HISTORICAL NEWS & VIEWS: EPIGENETICS

Beyond the maternal epigenetic legacy

In 2004, Weaver et al. published evidence in *Nature Neuroscience* for the lasting epigenetic impact of maternal care within the hippocampus of rat offspring. This conceptual and methodological leap contributed to the evolution of environmental and behavioral epigenetics and continues to inspire challenging questions about genes, environments, and their legacy.

Frances A. Champagne

What makes us unique? Across species, evidence for the role of genetics, environments, and their interactions in shaping phenotype provide a broad perspective on how our unique characteristics emerge. However, the critical question of mechanism emerges within this general framework, particularly when thinking about how environments exert lasting phenotypic influence. While the discovery of DNA was accompanied by investigation of how genes contribute to phenotype[1], the study of the relationship between environment and phenotype has proven more challenging. Environments are multilevel and multimodal experiences that are dynamically changing—an extremely complex signal compared to the genome. Epigenetic factors, broadly defined as molecular modifications that can alter gene activity without altering DNA sequence[2], are now believed to have the properties necessary to articulate this complexity. The path to that belief started over a decade ago with studies of the lasting impact of mother–infant interactions and a molecular leap of faith (Fig. 1).

Converging evidence for the role of mother–infant interactions in shaping the unique characteristics of offspring is suggested by our experiences as children and parents and supported by experiments in the lab. For example, variation in the frequency of maternal licking and grooming (LG) of rat pups is a significant predictor of the stress responsivity of these offspring as adults. Reduced expression of hippocampal glucocorticoid receptors impaired negative feedback on the hypothalamic–pituitary–adrenal axis, and higher stress responsivity characterizes offspring that receive low levels of LG, which may account for this phenotypic outcome[3]. Analyses of hippocampal mRNA levels of the gene encoding glucocorticoid receptors (*Nr3c1*) revealed that altered gene expression emerges in infancy in response to maternal LG and lasts into adulthood. When this phenomenon was first observed, it challenged the conventional view that genes were dynamically regulated by contemporary signals rather than historic ones. Weaver et al.[4] addressed the question of whether DNA methylation could account for these lasting effects of maternal care.

In a series of studies, Weaver et al.[4] assessed cytosine methylation within the promoter region of the *Nr3c1* gene in hippocampal tissue from adult male offspring that had experienced low versus high maternal LG during the first week of life. Remarkably, offspring of low-LG mothers had higher levels of DNA methylation within the *Nr3c1* gene promoter. Cross-fostering studies and analyses of *Nr3c1* at multiple developmental ages from late gestation through to adulthood confirmed that adult DNA methylation within the *Nr3c1* gene promoter was predicted by the postnatal experience of maternal care. Moreover, pharmacological targeting of the epigenetic state of the hippocampus could reduce DNA methylation of the *Nr3c1* gene promoter, increase *Nr3c1* gene expression, increase the levels of hippocampal glucocorticoid receptors, and reduce the stress responsivity of adult offspring that had experienced low levels of maternal LG. Taken together, Weaver et al.[4] provided evidence for the lasting epigenetic impact of maternal care in the brains of offspring and the functional relevance of this epigenetic variation for the way in which an individual responds to stress.

Beyond this comprehensive series of studies, the finding that postnatal maternal care could impact DNA methylation was antithetical to the molecular assumptions of the time. DNA methylation was considered a mechanism of gene regulation—primarily gene silencing—relevant to cellular differentiation and not a dynamically changing molecular mark. De novo DNA methylation was speculated to be rare[5], while exploration of the role of DNA methylation in behavior was limited to studies of genomic imprinting in which imprinted genes were mutated[6]. Yet despite all this, epigenetic plasticity was examined in response to a broad social cue and linked to phenotype. Why be constrained by studying only what is likely or possible?

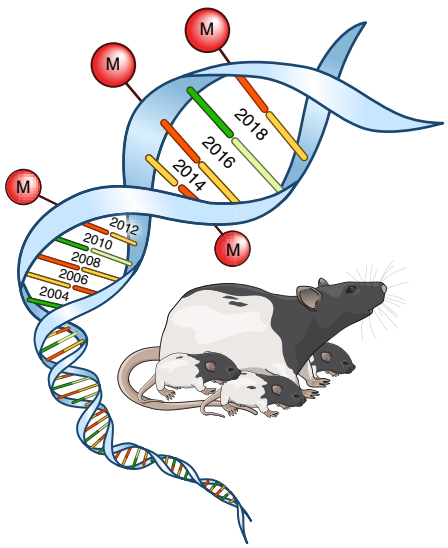

Fig. 1 | Maternal influence on offspring DNA methylation in rats was a starting point for a more dynamic view of epigenetics that has expanded over time.

