IN- VITRO GAMETOGENESIS: TECHNICAL AND ETHICAL PERSPECTIVES

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The human germline is a new research frontier as the gene regulatory network that drives the specification of human germline through induction of human primordial germ cells (hPGCs) has recently been identified. The hPGCs has been demonstrated to undergo epigenetic reprogramming that triggers wide-spread disassembly of facultative heterochromatin domains.

Such epigenetic reprogramming is likely essential in preparation for subsequent meiotic entry by upregulating early meiotic genes from 10th week onwards to subsequently enter meiosis on week 14. Subsequently facilitating erasure of genomic imprints in hPGCs, allowing re- establishment of the sex-specific imprints that are essential for normal development of the next generation.

However, the mechanism by which hPGCs undergo such epigenetic reorganization and subsequent meiotic entry remains unknown due to challenges in accessing these cells from aborted human fetuses at such early stages of development and in performing mechanistic experiments. Moreover, since hPGCs are specified in 3rd week of gestation and as the ethical regulations limits in vitro culture of human embryos beyond day 14, it is not possible to monitor and gain mechanistic insights about hPGC induction and their early development. Various attempts have been made to further the progress of in vitro-derived hPGC-like cells (hPGCLCs) by co-culturing them with mouse gonadal somatic cells. This led to a certain degree of epigenetic resetting, but unlike in mice, hPGCLCs do not subsequently enter meiosis. One possibility is that these hPGCLCs require further experimental interventions to reorganize their epigenetic landscape to the extent that is equivalent to their in vivo counterparts such that it is conducive for meiotic entry. Hence, it is crucial to identify the molecular underpinnings that intrinsically triggers epigenetic reprogramming in preparation for subsequent initiation of meiotic. This is supported by recent work in mice in which growing oocytes where directly induced from mouse embryonic stem cells (mESCs), without passage through a PGC-like state or undergoing epigenetic reprogramming. These directly induced oocyte-like cells fails to enter meiosis, emphasizing the importance of epigenetic reprogramming for activation of meiotic program.

Thus, the objective our ongoing research pursuit is to identify the molecular mechanism that links epigenetic reprogramming in hPGCs to initiation of meiosis.

The outcome of this work would facilitate future attempts of reconstituting human germline lineage in culture which would enable in vitro gametogenesis (IVG) to generate viable human gametes from somatic cell-derived-pluripotent cells. These synthetic gametes can be useful test the efficacy of germline gene editing to tackle congenital disorders. Besides, they can used for in vitro fertilization (IVF) to generate blastocysts which can be used for pre-implantation genetic diagnoses (PGD) to predict aneuploidy and thereby can serve as a model to investigate the mechanism of onset of various genetic disorders that attributed to age-related mutations in the germline or altered epigenetic inheritance as a consequence of chronic malnutrition or other environmental factors.