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Comment

Epigenetic information in gametes: Gaming from before fertilization 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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1. Introduction

In their interesting article [1] Wang et al. proposed a mathematical model based on evolutionary game theory [2] to tackle the fundamental question in embryo development, that how sperm and egg interact with each other, through epigenetic processes, to form a zygote and direct successful embryo development. This work is based on the premise that ***epigenetic reprogramming*** (referring to the erasure and reconstruction of epigenetic marks, such as DNA methylation and histone modifications) after fertilization might be of paramount importance to maintain the normal development of embryos, a premise we fully agree, given the compelling experimental evidence reported [3]. Wang et al. have specifically chosen to employ the well-studied DNA methylation reprogramming process during mammalian early embryo development, as a basis to develop their mathematical model, namely epigenetic game theory (epiGame). They concluded that the DNA methylation pattern in mammalian early embryo could be formulated and quantified, and their model can be further used to quantify the interactions, such as competition and/or cooperation of expressed genes that maximize the fitness of embryos. The efforts by Wang et al. in quantitatively and systematically analyzing the beginning of life apparently hold value and represent a novel direction for future embryo development research from both theoretical and experimental biologists. On the other hand, we see their theory still at its infancy, because there are plenty more parameters to consider and there are spaces for debates, such as the cases of haploid embryo development [4]. Here, we briefly comment on the dynamic process of epigenetic reprogramming that goes beyond

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DNA methylation, a dynamic interplay that involves histone modifications, non-coding RNAs, transposable elements et al., as well as the potential input of the various types of 'hereditary' epigenetic information in the gametes – a game that has started before the fertilization.

2. Multiple layers of epigenetic regulation on the zygotic genome activation (ZGA) of early embryo

Unlike the sequence of DNA, epigenetic information changes drastically during early embryo development right after fertilization [3]. The fusion of sperm and egg, two terminally differentiated cells that carry unique epigenetic signatures, can efficiently activate epigenetic reprogramming to set the zygote back into a totipotent state that can give rise to all cell types and tissues [3]. The reprogramming process after fertilization involves both active and replication-dependent passive DNA demethylation of the paternal and maternal genome, as nicely summarized and modeled by Wang, are essential to direct normal waves of zygotic genome activation (ZGA) [1]. Yet the dynamic chromatin state mediated by histone proteins and their associated modifications, as well as the role of non-coding RNAs, are less considered by the authors and not included in their modeling. Recently, a series of striking studies has revealed an updated view about how histone marks (three major types of histone modifications, H3K4me3, H3K27me3 and H3K27ac) that associated with sperm and oocytes are dynamically remodeled during early embryo development, which are also essential for the normal ZGA process [5–8]. In addition to the 'epigenetic marks' (DNA methylation and histone modifications) that associated with DNA sequences, other mobile elements such as LINE-1 retrotransposon-derived reverse transcriptase [9], small non-coding RNAs [10,11] and associated RNA modifications [12,13] are also strong candidates in regulating ZGA and early embryo development, in addition to the emerging discovery of 3D chromatin architecture [14]. We believe these emerging epigenetic regulators could be further incorporated as important parameters into the nascent model of epiGame proposed by Wang et al. in the future.

3. Epigenetic information in gametes – acquisitive and heritable

Another point we would like to mention to add to the complexity of the proposed epiGame model is the recent burgeoning research evidence for the epigenetic inheritance via gametes [13,15], which demonstrated that certain epigenetic information (that in addition to the information of genomic DNA sequence) in sperm or egg can be acquisitive and heritable, and transmit parentally acquired phenotypes such as metabolic and behavior disorders to the immediate offspring, and sometimes to subsequent generations [13,15]. These documented phenomena are believed to involve the transfer of epigenetic information from soma to germline [13], and the preservation and/or amplification of original epigenetic information carried by germline during embryo development, either by means of replication or reconstruction [15].

Interestingly, it has been recently shown that peaks in H3K4me3 distribution in sperm, but not oocyte, are first removed in zygote after fertilization but later on re-established in both paternal and maternal chromosomes since late 2-cell embryo stage [5,6], suggesting that certain paternal epigenetic information in the form of sperm H3K4me3 is memorized and inherited, by means of reconstruction in embryo development. In the contrary, the peaks of H3K27me3 in the sperm were globally erased upon fertilization [16]. On the other hand, in the oocytes, while the H3K27me3 peaks at promoter region were extensively erased, the distal H3K27me3 peaks are retained in the early embryo [16], suggesting that certain maternal epigenetic information in the form of oocyte H3K27me3 can be retained and inherited. In addition to the inheritance of histone marks, it has been also reported that the profile of tRNA-derived small RNAs (tsRNAs) that highly enriched in mature sperm [17] was later on reappearing in the 8-cell embryo [10], implicating a potential self-loop induction of sperm-borne RNA information in the early embryo.

