Review

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Nongenetic inheritance and transgenerational epigenetics

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The idea that inherited genotypes define phenotypes has been paramount in modern biology. The question remains, however, whether stable phenotypes could be also inherited from parents independently of the genetic sequence *per se*. Recent data suggest that parental experiences can be transmitted behaviorally, through *in utero* exposure of the developing fetus to the maternal environment, or through either the male or female germline. The challenge is to delineate a plausible mechanism. In the past decade it has been proposed that epigenetic mechanisms are involved in multigenerational transmission of phenotypes and transgenerational inheritance. The prospect that ancestral experiences are written in our epigenome has immense implications for our understanding of human behavior, health, and disease.

Evidence for nongenetic multigenerational transmission of parental experience

New adaptive phenotypes can emerge as a result of natural selection of genetic variants. Natural selection is highly inefficient and slow in responding to immediate environmental challenges. It is well known that physiological systems can respond and adapt to new changes in real time, but the question remains whether there are nongenetic processes that could establish stable phenotypes and whether these can be inherited through germline transmission across generations. Biological examples have been documented of phenotypic plasticity emerging in relatively fast time-scales, and of frequencies that are orders of magnitude higher than can be explained by natural selection (see e.g., [1]).

Epidemiological evidence from two important multigenerational studies has brought to the fore the prospect of epigenetic memory of ancestral dietary distress in humans. First, Pembrey and colleagues [2–4] examined records of the multigenerational Överkalix cohorts in Northern Sweden using harvest and birth and death records. Variation in the food supply during the early life of paternal grandparents was associated with variation in mortality rate (and diabetic deaths) in their grandchildren. There were striking sex-specific transmissions, such that the food supply of the paternal grandfather was associated with the mortality rate of grandsons only, while the early-life food supply of the paternal grandmother was only associated with the mortality rate of granddaughters [2–4]. Interestingly, the effects were seen only when exposures occurred before puberty, supporting the hypothesis that reprogramming of gametes was involved. Similarly, in the UK Avon Longitudinal Study of Parents and Children (ALSPAC48) cohort, growth effects associated with paternal smoking were only observed when paternal smoking took place before puberty [3].

A second landmark study showed that children of mothers exposed to the Dutch famine of 1944 during the last trimester of pregnancy and the first months of life were less obese than controls, whereas exposure in the first half of pregnancy resulted in higher obesity rates than in controls [5]. Famine exposure early in pregnancy was associated with hypermethylation of the imprinted insulin-like growth factor 2 (IGF2) receptor gene *IGF2R* 60 years later, pointing to the possibility that DNA methylation might be involved [6]. Examination of the F2 generation revealed higher weights and body mass index (BMI) in adult offspring of prenatally exposed F1 fathers than in offspring of unexposed F1, but this effect was sex-specific and was not found in offspring of prenatally exposed mothers [7].

Nongenetic transmission of memory of parental experience could happen at several time scales (Figure 1). First, it could be transmitted through *in utero* programming of the developing F1 embryo, as well as through postnatal parental behavior. Second, it could be transmitted from F1 gametes, which were exposed *in utero* to maternal experiences, to F2 offspring. Third, a true transgenerational transmission of ancestral memory via the unexposed F2 gametes to the F3 offspring.

The first two modes of nongenetic transmission could be explained by several known mechanisms which are triggered in response to exposures and that target either the embryo or gametes during embryogenesis. It is more difficult to understand how marks of exposure in gametes are replicated, escape programming during primordial germ cell differentiation [8] and early embryogenesis [9,10], and are transmitted across many generations that were not subjected to the same experiences. Real transgenerational nongenetic inheritance could potentially result in a stable new trait. Therefore, a provocative question is whether

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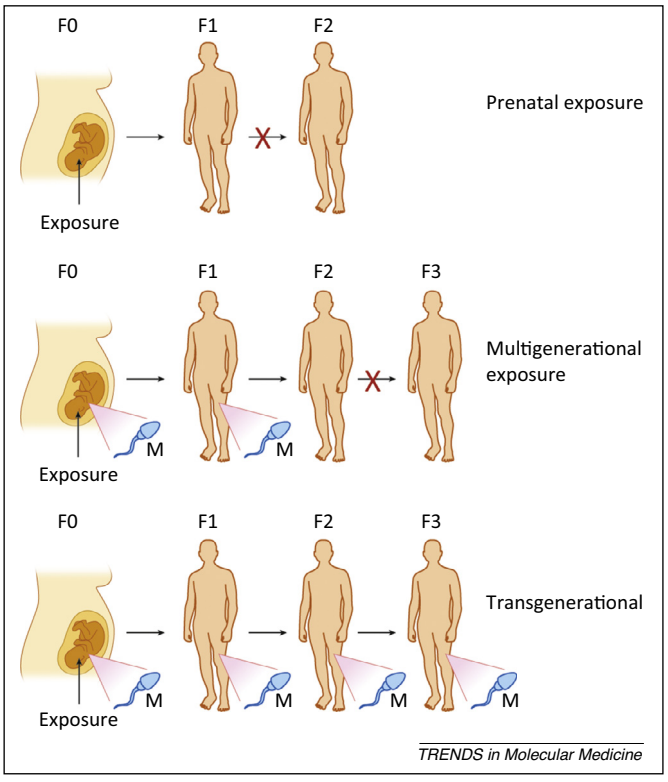

Figure 1. Modes of inheritance across generations. Three modes of multiple generational transmission of parental experience. Top row: prenatal exposure. The F0 mother is exposed during pregnancy with F1. F1 is programmed in response to exposure in different tissues but not the germline. Programming will alter the F1 phenotype but this will not be transmitted to next generation. Middle row: multigenerational exposures. The F1 generation is exposed during gestation and the developing germ cells are modified. The modified sperm of F1 will affect F2 development and phenotype. However, reprogramming of this modification during primordial germ cell differentiation of F2 will prevent transmission of the phenotype to F3. Bottom row: transgenerational inheritance. The F1 gametes are modified during gestation and exposure of the F0 mother. The modified F1 sperm affect F2 development. If gamete modification is not erased during primordial germ cell differentiation the sperm of F2 are modified as well and will transmit the phenotype to F3.

such mechanisms might play a role in 'rapid evolution' of traits in response to new experiences and environments at rates that are orders of magnitude faster than natural selection of stochastically arising genetic alterations.

