56.1 Epigenetic Pathways During Early Postnatal Life: How does a Neuron 'Know' to Modulate Its Epigenetic Machinery in Response to Early-life Experience?Tallie Z. Baram*

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Background: Exciting information is arising about epigenetic mechanisms and their role in long-lasting changes of neuronal gene expression. Whereas these mechanisms are active throughout life, recent findings point to a critical window of early postnatal development during which neuronal gene expression may be persistently re-programmed via epigenetic modifications. However, it remains unclear how modulation of the epigenetic machinery is triggered and executed. Here we focus on an important example of early-life programming: the effect of sensory input from the mother on expression patterns of key stress-related genes in the developing brain. We describe recent work that integrates organism-wide signals with intercellular and intracellular events that, in turn impact epigenetic regulation. We focus on the lasting effects of enriched early life experience on *Crh* gene expression in the hypothalamus, and describe the operational brain networks that convey sensory input to CRH expressing cells, highlighting the resulting 're-wiring' of synaptic connectivity to these neurons. We will then move from inter-cellular to intracellular mechanisms, delineating recent and emerging information about the induction and maintenance of life-long *Crh* repression provoked by early-life experience, and the responsible molecular mediators. Elucidating such pathways is critical for understanding the enduring links between experience and gene expression. In the context of the responses to stress, such mechanisms should contribute to vulnerability or resilience to number of stress-related disorders.
Methods: n/a
Results: Much work has centered on the enduring effect of maternal-derived sensory signals on gene expression. However, how these signals propagate within the brain and arrive at the target neurons is less well understood. We describe neuronal pathways activated by specific patterns of maternal behavior, that carry patterns of maternal care to stress-responsive hypothalamic neurons. How does activation of this neuronal network influence neurons to modulate cellular processes? We find that a week of early-life augmented maternal care reduces the number and function of excitatory synapses onto CRH-expressing hypothalamic neurons. This reduced excitatory input triggers intracellular cascades culminating in epigenetic chromatin changes, as evident from recent data showing that reduced glutamatergic neurotransmission suffices to repress *Crh* expression in hypothalamic slices *in vitro*. The responsible mechanisms involve the transcriptional repressor NRSF/REST.
Conclusions: As shown above, the resulting life-long repression of *Crh* contributes to attenuated response to stress throughout the life-time. However, neuronal programming likely involves epigenetic, coordinate changes in the expression of large gene networks that, together, underlie the life-long phenotype of resilience to stress-related disorders induced by enriched early-life experience in animal models- and possibly in humans.
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