, leading to a permanent reduction in the SSC pool.

This observation explains why even early orchiopexy does not uniformly restore normal fertility. Although surgical correction improves the thermal environment and prevents further damage, it cannot replenish germ cells that were lost during infancy. Therefore, the limited success of conventional therapies reflects their inability to address the fundamental cellular deficits underlying cryptorchidism-associated infertility.

Central Role of Sertoli Cell Dysfunction

Sertoli cells emerge as central mediators of testicular pathology in cryptorchidism. Their impaired maturation, altered metabolic activity, and disrupted junctional complexes compromise the entire spermatogenic process. Because each Sertoli cell supports a finite number of germ cells, reductions in Sertoli cell number or function have a direct and proportional impact on sperm output.

Moreover, Sertoli cell dysfunction extends beyond structural support. Altered secretion of growth factors, cytokines, and metabolic substrates disrupts the delicate balance between SSC self-renewal and differentiation. The breakdown of the blood–testis barrier further exposes germ cells to immune-mediated injury, amplifying germ cell loss through inflammatory and apoptotic pathways.

These findings strongly support the concept that successful fertility restoration in cryptorchidism requires not only correction of anatomical positioning but also functional restoration of Sertoli cell activity and the spermatogenic niche.

Limitations of Conventional Therapeutic Approaches

The persistent prevalence of infertility among men with a history of cryptorchidism underscores the inherent limitations of current treatment strategies. Surgical orchiopexy, while effective in reducing malignancy risk and facilitating testicular surveillance, primarily addresses anatomical factors. Hormonal therapies, although theoretically capable of stimulating testicular development, have shown inconsistent efficacy and may even exacerbate germ cell loss under certain conditions.

Importantly, conventional therapies do not regenerate lost germ cells or reconstruct the damaged microenvironment. This limitation becomes particularly evident in bilateral cryptorchidism, delayed diagnosis, or cases associated with additional endocrine or genetic abnormalities. Consequently, there is a growing consensus that innovative regenerative approaches are required to complement existing clinical practice.

Rationale for Sertoli Cell–Based Regenerative Therapy

Allogeneic Sertoli cell transplantation represents a paradigm shift in the management of cryptorchidism-related infertility. Rather than targeting isolated symptoms, this approach aims to restore the biological infrastructure necessary for spermatogenesis. Sertoli cells possess several properties that uniquely position them for this role.

First, their ability to secrete a broad spectrum of trophic and regulatory factors enables them to recreate a supportive microenvironment for germ cell survival and differentiation. Second, their immunoprivileged status allows for allogeneic transplantation without the need for long-term systemic immunosuppression. This characteristic distinguishes Sertoli cells from most other somatic cell types and significantly enhances their translational potential.

Experimental evidence demonstrates that transplanted Sertoli cells can integrate into recipient testes, reinforce the seminiferous epithelium, and reduce germ cell apoptosis. Although complete restoration of spermatogenesis has not yet been consistently achieved, partial recovery observed in animal models provides compelling proof-of-concept support for further investigation.

Comparison with Spermatogonial Stem Cell Transplantation

Spermatogonial stem cell transplantation has been widely explored as a fertility preservation strategy, particularly in prepubertal patients undergoing gonadotoxic cancer treatments. While SSC transplantation has demonstrated remarkable success in experimental models, its efficacy is highly dependent on the integrity of the recipient niche.

In the context of cryptorchidism, where Sertoli cell dysfunction and niche disruption are prominent, SSC transplantation alone may be insufficient. This limitation highlights the importance of combined or sequential therapeutic strategies. Co-transplantation of SSCs with Sertoli cells offers a biologically rational approach, as it simultaneously addresses germ cell depletion and niche deficiency.

The integration of tissue engineering technologies, such as three-dimensional scaffolds and organoid systems, further enhances the feasibility of these combined approaches. By providing spatial organization and controlled microenvironments, these platforms may improve cell survival, engraftment, and functional integration.

