Epigenetic Clues to the Biological Embedding of Early Life Adversity

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The concept of biological embedding has gained substantial traction as a framework for understanding the roots of complex multifactorial phenomena in health and disease. A body of research over several decades indicates that early life experiences have profound consequences for health in adulthood, including mental health, as a consequence of establishing long-term health gradients (1). Early interventions have been proposed to have an enhanced impact on health trajectories in part because they act at a time of enhanced plasticity (2). Early-life adversity in the form of physical and sexual abuse or severe neglect is well recognized to increase the risk of suicide (3). It has been challenging, however, to elucidate biologic mechanisms that underlie long-term changes in brain and behavior that are associated with the increased risk.

Epigenetic mechanisms may hold a clue. Changes in gene function without changes in gene sequence are regulated by DNA methylation, histone modifications, and noncoding ribonucleic acids. These molecular mechanisms appear to be a biologic manifestation of gene-environment interactions. They have been proposed as an alternative to the dichotomization inherent in classic models of environmental and heritability measures of phenotypes (4). Whether competing or complementary, alterations of epigenetic mechanisms are associated with a variety of psychopathologies linked to suicide and suicidal behaviors. A recent study suggested that early-life adversity but not suicide per se alters DNA methylation of the GR1F splice variant of the glucocorticoid receptor gene (also known as GR, NR3C1), affecting the binding of the transcription factor nerve growth factor-inducible protein-A (also known as Zif268, EGR1, Krox24, and ZENK) to its promoter and reducing overall glucocorticoid receptor gene expression (5). Glucocorticoid receptor is a key player in regulating negative feedback inhibition of the endocrine response to a stressor. Although this study focused on only one splice variant expressed in hippocampus, overall glucocorticoid receptor expression is regulated by a number of untranslated first exons that determine levels of glucocorticoid receptor expression throughout the body. In the hippocampus, the role of glucocorticoid receptor alternative first exon expression in psychopathology is not well understood, less so for other brain areas.

The study by Labonte *et al.* (6) in this issue of *Biological Psychiatry* reports tantalizing new data on the association of DNA methylation with other glucocorticoid receptor splice variant activity in human brain and clues to its possible link with early-life adversity. The authors found that the coding region of glucocorticoid receptor shows lower gene expression in the hippocampus of adult suicide victims who were abused or severely neglected in childhood compared either with nonabused suicide victims or control individuals who died of unrelated causes, corroborating previous data (5). Furthermore, lower glucocorticoid receptor gene expression was observed across all three untranslated variants of glucocorticoid receptor examined in suicide victims with a history of childhood abuse or neglect but not the other groups. This effect appears to be brain region specific because it was not observed in the anterior cingulate cortex. The differences in expression in the hippocampus were accompanied by altered DNA methylation in the promoter regions of these genes. Intriguingly, although GR1B and GR1C promoters showed an increase in site-specific DNA methylation among abused suicide victims, DNA methylation was lower across many CpG sites in the GR1H promoter among abused suicide victims compared with the other groups. Correlational analysis revealed that some CpG sites showed the expected inverse correlation of DNA methylation and gene expression for GR1B and GR1C, whereas GR1H showed a positive correlation. The data indicate that the epigenetic response to early-life adversity extends across multiple glucocorticoid receptor genes. The data also highlight the complex nature of DNA methylation and its relationship to gene regulation. Clearly, approaches aimed at characterizing epigenetic differences in populations of interest are necessary. Clearly, more is needed. We do not understand the manner in which select transcription factor binding sites or chromatin binding protein complexes are altered as a function of site-specific DNA methylation differences in these promoter regions. We also do not know whether the observed DNA methylation differences are the direct result of epigenetic changes in glucocorticoid receptor during early life or whether they are outcomes precipitated by still other mechanisms.

Challenges inherent in epigenetic studies relate to the specific nature of epigenetic patterns across functionally distinct cells. It is likely that epigenetic patterns are specific not only to cell type (e.g., [7]) but also to distinct neuronal pathways within the same anatomically defined brain region. An important issue for future studies of early-life adversity in living humans is the correspondence between epigenetic alterations in the brain and those in peripheral tissues, which would allow resampling over time and after intervention. In this regard, there is evidence that glucocorticoid receptor is epigenetically sensitive across multiple tissues to alterations in the early life environment that affect risk for psychopathology (8,9). Selecting the right study populations is paramount. Genome-wide sequencing approaches yield substantial power in the analysis of individual epigenomes, yet such approaches need to be counterbalanced with analogously sensitive phenotypic screens to identify populations of interest. Appropriate animal models of early life influences on glucocorticoid signaling pathways will also help elucidate epigenetic mechanisms, and several have emerged. In an interesting parallel to the study by Labonte *et al.* (6), a recent study in which the glucocorticoid receptor gene locus was examined by tiling microarray in rats found widespread epigenomic alterations in adult hippocampus as a function of naturally occurring differences in early maternal care in rats. Altered DNA methylation and suppressed gene expression were observed across multiple untranslated first exons of the glucocorticoid receptor in manner that appears akin to what was observed by Labonte *et al.* (6) in human hippocampus (10). Transcription factors like glucocorticoid receptor target other genes, and it will be important to examine downstream genomic targets of this altered transcriptional activity. Newly accessible technologies for epigenomic mapping combined

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with such systems biology approaches are providing powerful methods toward a mechanistic understanding of the biologic embedding of adversity.

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