By challenging the existing scientific dogma of the time, Weaver et al.[4] opened the door to a broader study of environmental impacts at the level of gene regulatory mechanisms that can 'maintain' the effect of environmental exposure long after the exposure has ended. It is now evident that the environments we experience across the lifespan, including stress, nutrition, and toxins, can have an epigenetic impact. Nurture via Nature[7], rather than Nature versus Nurture, has transitioned from a compelling concept to biological reality. Twin studies in humans have suggested that epigenetic variation might be acquired

across the lifespan in humans and contribute to discordance in phenotypic traits[8]. Though a genetic perspective continues to thrive within the health sciences as a predictor of individual risk, there is increasing integration of epigenetic or more global epigenomic profiling to better characterize the complexity of individual differences in health and disease[9].

The DNA-centric view of inheritance and the assumption that development of an organism necessarily requires the removal of any acquired 'epigenetic baggage' are also changing as a downstream consequence of integrating DNA methylation into studies of the link between environment and phenotype. In laboratory mice, the experiences of fathers before conception can lead to epigenetic and behavioral effects in offspring with possible transmission across multiple generations[10]. The capacity to transmit phenotypic variation from fathers to offspring has been linked to epigenetic variation in the sperm[11], resulting in a growing revival of the Lamarckian notion of the inheritance of acquired characteristics. However, this paternal germline inheritance occurs in the context of maternal transmission of epigenetic variation through mother–infant interactions[12], and mothers may be able to modulate the impact of paternal germline influence[13]. Therefore, an expanded or inclusive view of inheritance is suggested by epigenetics and by the transmission of environmentally induced traits across generations, with implications for evolutionary theory[14].

The rapid integration of epigenetics into the biological and social sciences over the past 15 years is extraordinary. Aided by advances in DNA sequencing technology, interdisciplinary collaborations, and the seductiveness of a dynamic yet potentially stable modulator of genome function, epigenetics offers biological sophistication and complexity to the exploration of the origins of our uniqueness. But there are many hurdles to overcome before integration of this perspective into our understanding of gene–environment interactions can be achieved. Despite accumulating evidence for a molecular impact of environmental experiences, the 'process' by which this occurs remains elusive. In vitro and in vivo studies indicate that the effect of maternal care on *Nr3c1* DNA methylation in the hippocampus may be mediated by tactile stimulation[15]. Though this somatosensory cue is attractive as an evolutionarily conserved pathway fostering neurodevelopment, there are still gaps in our understanding of the cascade of neural, physiological, and molecular responses that account for the effects of maternal care. The pathways linking the environment, epigenome, and phenotype are relatively unknown for most experiences. Given the complexity and variety of experiences an organism will have across its lifespan, not to mention ancestral experiences, the task of revealing these pathways is not trivial. Yet elucidating this cascade will be essential to the process of moving forward in the fields of behavioral and environmental epigenetics.

Molecular epigenetics offers a perspective that can be most impactful if carefully integrated with genomics, neuroscience, and psychology to foster the future of behavioral epigenetics. Focusing on how to achieve that integration using novel theoretical, methodological, and analytical strategies will be the next phase of this evolving research framework. Finally, while mothers and their experiences will have a lasting legacy within the field of behavioral epigenetics, the ecological contexts of development and of ancestral environments more broadly defined will be essential to revealing the predictive architecture of our unique characteristics. ❐

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Competing interests

The author declares no competing interests.

SYNAPTIC PLASTICITY

Synaptic homeostasis: quality vs. quantity

Synaptic connections adapt homeostatically to changes in experience to maintain optimal circuit function. A study demonstrates that different forms of synaptic homeostasis respond to distinct aspects of circuit activity, suggesting that neurons can gauge and adapt to the both the quality and quantity of circuit activity.

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In a changing world, neural networks require homeostatic adjustments to maintain neuronal firing within optimal range for information encoding, but without compromising information stored as distributed synaptic weights. The two known mechanisms that can accomplish this task are synaptic scaling[1] and the sliding modification threshold for Hebbian plasticity[2]. If or how these two homeostatic mechanisms work together to maintain circuit function in response to changes in sensory experience is unknown. A study by Bridi et al.[3] now finds that both homeostatic mechanisms are engaged in response to changes in sensory experience, but operate within different dynamic ranges of activity and respond differently to levels of patterned and spontaneous activity (Fig. 1).

In response to chronic changes in neural network activity, both synaptic scaling and a 'sliding modification threshold' elicit compensatory synaptic changes to maintain firing levels within a target range, but do so