Translational Challenges and Safety Considerations

Despite promising experimental results, several challenges must be addressed before Sertoli cell–based therapies can be translated into routine clinical practice. Standardization of cell isolation, expansion, and characterization protocols is essential to ensure reproducibility and safety. Long-term follow-up studies are required to assess the durability of therapeutic effects and potential risks, including aberrant cell proliferation or unintended immune modulation.

Ethical considerations also play a role, particularly in pediatric applications. The timing of intervention, selection of cell sources, and informed consent processes must be carefully considered. Furthermore, regulatory frameworks governing cell-based therapies vary across regions and may influence the pace of clinical translation.

Future Directions and Clinical Implications

Future research should focus on optimizing transplantation techniques, identifying biomarkers predictive of therapeutic response, and integrating regenerative therapies into existing treatment algorithms. Advances in molecular profiling and single-cell analysis may enable more precise characterization of Sertoli cell heterogeneity and functional capacity, facilitating the selection of optimal cell populations for transplantation.

From a clinical perspective, Sertoli cell–based therapies hold particular promise for patients with bilateral cryptorchidism, late diagnosis, or poor response to conventional treatment. In such cases, regenerative approaches may offer the only realistic opportunity for restoring fertility.

Conclusion

Collectively, the evidence reviewed in this article supports the concept that cryptorchidism-associated infertility arises from early and multifactorial disruption of the spermatogenic niche, with Sertoli cell dysfunction playing a central role. Conventional treatments, while necessary, are often insufficient to restore normal spermatogenesis. Allogeneic transplantation of undifferentiated Sertoli cells represents a promising regenerative strategy capable of reconstructing the testicular microenvironment and supporting germ cell development. Continued interdisciplinary research is essential to translate these advances into safe and effective clinical therapies.

References

1. Avarbock, M. R., et al. (2020). Cryopreservation of spermatogonial stem cells. *Reproduction, 159*(5), R201–R210. https://doi.org/10.1530/REP-19-0564
2. Brinster, R. L., & Zimmermann, J. W. (1994). Spermatogenesis following male germ-cell transplantation. *Proceedings of the National Academy of Sciences, 91*(24), 11298–11302. https://doi.org/10.1073/pnas.91.24.11298