It should be noted, however, that nongenetic multigenerational inheritance is not necessarily mediated by gametes. Multigenerational transmission could occur when the phenotypic response to the ancestral parental experience creates and sustains across generations the same social and physical environments that triggered the phenotype in the first place. For example, offspring of maternal adverse experience (such as violence, stress, poverty) which triggers a pattern of behavior in the offspring (e.g., aggression) would create the same adverse experience (aggression) for their offspring, leading to perpetuation of the phenotype across generations (Figure 2). The perpetuation of such traits could be interrupted by changing the parental environment or through cross-fostering [11,12].

Although epidemiological and animal experiments have provided data that support each of the different forms of nongenetic inheritance, in the absence of a plausible mechanism the interpretation of these data remains a matter of intense controversy. Moreover, questions are raised regarding the robustness of the data and its reproducibility.

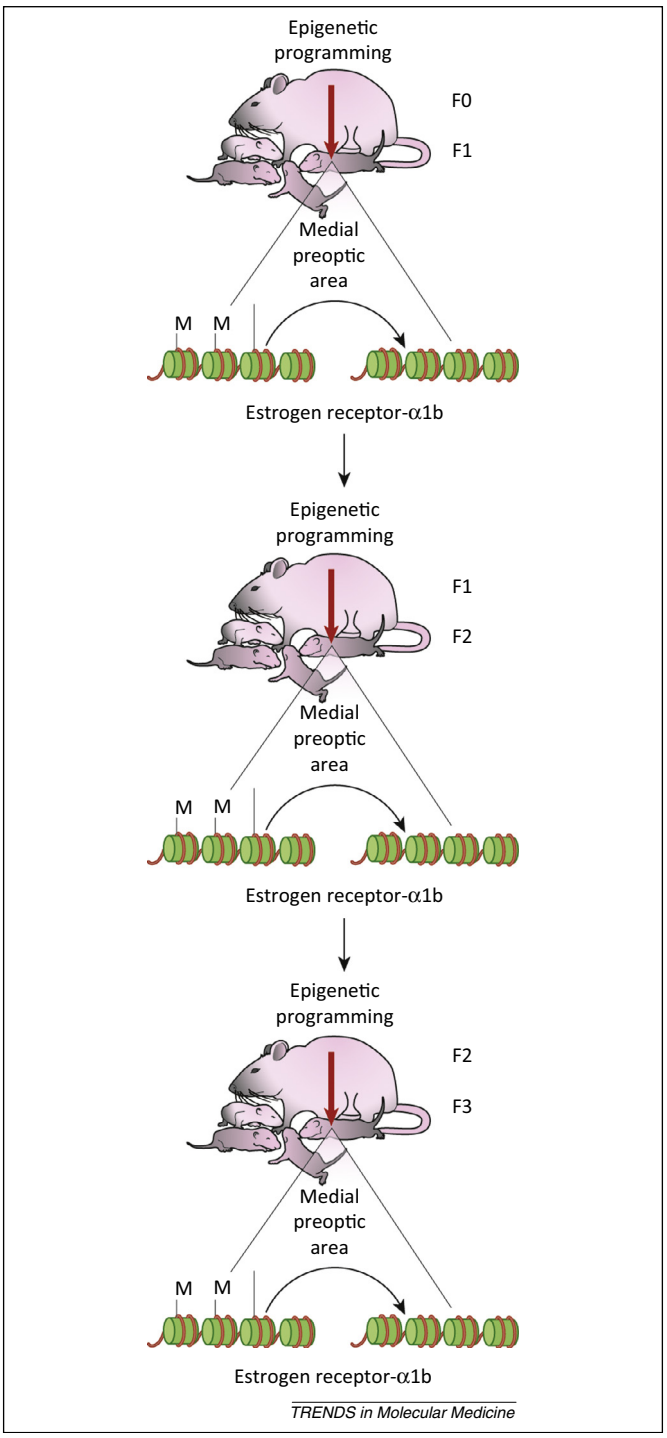

Figure 2. Gamete-independent multigenerational transmission. Maternal care in rodents programs stress-responsivity of the offspring as well as their maternal phenotype through the epigenetic modulation of genes such as that for estrogen receptor α1b in the medial preoptic area in the brain. Maternal care behavior of F0 will program genes in the brain of F1, which develops a maternal care phenotype as a result of this epigenetic programming that parallels F0 maternal care behavior. When F1 matures it epigenetically programs F2, which develops a maternal care behavior as a result that parallels F1. F2 similarly programs F3 and alters its brain gene program.

The cardinal issue is defining a fundamental common mechanism, or several different mechanisms, that can explain the different modes of nongenetic inheritance. Progress in epigenetics in the past decade has started to provide plausible mechanisms for the different forms and timescales of nongenetic inheritance.