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Commentary

Transgenerational epigenetic inheritance: Emerging concepts and future prospects

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ABSTRACT

Evidence for transgenerational epigenetic inheritance has accumulated in recent years. However, the perceived implausibilities of epigenetic memory survival across chromatin remodeling and reprogramming, and phenotypic information transfer from soma to germline have caused skepticism about its existence, especially in mammals. Importantly, these supposed fundamental impediments seem to be disappearing with recent advances. Evolutionary significance of epigenetic inheritance is another area of debate. Notably, the idea that induced variations may play a role in evolution is gaining ground with newer analysis. Overall, emerging concepts are increasingly calling for integration of nongenetic inheritance in the contemporary evolutionary theory that does not completely explain heritability of complex traits and diseases. Interestingly, a conceptual framework of "evolutionary transgenerational systems biology" has recently been proposed to integrate epigenetics and physiology with inheritance and evolution. A proof of concept analysis is warranted to test the future prospects of this unified theory of biology.

In recent years, accumulating evidence has increasingly suggested that environmentally acquired phenotypic traits can be transmitted across generations through the germline in animals including mammals.[1–3] With epidemiological studies supporting its possible occurrence in humans, transgenerational epigenetic inheritance is considered to possibly play a role in health and disease.[4–8] Two major challenges, however, confront this unconventional mode of inheritance, especially in mammals.[1,2] First, even though it is supposedly mediated by nongenetic factors such as DNA methylation, histone modifications, and noncoding RNA, the molecular mechanisms underlying epigenetic memory survival across zygotic and germline reprogramming, and chromatin remodeling are unclear.[1,2] Second, factors mediating transmission of phenotypic information from somatic cells to the germline remain elusive, although it has been hypothesized that exosomes, exosomal microRNAs (miRNAs) in particular, may potentially act as mediators.[1,2] Importantly, recent advances have begun to address these challenges. As regards the epigenetic memory, DNA methylation and histone marks in mammals are known to undergo efficient resetting during reprogramming events in the zygote and in the germline.[1] Inheritance of epigenetic modifications, therefore, may seem improbable. However, recent evidence suggests that certain modifications

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do escape erasure during reprogramming. For example, despite large-scale replacement of histones by protamines in human and mouse mature sperm, the modified nucleosomes retained therein show enrichment for histone H2 trimethylated at lysine 27 (H2K27me3) and are found to functionally influence the expression of genes that play a role in embryonic development. This suggests that H2K27me3 may constitute an inherited signal.[1,9] Additionally, it has been observed that canonical histone modifications in constitutive heterochromatin are retained in human sperm, transmitted to the oocyte, and integrated in the paternal constitutive heterochromatin in the embryo. Following recognition by maternal chromatin modifiers, these modifications are propagated further.[1,9] As regards the mechanisms involved in restoration of histone modifications after replication, studies in *Caenorhabditis elegans* and *Drosophila* have suggested both the possibilities; either the modifications themselves may remain associated with the daughter chromatin, or they may be reestablished by the histone modifying complexes that are anchored to the daughter DNA.[1,9] Further support for post-replication conservation of histone modifications comes from theoretical modeling of experimental data; analysis of nucleosome modification associated enzyme recruitment and nearest-neighbor lateral enzyme interactions suggests that stochastic cellular processes may not hinder propagation of histone marks.[1,9]

