Integrated understanding of human PGCLC development using multi-scale mathematical modeling of gene-cell-BMP dynamics

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Understanding of germ cell fate is one of the most challenging problems in biology and medicine. Primordial Germ Cell (PGC) is the origin of germ cell lineage, which differentiate into spermatozoa or oocytes. Recently, many extracellular morphogenic substances, such as BMP, and genetic regulatory networks required for PGC development have been identified by experiments [1]. However, the spatial effect of BMP distribution is still poorly understood in the dynamics of germ cell differentiation.

To understand the mechanism of germ cell development and its relationship with BMP integrally, we developed a multi-scale mathematical model composed of genetic/transcriptomic networks of ordinary differential equations (ODE), stochastic model for differentiation decision, and BMP-individual cell interaction model of partial differential equation (PDE) combining discrete cellular dynamics. The models have been constructed based on the scRNA-seq data and other experimental data.

Using the model, we tested several scenarios of BMP concentrations on germ cell development and confirmed that GATA3 commit to differentiation earlier, as shown in experiments [2]. In addition, we conducted sensitivity analysis to investigate the essential genetic network pathways for PGC development and found that GATA3 related pathway is essential for PGC development, as shown in the experiment of GATA3 knockout that significantly impaired PGC development [1]. With the model verification based on the results above, we finally explored the spatial effect of BMP on PGC development through in silico experiments using the multi-scale model of PGC development. In this study, we show that the spatial pattern of BMP is crucial for efficient production of PGCs and propose a new in vitro experiment framework for PGC manipulation based on gene-cell-BMP dynamics.

[1] Kojima Y, Yamashiro C, Murase Y, et al. GATA transcription factors, SOX17 and TFAP2C, drive the human germ-cell specification program. Life Sci Alliance. 2021;4(5):e202000974. Published 2021 Feb 19. doi:10.26508/lsa.202000974

[2] Gunne-Braden A, Sullivan A, Gharibi B, et al. GATA3 Mediates a Fast, Irreversible Commitment to BMP4-Driven Differentiation in Human Embryonic Stem Cells. Cell Stem Cell. 2020;26(5):693-706.e9. doi:10.1016/j.stem.2020.03.005