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Integrating evolutionary game theory into epigenetic study of embryonic development Comment on “Epigenetic game theory: How to compute the epigenetic control of maternal-to-zygotic transition” by Qian Wang et al

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DNA methylation is an essential component in the epigenetic regulation of embryonic development, and plays a crucial role in various biological processes, including repression of gene transcription, parent-of-origin genomic imprinting, and X-chromosome inactivation [1–5]. Understanding the epigenetic processes in different stages of embryo development has become an important research topic in the field. It has potential to offer new insight into reproductive medicine and contribute to the improvement of long-term health outcomes.

At the zygotic stage during the normal development of an embryo, Wang et al. [6] present an elegant overview of a modeling framework, called epiGame, to study the epigenetic interactions of sperms and oocytes' genomes. The central theme of their model is based on the universal principle under natural selection toward optimizing the offspring fitness [7]. By integrating evolutionary game theory and the epigenetic interactions of zygotic genomes, epiGame offers a sophisticated quantification to characterize the impact of maternal and paternal methylomes on the early development of embryos. epiGame is built on a system of ordinary differential equations describing the competition and cooperation of male and female genomes mediated by DNA methylation dynamics. This framework is attractive in its conceptual generality. It accommodates not only the methylome data from both sexes, but also the transcriptome information. This approach allows one to study multifactorial and dynamic interactions in embryogenesis: (1) the epigenetic interactions of zygotic genomes; and (2) the relationship of DNA methylation and gene expression.

During embryo formation, the environment experienced by the early embryo can influence the growth trajectory of the fetus and neonate, and may also have an important whole-of-life impact on human health and disease [8]. epiGame is designed to model the male and female DNA methylation dynamics during the normal embryonic development. It would also be interesting to generalize the model to account for a range of environmental stresses when various forms of assisted reproductive technologies are used. For example, quantitative models may help to select the best embryos to transfer during the in vitro fertilization (IVF) treatment by examining the maternal and paternal methylation profiles during preimplantation development. Therefore, conceptual generality for environmental stresses in the embryo development would be a nice addition to the modeling framework of Wang et al.

Genome-wide epigenetic reprogramming occurs at stages when developmental potency of cells changes [9]. How does evolutionary game theory link different epigenetic marking

systems would be an exciting research question that deserves further elaborations. Furthermore, the modeling framework can be improved by incorporating the emerging knowledge on the candidate reprogramming factors for embryonic development.

In conclusion, Wang et al. present a timely and important research direction to study embryo epigenetics incorporating evolutionary game theory. The conceptual framework is broadly applicable to a variety of research questions related to the knowledge of epigenetic reprogramming and epigenetic marking systems. The current approach needs to be improved by implementing more computationally efficient software to handle methylome and transcriptome data in different stages of human early embryo generated by next-generation sequencing technologies.

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