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Environmental Epigenetics: Myth and Reality

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Abstract

The field of epigenetics is primarily interested in the epigenetic basis of development and disease, the transgenerational transmission of epigenetically controlled traits, and the role of the environment in modulating epigenetic traits. The term "epigenetics" itself has evolved. Initially it designated that a limited number of molecular modifications to DNA can influence gene expression as one of the mechanisms controlling cellular differentiation and divergent phenotype despite containing the same genetic code. Today, a broad and imprecise classification of many other cellular regulatory processes that can influence gene expression and which may or may not be heritable are commonly referred to as "epigenetic". Two recent papers, one by Ute Deichmann and the other by Corrado Spadafora, expose the overly broad use of the term. Accepting their challenge to redefine epigenetics in a more precise and rigorous way could have significant consequences. It could help us avoid attributing alterations in an offspring's phenotype due to environmental stresses experienced by its parents to epigenetic mechanisms, and misuse of the term outside the narrow confines of scientific discourse in the life sciences. Moreover, such precision would ensure setting an appropriately high bar for testing whether newly identified aspects of DNA methylation and micro RNA transmission could be transmissible from parent to offspring through the germline, and more stringently verifying as yet unfounded claims for the transgenerational heritability of environmentally acquired traits that could discredit this important field of inquiry.

Keywords: epigenetics, DNA methylation, histone modifications, miRNAs, environmental epigenetics, transgenerational epigenetics

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Epigenetics, which may be defined as "the study of mitotically and meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" (Waddington 1942; Riggs *et al.* 1996; Deichmann 2015), has become a very popular topic in the biomedical sciences. Emerging from early studies in the fields of cellular differentiation and embryonic development, which showed how DNA methylation and histone modifications could alter the phenotype of cells (Nakao 2001), Epigenetics garnered broad interest after the discovery that it was involved in carcinogenesis (Sugimura & Ushijima 2001). Paradoxically, insight into the association of epigenetics and cancer raised doubts regarding the role of epigenetic mechanisms in regulating cellular processes. A proliferation of studies showing that tumors could carry different, contrasting epigenetic profiles, led to questioning whether epigenetic changes observed in cancer might also reflect normal regulatory processes (Jones & Buckley 1990). The significance of epigenetics has been ambiguated by the

gradual loosening of the above-mentioned definition of "epigenetic traits". Initially, the term "epigenetic" was limited to DNA methylation and histone modifications, however today, the term means different things to different scientists who commonly use it to refer to many other cell molecular events. This has led to confusion in interpreting epigenetic studies. A common joke among biologists illustrates this point: "If they ask you anything you don't know, just say it's due to epigenetic modifications".

Nevertheless, the field of epigenetics continues to attract considerable interest. This is due to its apparent involvement in many diseases (Feinberg 2018; Tollefsbol 2018) and to the intriguing notion that some sort of yet unidentified "epigenetic" process might be a mechanism that allows acquired traits to be inherited. This would mean environmentally determined parental phenotypes could be stably transmitted to offspring without a change in the germline's DNA sequence (Casas & Vavouri 2020; Senaldi & Smith-Raska 2020). *If* such a mechanism were revealed, it would have important implications for understanding health and disease, and would fundamentally change our understanding of evolution. Nevertheless, the value of the burgeoning research into these questions is limited by widespread and inaccurate use of the term, and by the tendency to mislabel a wide variety of cellular regulatory processes as "epigenetic".

The scientific problem and its broader implications are superbly discussed by science historian Ute Deichmann, in her insightful and incisive review "The social construction of the social epigenome and the larger biological context" (Deichman 2020, p. 37). She surveys the foundations of epigenetic science, highlighting the milestones and discoveries that we can rely on, and criticizing the misuse and over-interpretation of the biological epigenetic discourse by the social sciences. These have often ignored the narrow bio-molecular context of the findings, relying on flawed studies and limited findings to draw overarching inferences. It bears repeating that few phenomena in fact meet the strict definition of epigenetic traits, stipulating that such modifications 1) must not alter the DNA sequence and 2) must be transmittable from parent to progeny, at least during somatic cellular proliferation or gametogenesis. To date, DNA methylation and covalent histone modifications, which together can determine nucleosomal occupancy, are the only phenomena proven to meet these essential criteria.

Whether microRNAs (miRNA), commonly referred to in the biological literature as somehow being epigenetic also meet these criteria is still very much an open question. MicroRNAs can be transmitted, but given the apparently stochastic mode of their transmission, it is not evident they can indeed give rise to stably inherited traits not encoded by the offspring DNA (Gapp & Bohacek 2018; Fuso *et al.* 2020). In another recent review, Corrado Spadafora offers an intriguing hypothetical model, whereby miRNAs might be transmitted from the parental germlines to the developing embryo by circulating vesicles, and then stably acquired (Spadafora 2020).