Regarding DNA methylation, genome-level analysis in mice has provided evidence that rare but functionally relevant marks may be transgenerationally inherited by surviving through reprogramming events.[1,9] Notably, cytosine methylation in nonimprinted genes and nonrepetitive sequences has been found to escape erasure. As regards the mechanisms involved in restoration of DNA methylation following replication, a potential role of the maintenance DNA methyltransferase DNMT1 has been suggested.[1] Overall, recent evidence supports the plausibility of DNA and histone-based memory survival across generations.[1,9–11] Concerning RNA, it is considered to play a significant role in epigenetic inheritance. Besides mediating epigenetic modifications in the nucleus, the noncoding RNAs may move away from their cells of origin and influence gene expression in the recipient cells. It is an emerging concept that RNA contributed by gametes during fertilization influences embryo development through different gene regulatory processes.[1] With experimental demonstration in worms, the idea is also emerging that circulating miRNAs, that are released in body fluids and, hence, represent the physiological conditions, may possibly mediate soma to germline communication in epigenetic inheritance in mammals. This was first predicted by a bioinformatic analysis of available genome scale data, wherein it was observed that circulating miRNAs are over-represented in differentially expressed miRNAs, or miRNAs that are known to target the differentially expressed mRNAs, reported in studies related to persistence of environmental effects across generations.[12] Interestingly, empirical findings and theoretical considerations consistent with this prediction have later been reported by different groups.[1,9] For example, soma to germline transfer of an exosomal RNA and altered levels of a serum miRNA in a model of epigenetic inheritance have been demonstrated in mouse.[1,9] Similarly, in order to explain the transgenerational effects of stress observed in mice, it has been hypothesized that activation of hypothalamic-pituitary adrenal axis may cause shuttling of exosomal miRNAs from epididymis to sperm, and ultimately to ovum.[1]

Notwithstanding the present limitations in the mechanistic understanding of transgenerational epigenetic inheritance,

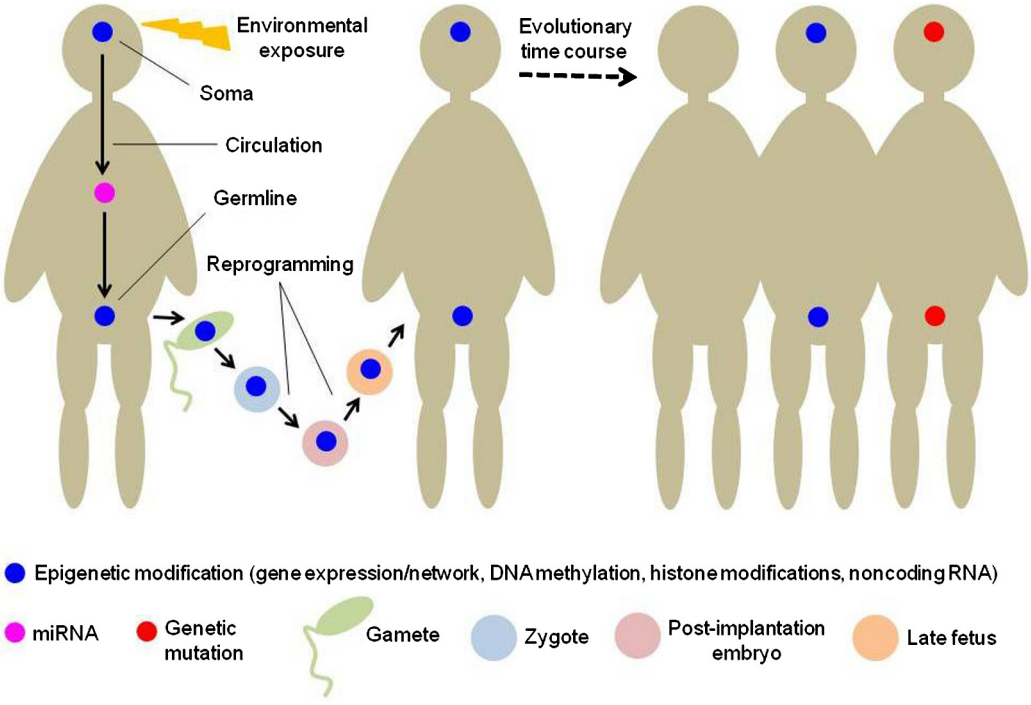

Fig. 1 – Transgenerational systems biology and its evolutionary significance. The model depicts the previously proposed[1,9,17] concepts seeking integrating of epigenetic inheritance, systems biology, and evolution.