nature neuroscience

Focus on epigenetics

We present a special focus on epigenetics in the nervous system, highlighting recent advances in our understanding of epigenetic mechanisms and their regulation in neurons, as well as their role in nervous system function.

Life experiences affect behavior, in part via epigenetic modifications that alter DNA transcription. These epigenetic changes can include chromatin or DNA modifications and can silence genes or boost their transcription. Traditionally, molecular biologists have defined epigenetic modifications as those that are stable enough to be heritable through the germ line or across cell divisions. This definition presents a conundrum for neuroscientists: because neurons do not generally divide, nothing that occurs in neurons in the adult CNS would therefore be considered to be epigenetic. However, neuroscientists have found evidence that changes in epigenetic marks can explain how experiences early in life can shape behavior in adulthood and they have also discovered that regulation of chromatin structure and DNA-modifying enzymes can critically regulate the development and function of the nervous system, even in adulthood. We highlight some of the latest advances in this growing field of 'neural' epigenetics, featuring perspectives and reviews that report recent advances in our understanding of the processes that regulate the epigenome in the nervous system. Our authors also discuss some of the key issues that neuroscientists need to resolve before they can truly connect the dots between nature and nurture.

We kick off the focus with a commentary by Michael Meaney and Anne Ferguson-Smith, who write about the caveats neuroscientists need to be aware of when studying epigenetic marks. Although epigenetic modifications have become enticing candidates for explaining experience-dependent modifications of behavior, the challenge for neuroscientists is to come up with causal pathways linking environmental effects, epigenetic marks, genomic structure, and, ultimately, the downstream transcriptional and translational changes that cause long-term changes in behavior. For instance, Meaney and Ferguson-Smith point out that the assumption that epigenetic marks (whether DNA methylation or histone post-translational modifications) are uniformly associated with an on or off transcriptional state is overly simplistic and that epigenetic marks often have bi-directional effects on transcription depending on the interacting and regulatory proteins. Thus, taking a static snapshot of the associations of epigenetic marks with a particular neuronal state or phenomenon may not tell us much about how they dynamically regulate neural function. The authors make a case that a complete understanding of the manner in which epigenetic influences affect nervous system function requires an integrative approach incorporating multiple levels of analysis and propose that studies in genomic imprinting may serve as a model for such approaches.

On page 1330, Antonella Riccio picks up on the issue of how epigenetic changes are regulated. Although much is known about the nature of the DNA-modifying enzymes that dictate epigenetic changes in neurons, neuroscientists are only now beginning to unravel the complex regulation and interplay between the signaling pathways that affect the function of these enzymes. Riccio reports on recent work indicating that physiological signals and developmental cues influence transcriptional responses in neurons via epigenetic modifications. Her review also analyzes the regulation of histone acetylation and DNA methylation in response to neutrotrophin signaling and neural activity and illustrates how external stimuli can modify chromatin architecture and nuclear structure in the nervous system.

Ma and colleagues review the control of adult neurogenesis by epigenetic mechanisms on page 1338. They analyze the evidence suggesting that mechanisms such as DNA methylation, histone modification and transcriptional feedback loops promote self-renewal and differentiation of adult neural stem cells. They point out the recent technical innovations that have provided a good toolkit for studying the small, but important, numbers of cells involved in adult neurogenesis and propose the idea that adult neurogenesis affords us a unique model for understanding the role of epigenetic mechanisms in the interface between genes and the environment. They conclude by discussing the implications of disruptions of these mechanisms on disease, including brain tumors and neuropsychiatric disorders.

Jeremy Day and David Sweatt examine the controversial topic of DNA methylation and memory in their engaging perspective on page 1319. Is DNA methylation reversible? How do changes in DNA methylation promote memory formation and how can variations in methylation patterns between different brain regions enable consolidation and storage of memories? Can DNA methylation be selective enough, and dynamically/temporally compatible with, the formation and storage of memories?

Finally, Selma Masri and Paolo Sassone-Corsi discuss how epigenetic events could contribute to circadian 'memory' and influence the plasticity of the circadian system to adapt to changing rhythms on page 1324. They review the involvement of epigenetic regulators such as DNA methylation in regulating circadian clocks and evaluate the evidence that suggests that metabolic signals can modulate the circadian epigenome. A better understanding of the epigenetic regulators of the circadian system should also shed some light on the key features that differentiate central from peripheral clocks.

Of course, these reviews and perspectives only cover a fraction of the accumulating literature on the epigenetic modifications that occur in the nervous system. Nevertheless, we hope these articles will offer our readers a stimulating snapshot of some of the major advances in this area, as well as the more challenging problems this field faces. We are very grateful to our authors, reviewers and advisors for their help with this collection. ■