Using game theory to investigate the epigenetic control mechanisms of embryo 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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A body of research [1-7] has already shown that epigenetic reprogramming plays a critical role in maintaining the normal development of embryos. However, the mechanistic quantitation of the epigenetic interactions between sperms and oocytes and the related impact on embryo development are still not clear [6, 7]. In this study, Wang et al., [8] develop a modeling framework that addresses this question by integrating game theory and the latest discoveries of the epigenetic control of embryo development.

1. Epigenetic reprogramming may be of paramount importance in maintaining the normal development of embryos.

Recently, a lot of embryos research [1-7, 9-11] focuses on investigating the critical role of the epigenetic reprogramming for the development of the embryos. For example, Kouzarides et al., [10] indicate that histone modifications are fundamental epigenetic regulators that control many crucial cellular processes. Also, Zhang et al., [11] investigate mechanism of the allelic reprogramming of the histone modification H3K4me3 in early mammalian development. However, to the best of knowledge, this study [8] is the first to employ game theory[12] to understand the embryos development from the computational perspective.

2. We describe and assess a modeling framework based on evolutionary game theory to quantify how sperms and oocytes interact through epigenetic processes to determine embryo development.

Different from most of the theoretical biological research [13-15], this study [8] employs the sequencing data [16, 17], which can monitor the embryo development, to optimize the key parameters of the game theory model. Moreover, it also performs a computer simulation study to demonstrate the usefulness and utility of the model with three designed scenarios, shown by Figure 1A. However, we consider this model can be improved in the following three potential directions. First, since the embryos development process is very complicated, we could add several time varying variables for F or H function of Eq. 2 to detail this process as well as design related experiments

to measure the time series data for these time varying variables. And then, it will make the model mimic the embryos development more realistic than before. Second, authors employ all the ICSI data [8] to optimize key parameters of the model, but they do not consider the model testing process. Thus, we suggest using training and testing procedure to train the key parameters and test the predictive power of the model as many previous studies [18-20], respectively. Third, since this research describes the complex interactions of reprogramming between sperms and oocytes in a fertilized zygote, may we employ game tree[21]to simulate this process from the graph theory perspective?

3. This framework can provide a mechanistic understanding of reproductive biology with results that have a potential implication for personalized medicine.

Although previous reports [1-6, 9] demonstrate that epigenetic modifications may play a pivotal role in the embryo development, it is unclear how the joining of sperms and oocytes generates the totipotent state to develop into a living embryo. For this reason, this study employs epigenetic game theory (epiGame) to model embryogenesis as an ecological system under Darwinian selection. As we know, DNA methylation is an epigenetic mechanism that occurs by the addition of a methyl group to DNA, thereby often modifying the function of the genes [22]. Since methylation is dynamically regulated during embryo development, especially the stage of gametogenesis and after fertilization, epigenetic game theory could have potential to predict the abnormal embryonic genesis by quantitatively computing the methylation dynamics.

In summary, this research puts forward such an epiGame framework that not only employs ordinary differential equations to describe the complex interactions of reprogramming between sperms and oocytes in a fertilized zygote, but also uses related sequencing data to optimize the key parameters of the model. Therefore, we consider that this study is able to help us understand the mechanistic basis underlying the normal development of embryos.

Acknowledgement

This work is supported by the National Science Foundation of China under Grant No. 61372138 and 61190122, Chongqing excellent youth award, the Chinese Recruitment Program of Global Youth Experts, Fundamental Research Funds for the Central Universities of China No. XDJK2014B012 and NO. XDJK2016A003.

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