The crucial questions raised by these reviews concern if and how the environment can modulate epigenetic traits in such a way that acquired traits could be transmitted across generations. Although as Deichmann cogently argues, it is abundantly evident that a wide range of environmental factors including chemical agents, nutrition, pollutants, physical activity, and even behavioral stress, can induce changes in the epigenome, the evidence is a far cry from the "revenge of Lamarkism" (Deichmann 2016). Deichmann extensively documents the fact that to date we have no credible evidence for transgenerational epigenetic inheritance in humans, and even in other species the evidence is exceptionally rare and has no permanent impact on the epigenetic marks. Furthermore, there is scant evidence of extensive environmentally induced demethylation of CpG islands in differentiated tissue.

In this regard, it should be noted that most studies of mammalian DNA methylation to date have focused on highly stable CpG methylation in CpG islands. Much less is understood about more dynamic changes that are increasingly documented in gene promoters outside of dense CpG regions. It is indeed difficult to imagine that a CpG-dense, heavily methylated promoter could be easily demethylated in a differentiated tissue. However, emerging evidence suggests that environmental-dependent differential methylation may play a functional role in promoters with low CpG density, even in non-proliferating tissues (Lee *et al.* 2020). We have demonstrated, for example, that B vitamin imbalances can induce differential non-CpG methylation in the promoter of the PSEN1 gene (related to amyloid processing) in adult mice, modulating gene expression and eventually exacerbating their Alzheimer-like phenotype (Fuso *et al.* 2012). Similar non-CpG differential methy-

lation has been observed in the post-mortem brain from Alzheimer's patients and healthy controls (Monti *et al.* 2020; Nicolia *et al.* 2017). Such environmental modulation of non-CpG epigenetic patterns in tandem with altered gene expression, even in non-proliferating tissues, might shift the organism between health and disease. Further research into environmental effects on non-CpG methylation is warranted, and remains to be explored both in quiescent and proliferating somatic cells. Nevertheless, this type of environmental influence on what is generally regarded as an epigenetic marker, does not meet the essential criterion of being a heritable change. It would be of considerably greater interest if such adaptive or maladaptive changes were also observed in meiosis, because as far as we know, epigenetic modifications to non-mutated DNA would have to occur in the germ-line in order to stably influence the phenotype of the progeny without changing their inherited DNA sequence (Jawaid *et al.* 2020).

Spadafora proposes an alternative potential mechanism for transmitting acquired environmental traits involving miRNA in his review. He postulates that miRNAs released from parental somatic tissues that have been exposed to stress, can be taken up in vesicles by the gametes and transmitted as "epigenetic information" to somatic tissues in the developing embryos, potentially establishing stably inherited traits. It is difficult to see how vesicle-transported miRNAs could resolve the critical issues addressed in Diechmann's review since no evidence has yet been found for stable epigenetic inheritance in humans and scant evidence supports it in mammals. Another problem is the stochastic way the developing embryo would have to take up circulating miRNAs to ensure the offspring would preferentially express the parents' acquired phenotype. It is difficult to reconcile what we know of evolutionary selection with such "environmental epigenetics". Indeed, in the few documented mammalian models, transgenerational changes have never been observed to last beyond three generations (Heard & Martienssen 2014).

Until environmentally acquired phenotypes can be shown to be stably transmitted to offspring across multiple generations, independent of their inherited DNA sequence, the field of epigenetics would benefit from a renewed consensus on precise criteria for "epigenetic" traits and for designating newly discovered phenomena as epigenetic. It is clear that DNA methylation, histone modification, and non-coding RNAs represent different molecular species with different functional characteristics. Therefore, any new molecule or process can only be termed epigenetic through its functional epigenetic effects. In order to uphold the hypothesis that environmental conditions can produce a stably heritable, acquired phenotypic response, without altering the DNA sequence, we need a more precise understanding of how an organism might adapt to environmental conditions by specifically modifying the expression of relevant target genes and pathways in a beneficial manner to enhance evolutionary fitness. Until such evidence is available, we can advance the field by not using the term epigenetic indiscriminately. Overreaching inferences rooted in social and disciplinary arguments over the relative importance of nature and nurture are unlikely to carry us forward. We will do more to advance the field of epigenetics along with all the life sciences by testing novel hypotheses that can identify, deepen and refine our understanding of the master commands that direct the adaptive cellular response of target genes to environmental cues, without changing the gene sequence.

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