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Review

Possibilities in Germ Cell Research: An Engineering Insight

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Germ cells (GCs) are responsible for fertility and disruptions in their development or function cause infertility. However, current knowledge about the diverse mechanisms involved in GC development and function is still in its infancy. This is mainly because there are low numbers of GCs, especially during embryonic development. A deeper understanding of GCs would enhance our ability to produce them from stem cells. In addition, such information would enable the production of healthy gametes for infertile couples. In this regard, pluripotent stem cells (PSCs) demonstrated a promising ability to produce GCs *in vitro*. In this review, we highlight recent advances in the field of tissue engineering that suggest novel strategies to enhance GC research.

Trends

Advanced therapies for infertility require developing systems for the efficient production of germ cells from stem cells in the laboratory.

We discuss recent advances and challenges of germ cell research.

Here, we propose engineering approaches for designing an artificial niche for germ cell development *in vitro*.

Novel platforms are demonstrated for the epigenetic analysis of germ cells.

Innovative approaches are detailed for the efficient production of germ cells from pluripotent stem cells.

Call for Engineering Approaches in Germ Cell Research

It is now well understood that GCs can generate a new body. However, current knowledge of the diverse mechanisms involved in GC development is still in its infancy. This is mainly because there are low numbers of GCs, especially during embryonic development, and the analysis of these cells is tricky. Even minor damage to GCs during their developmental stage can cause infertility, which is a major medical problem that affects 10–15% of couples worldwide [1]. Accordingly, differentiation of PSCs to GCs would provide an unlimited source of GCs. PSC-derived GCs can be used to explore the basic underlying principles of reproduction, with the eventual goal of producing healthy gametes for infertile couples [2]. To that end, mouse PSCs have been differentiated to functional **primordial GC-like cells** (PGCLC; see Glossary) that can restore **spermatogenesis** in infertile mice and contribute to healthy offspring [3]. However, this differentiation method was unable to produce PGCLCs needed for supporting research regarding the development of GCs. The use of new technologies (e.g., microfabrication, and high-throughput array analysis) as novel platforms can enable the 'safe' evaluation of the low quantity of GCs. Deeper knowledge of GCs could enhance our capability to produce them from stem cells. In addition, integration between GC knowledge and engineering approaches (e.g., growth factor delivery technology) has the capability to open new opportunities for effective GC production from PSCs. Another issue with GC research is that researchers have not yet been successful in the development of a system to support PGCLCs for *in vitro* spermatogenesis. Recent advances in the field of tissue engineering suggest strategies (e.g., microfluidic systems and micropatterning technology) to enhance GC research. Nevertheless, engineering technologies can be considered as innovative platforms to fabricate an artificial niche for PSC-derived PGCLCs to enter meiosis and produce sperm in the laboratory.

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In this review article, we highlight recent advances in GC development followed by studies demonstrating the production of GCs in the laboratory. Additionally, we focus on *in vivo* spermatogenesis. This discussion is essential to establish a strong conceptual structure to cover potential opportunities to design an 'artificial spermatogenesis niche'. Finally, we propose novel platforms for the reconstitution of specific niches that provide essential requirements for PGCLCs to produce sperm in the laboratory. We also review engineering approaches for the evaluation of **epigenetic** mechanisms of GCs and efficient PGCLC production from PSCs.

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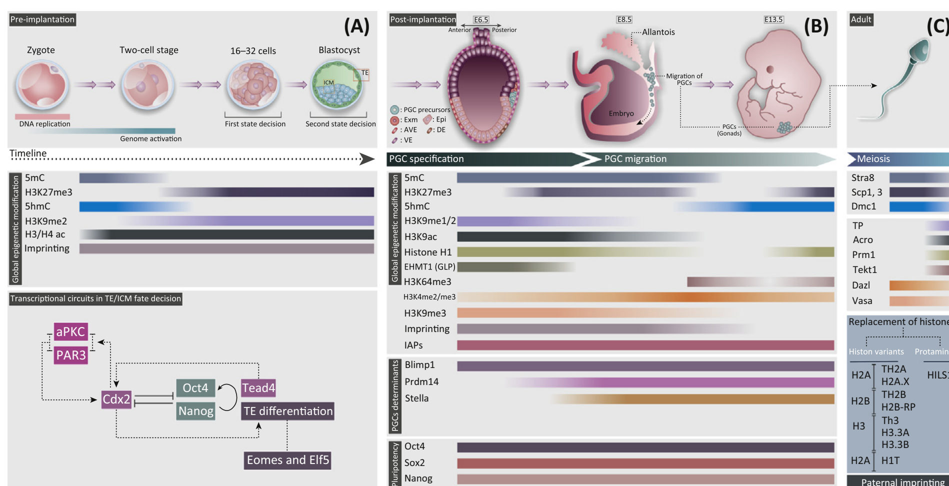
Male Germ Line Development

How are GCs created in the testis? The answer lies in embryonic development. Mammalian development commences with fertilization that results in the formation of zygote. Zygotes have the ability to build a body by sequential cell fate decisions. In the first cell fate resolution, the inner cell mass (ICM), which produces the future body, becomes set apart from the trophectoderm (TE), developing into extra embryonic tissues. During the second cell fate decision, the epiblast is separated from primitive endoderm [4,5]. These decisions are taken during preimplantation development, which is coincident with epigenetic reprogramming [6–8] (Figure 1A). Soon after implantation, **PGCs** are specified from the proximal epiblast by receiving bone morphogenetic protein 4 (BMP4) from extra-embryonic ectoderm [9]. It was recently shown that mesodermal factor *T* in the presence of BMP4 signaling activates the expression of germ line determinants, including *Blimp1* [10]. Blimp1 launches the sequence of events that includes suppression of somatic gene expression, and upregulates its partner, PR Domain Containing 14 (Prdm14), to induce re-expression of pluripotency factors and start epigenetic reprogramming [11,12]. The most stunning epigenetic reprogramming in PGCs is genome-wide DNA demethylation, which involves genic and intergenic sequences and also imprinted genes [13,14]; by contrast, the most



Trends in Biotechnology

Figure 1. Male Germ Line Development. (A) Preimplantation development is coincident with genome-wide DNA demethylation (reducing 5mC and 5hmC) with the exception of imprinted genes. Moreover, Histone H3 trimethyl Lys27 (H3K27me3), H3k9me2 and H3/H4ac follow an increasing pattern. During this period, the inner cell mass (ICM) separates from the trophectoderm (TE) by dominant expression of Octamer 4 (Oct4) and Nanog, which repress Caudal Type Homeobox 2 (Cdx2), important for TE specification. (B) Soon after implantation of the embryo in the uterus, primordial germ cells (PGCs) are specified from proximal epiblast and are localized in the yolk sac wall at the base of allantois. They then migrate inside the embryo to become localized in the primitive gonad. PGC migration is coincident with genome-wide DNA demethylation, which involves imprinted genes and dynamic chromatin modification. *Blimp1* is the key gene that is expressed first and leads to expression of PR Domain Containing 14 (*Prdm14*) and *Stella*. The pluripotency factors, Oct4, Nanog, and Sex-determining Region Y (SRY)-Box 2 (Sox2), are re-expressed in PGCs. (C) in adult testis, PGC-derived spermatogonia go through meiosis to produce sperm; this transition includes specific gene expression, histone replacement, and paternal imprinting.

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