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In Vitro Germ Line Differentiation from Pluripotent Stem Cells

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Editorial

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Editorial

Germ cells carry hereditary information and genetic diversity. The production of functional germ cells is a key component of successful reproductive processes. Pluripotent stem cells can differentiate into any type of cells derived from the three embryonic germ layers, giving them significant potential in the field of regenerative medicine [1]. The ability to induce pluripotent stem cells into germ cell like-cells not only may provide substantial clinical benefits in human reproductive medicine and the development of assisted reproductive technologies, but it also may have a significant impact on animal reproduction and may help to develop new strategies to conserve endangered species and preserve genetic diversity. In this editorial, we describe the brief history of in vitro germ cell development and summarize the major breakthroughs and current state of these cutting-edge techniques for germ cell differentiation. We also discuss the potential future applications of this promising, new technology.

Among the multiple stem cell sources that have been evaluated for the in vitro differentiation of germ cells, embryonic stem cells and induced pluripotent cells have been the most studied due to their pluripotency. Most of our knowledge about in vitro germ line development has derived from research in mice [2-6]. The specification of primordial germ cells (PGCs), the precursors of gametes, begins at gastrulation, after which PGCs must migrate to the gonad and undergo further maturation, including meiosis, and extensive epigenetic reprogramming [7]. The formation of PGC-like cells (PGCLCs) were achieved both in mice and humans [4,5,8-10].The production of PGCLCs was most efficient when the stem cells were converted into mesodermal-like cells first before they were exposed to BMP4 for further differentiation. The PGCLC identity is usually confirmed by the expression of both pluripotent markers (OCT4, NANOG, SOX2) and PGC markers (ABLIMP1, PRDM14, TFAP2C) [11]. The identification can also be confirmed by comparing the transcriptome or epigenome analysis with the in vivo PGCs [12].

Despite the high complexity of gametogenesis, production of offspring using the *in vitro* differentiated PGCs has been successfully achieved in mice using both ESC and iPSCs [13,14]. In mice, meiotic sperm cell-like cells were successfully generated by co-culturing PGCLCS with testicular somatic cells [13,15,16]. Normal, live offspring were produced after injecting these haploid cells into oocytes. The generation of oocytes was achieved by co-culturing the PGCLCs with ovarian fetal somatic cells. These in vitro differentiated oocytes were able to complete both nuclear and cytoplasmic maturation, resulting in the birth of normal offspring after in vitro fertilization [6]. Recently, the PGCLCs were also generated in pigs using the expanded potential stem cells derived from blastocysts [17].

Compared to mice, in vitro gametogenesis in humans seems to encounter more difficulties. However, progress has been made in a recent study by Saitou's group, in which human oogonia-like cells were generated by co-culturing PGCLSs with mouse fetal somatic cells. These oogonia-like cells display hallmarks of epigenetic reprogramming [18]. The differentiation of ovarian follicle-like cells has also been achieved by overexpression of two RNA binding proteins, DAZL and BOULE, in hESCs in recombinant human GDF9 and BMP15 cultures. While overexpression of DAZL and BOULE regulates the exit of pluripotency of germ cell-like cells and promotes their entry into meiosis, GDF9 and BMP15 induce these differentiated hESCs to form ovarian follicle-like cells [19]. These breakthroughs, combined with the

improving strategies of in vitro follicle culture, might further lead to the generation of mature fertile oocyte-like cells.

The in vitro germ cell differentiation technology holds great potential in several biomedical fields. The efficient generation of large quantities of germ cells will provide an in vitro platform for studies of infertility and improved reproductive technologies. Functional germ cells induced from iPSCs will revolutionize infertility treatment. Implementation of this technology in the clinical setting will help patients who are incapable of producing functional gametes conceive biological children, through which ethical and social issues regarding the use of donor gametes can be avoided. This technology also provides an ideal platform to inform studies of germ cell biology in humans. Additionally, it is expected that this technology will be developed for other animal species in the future, which will advance animal reproduction, genetic improvements in livestock, and the preservation of endangered species.

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