By far, the epigenetic factors in the gametes being reported to pass parental hereditary information include DNA methylation [18], histone modifications [19], small RNAs [20–24], RNA modifications [25], mitochondria [26,27], genetic variations of ribosomal DNA (rDNA) [28] and prion-like proteins [29] et al. (**Fig. 1**) – a list expected to further expand in the future. While it remains unclear how these various types of epigenetic information carriers could work in concert and together drive embryo development, it is becoming increasingly clear that any gametic input/regulation of these above epigenetic factors has the potential to change the epigenetic gaming process that happens after fertilization. Their generated effects, via a butterfly effect, may not only influence the ZGA process and the trajectory of embryo development, but may also drive evolution, if the altered traits are adaptive under certain environmental conditions.

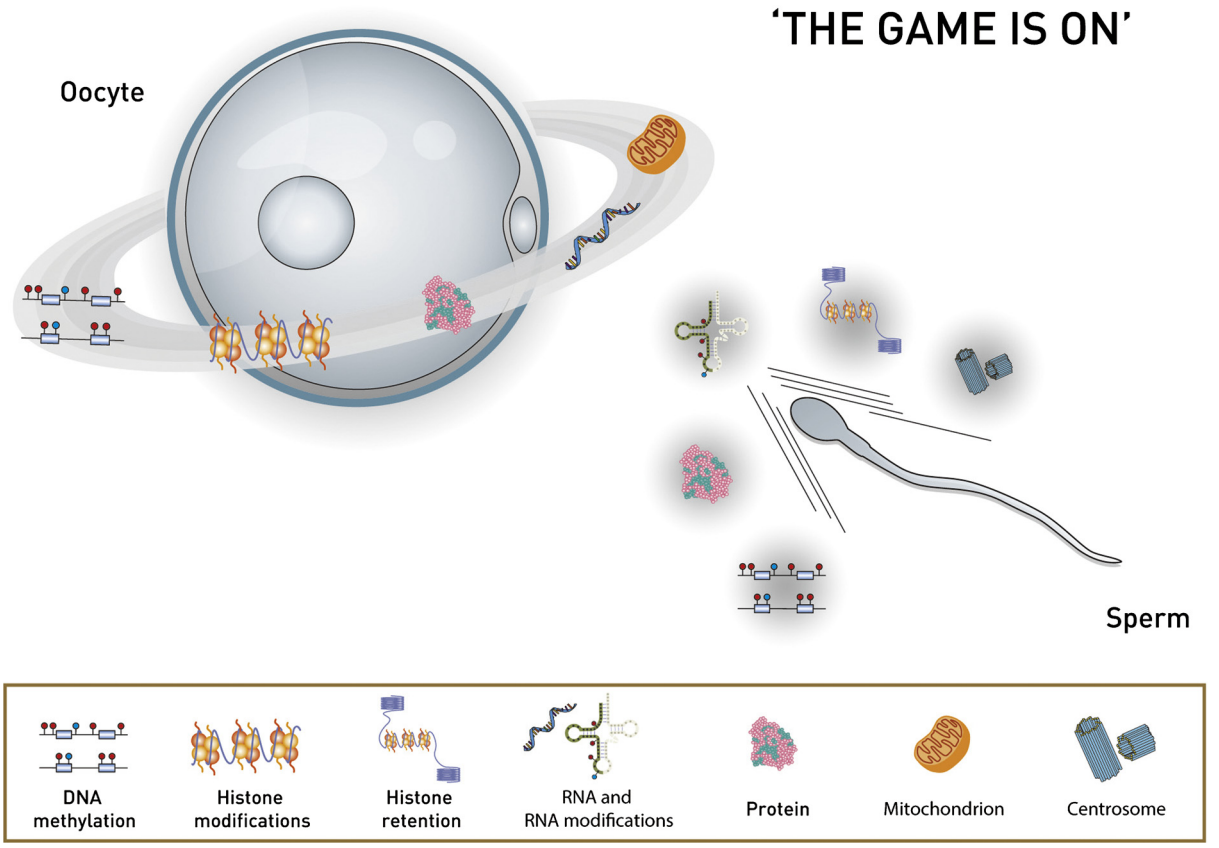

Fig. 1. **'The game is on'**. Illustration of the potential non-DNA sequence-based hereditary materials in sperm and oocyte, and the complex interplay between each of these epigenetic information carriers, both before and after fertilization.

4. Summary

The fascinating processes of epigenetic reprogramming and epigenetic inheritance, particularly regarding the molecular and biochemical basis, remain a brave new world to explore. Therefore, it is in our opinion that these processes may be too complicated for by far even the most sophisticated mathematical models to fully simulate with. While the enthusiastic introduction of the modeling and theoretical attempts Wang et al. provided are greatly appreciated, we should keep cautious on being overconfident to use simplified models to explain complicated biological processes – anyway, life may never be that simple.

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