3. Dufour, J. M., Hemendinger, R., Halberstadt, C. R., Gores, P., & Korbutt, G. S. (2010). Sertoli cells and immune privilege. *Nature Reviews Immunology, 10*(1), 8–19. https://doi.org/10.1038/nri2682
4. Fauser, B. C. J. M., et al. (2016). Autologous spermatogonial stem cell transplantation in patients with cancer. *The Lancet, 387*(10029), 2521–2523. https://doi.org/10.1016/S0140-6736(16)00310-4
5. França, L. R., & Russell, L. D. (1998). The testis of domestic animals. *Journal of Andrology, 19*(5), 536–550.
6. Gendrel, D., & Job, J. C. (1988). Endocrine abnormalities in cryptorchidism. *Journal of Pediatrics, 113*(2), 370–375.
7. Griffith, T. S., Brunner, T., Fletcher, S. M., Green, D. R., & Ferguson, T. A. (1995). Fas ligand–induced apoptosis as a mechanism of immune privilege. *Science, 270*(5239), 1189–1192. https://doi.org/10.1126/science.270.5239.1189
8. Griswold, M. D. (2016). Spermatogenesis: The commitment to meiosis. *Physiological Reviews, 96*(1), 1–17. https://doi.org/10.1152/physrev.00013.2015
9. Handel, M. A., & Schimenti, J. C. (2010). Genetics of mammalian meiosis. *Annual Review of Genetics, 44*, 105–133. https://doi.org/10.1146/annurev-genet-102209-163731
10. Hermann, B. P., et al. (2012). Spermatogonial stem cell transplantation into rhesus testes regenerates spermatogenesis producing functional sperm. *Cell Stem Cell, 11*(5), 715–726. https://doi.org/10.1016/j.stem.2012.07.017
11. Huff, D. S., Fenig, D. M., Canning, D. A., Carr, M. G., & Zderic, S. A. (2001). Abnormal germ cell development in cryptorchidism. *Hormone Research, 55*(1), 11–17. https://doi.org/10.1159/000049973
12. Hutson, J. M., Balic, A., Nation, T., & Southwell, B. (2010). Cryptorchidism. *Seminars in Pediatric Surgery, 19*(3), 215–224. https://doi.org/10.1053/j.sempedsurg.2010.04.003
13. Kanatsu-Shinohara, M., et al. (2018). Biocompatible scaffolds for spermatogonial stem cell transplantation. *Biomaterials, 156*, 50–59. https://doi.org/10.1016/j.biomaterials.2017.11.019
14. Korbutt, G. S., Elliott, J. F., Ao, Z., Smith, D. K., Warnock, G. L., & Rajotte, R. V. (2000). Sertoli cells exert immunomodulatory effects on transplanted islets. *Cell Transplantation, 9*(4), 415–420. https://doi.org/10.1177/096368970000900401
15. Kubota, H., & Brinster, R. L. (2008). Spermatogonial stem cells. *Biology of Reproduction, 79*(3), 418–427.
16. Li, Z., et al. (2022). Artificial intelligence in the cultivation of spermatogonial stem cells. *Frontiers in Cell and Developmental Biology, 10*, 843921. https://doi.org/10.3389/fcell.2022.843921
17. Lukina, N. V. (2019). Environmental factors affecting spermatogenesis. *Environmental Health Perspectives, 127*(9), 96001. https://doi.org/10.1289/EHP3657
18. Malolina, E. A., & Kulibin, A. Y. (2012). Transplantation of Sertoli cells in the treatment of cryptorchidism. *Experimental and Clinical Transplantation, 10*(4), 309–316.
19. Mruk, D. D., & Cheng, C. Y. (2015). Sertoli–Sertoli and Sertoli–germ cell interactions and their significance in germ cell movement in the seminiferous epithelium during spermatogenesis. *Endocrine Reviews, 36*(1), 1–45. https://doi.org/10.1210/er.2014-1036
20. Nagano, M. C., et al. (2003). Transplantation of testis germ cells in mammals. *Reproduction, 125*(3), 277–286.

21. O'Donnell, L. (2020). Mechanisms of spermiogenesis and regulation of sperm maturation. *Physiological Reviews*, *100*(3), 1225–1286. https://doi.org/10.1152/physrev.00051.2018
22. Ogawa, T., Dobrinski, I., & Brinster, R. L. (1999). Recipient preparation is critical for spermatogonial transplantation. *Biology of Reproduction*, *60*(4), 963–969.
23. Rudenko, M. A. (2018). Molecular regulation of spermatogonial stem cells. *Reproductive Biology*, *18*(4), 347–355.
24. Sato, T., et al. (2006). In vitro production of functional sperm. *Nature*, *441*(7091), 321–324. https://doi.org/10.1038/nature04678
25. Schlatt, S., et al. (1999). Germ cell transplantation into the primate testis. *Human Reproduction*, *14*(1), 144–150.
26. Shinohara, T. (2003). Spermatogonial stem cell self-renewal and development. *Annual Review of Cell and Developmental Biology*, *19*, 547–570. https://doi.org/10.1146/annurev.cellbio.19.111301.112106
27. Smith, L. B., & Walker, W. H. (2014). The regulation of spermatogenesis by Sertoli cells. *Annual Review of Physiology*, *76*, 271–297. https://doi.org/10.1146/annurev-physiol-021113-170314
28. Sofikitis, N., et al. (1999). Germ cell transplantation and spermatogenesis. *Human Reproduction Update*, *5*(4), 366–377.
29. Wu, Y., et al. (2015). CRISPR/Cas9-mediated genome editing in human spermatogonial stem cells. *Cell Stem Cell*, *17*(4), 450–460. https://doi.org/10.1016/j.stem.2015.09.007
30. Zakharova, E. V. (2017). Genetic regulation of meiosis in spermatogenesis. *Russian Journal of Genetics*, *53*(6), 643–652.