RESEARCH HIGHLIGHT

Cultured human stem cells undergoing gastrulation

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In a recent study published in *Cell Research*, Huang et al. established human gastrulating stem cells (hGaSCs), a stable in vitro population capable of differentiating into multiple gastrulating lineages. These cells self-organize into embryo-like structures both in vitro and in vivo, offering an ethically viable platform for modeling early human development and assessing drug teratogenicity.

Pluripotent stem cells (PSCs) have significantly advanced the field of developmental biology. However, conventional culture systems fail to recapitulate the complexity of the in vivo human gastrulating epiblast, thereby limiting their applicability in modeling human embryogenesis and organogenesis. Co-culture of embryonic and extraembryonic stem cells from mice and monkeys reveals the intercellular crosstalk among different lineages that may be crucial for proper embryonic development.[1] This suggests that culture systems capable of maintaining cellular heterogeneity and communication would be beneficial for modeling human embryogenesis in vitro using stem cell-based approaches.[2] Although human embryology holds significant importance, research on post-implantation stages has been constrained by ethical considerations[2] and limitations in the understanding of human development (Fig. 1). Recently, several research groups have attempted to model post-implantation stages of human development using mixed populations of stem cells[3,4]; however, alternative experimental approaches and the developmental potential of human embryo models to reach gastrulation and early organogenesis remain to be further elucidated.

In this study, Huang et al.[5] report the derivation of human gastrulating stem cells (hGaSCs) under culture conditions — a metastable and clonogenic stem cell population that simultaneously maintains multiple gastrulating cell types, including epiblast-like cells (EpiLCs), mesoderm-, endoderm-, ectoderm-, amniotic ectoderm-like cells, and primordial germ cell-like cells (PGCLCs) (Fig. 1). Previous studies have identified transient pluripotent cell populations during the in vitro differentiation of human primordial germ cell-like cells (hPGCLCs),[6,7] which exhibit characteristics of both amniotic and gastrulation-stage cells.[8] Following a comprehensive reanalysis of published transcriptome data from in vitro induction of hPGCLCs,[9] and comparing these data with those obtained from 3D-cultured human embryos[10] and naturally occurring Carnegie Stage 7 human embryos,[11] the authors established an experimental protocol that enables the derivation of hGaSCs from early hPGCLCs using an optimized culture medium designated as GK10. These cells remained stable during culture for over 30 passages.

Through single-cell and bulk transcriptomic analyses, hGaSCs exhibit remarkable similarity to post-implantation human embryos, particularly Carnegie Stage 7. Moreover, Huang et al. performed CUT&Tag analysis, specifically focusing on histone modifications such as H3K4me3 and H3K27me3. Compared to hPSC, a marked decrease in H3K27me3 levels and a slight reduction in H3K4me3 enrichment were observed around the transcription start site regions in hGaSC. In 3D cultures, hGaSCs spontaneously form gastruloids that recapitulate early lineage specification and gastrulation-like morphogenesis, including spatial organization of germ layers and the emergence of notochord-like cells. These gastruloids also model teratogenic responses: upon exposure to valproic acid (VPA), a known teratogen, the gastruloids show disrupted proliferation, loss of notochord markers (e.g., SHH, CHRD), and failure in axial mesoderm differentiation — mirroring developmental defects seen in vivo (Fig. 1).

Strikingly, when transplanted into mouse seminiferous tubules, hGaSCs form t-Gastruloids — embryo-like structures that develop into neuroepithelial, endodermal, and mesodermal derivatives, including neurons, retinal cells, and gut-like tissues, over 90 days. These t-Gastruloids exhibit orderly, stepwise tissue differentiation, in contrast to the disorganized growth observed in teratomas derived from conventional hPSCs. Single-cell RNA-seq confirms its faithful recapitulation of in vivo lineage trajectories and reveals that hGaSC-derived EpiLCs give rise to both neural and non-neural lineages via distinct, temporally controlled pathways. The testicular niche introduced in this study may provide a more accessible platform for the development of tissues and organs that could potentially be derived from hGaSCs.

This work provides both a technical advancement and a conceptual shift in human stem cell-based modeling. By stabilizing gastrulating lineages in a unified culture system, hGaSCs allow for the study of human gastrulation, early organogenesis, germ cell development, and drug toxicity within an ethical, reproducible framework. Furthermore, the ability of hGaSCs to generate organized embryo-like structures in vivo highlights their potential for regenerative medicine and tissue engineering. With the proliferation of protocols for modeling human gastrulation in vitro using stem cell-based approaches, there is an increasing demand for comprehensive benchmarking studies to systematically compare and evaluate their distinct features and functional properties, thereby facilitating their more effective application in specific biological contexts.

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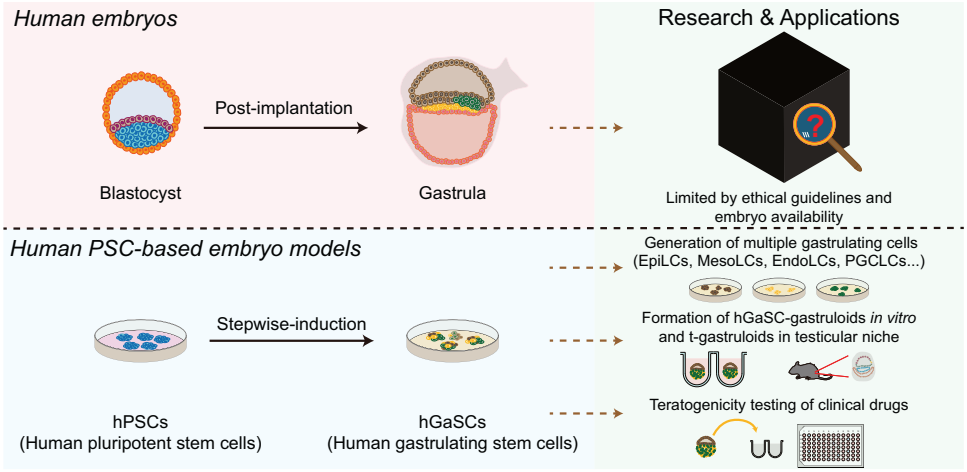

Fig. 1 Establishment and applications of hGaSCs. Schematic diagram showing the derivation of hGaSCs from hPSCs, characterization of their cellular composition, the formation of in vitro gastruloids and in vivo t-gastruloids, as well as their applications in teratogenicity testing and modeling organogenesis. hGaSCs provide an ethically acceptable platform for studying early human development and drug-induced teratogenic effects, particularly under conditions where the availability of natural human embryos is limited.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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