New insights into the link between childhood adversity and epigenetic changes

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Accumulating evidence indicates that early childhood adversity might modify epigenetic patterns, particularly for DNA methylation. Although this relationship holds promise for new avenues of understanding the effects of early-life experiences, the mechanisms underlying such environmental effects on epigenetic profiles remain elusive. In *The Lancet Child & Adolescent Health*, Alexandre Lussier and colleagues[1] investigated the relationship between childhood adversity and DNA methylation across different developmental stages. They found that adversity experienced between the ages of 3 and 5 years was more strongly associated with differences in DNA methylation patterns at age 15 years, compared with adversity experienced at other periods between birth and age 11 years.[1] These findings not only support the well documented role of childhood adversity in behavioural and epigenetic regulation,[2,3] but also unveil how the timing of environmental exposure can influence the effect of early-life adversity on epigenetic regulation.[4] This study provides compelling evidence that the early (preschool) childhood period might be particularly sensitive to adverse environmental factors.

Lussier and colleagues[1] discovered that associations between adversity and childhood DNA methylation patterns at 7 years did not persist into adolescence. Additionally, their findings indicate that most of the early childhood adversity-associated DNA methylation changes observed at age 15 years were not observed at birth or at 7 years.[1] These data reveal the dynamic process of epigenetic changes in response to early childhood adversity and provide some clues as to the length of time needed for early childhood adversity to generate significant epigenetic changes. Therefore, future research on epigenetic changes in response to environmental events might need to consider the length of the time between the exposure and the identification of the modification.

Lussier and colleagues[1] also found that the genes with epigenetic changes responsive to early childhood adversity overlap with genes reported to be associated with several psychiatric disorders, and speculated that such epigenetic changes might account for mental illnesses later in life. Caution needs to be exercised when interpreting associations between epigenetic changes and neuropsychiatric disorders because the relationship could be bidirectional, wherein epigenetic modifications might be both a consequence and a cause of psychiatric symptoms. For example, increased DNA methylation in the glucocorticoid receptor gene has been linked to childhood adversity and a higher risk of developing depression, and depression can cause stress that affects epigenetic patterns of this gene.[5,6] Nevertheless, stress caused by psychiatric symptoms might continue to modulate long-lasting epigenetic regulation by altering the expression of genes involved in epigenetic regulation.[7]

The translation of these findings into clinical practice relies on establishment of a causal relationship between childhood adversity and epigenetic changes; however, this could be challenging. Experimental studies to appraise causality in humans are often not feasible, meaning that convergent results from clinical and preclinical studies must be relied upon. For example, although DNA methylation patterns associated with prenatal exposure to bisphenol A are found to correlate with DNA methylation changes in the glutamate receptor subunit gene in both rats and humans, this chemical exposure has been shown to result in hypermethylation in humans and hypomethylation in rats.[8] Future research is needed to clarify the implications of such paradoxical findings. Without convergent findings in clinical and preclinical studies, the association of epigenetic changes with childhood adversity lacks biologically plausible evidence of causality.

Epigenetic modifications are merely one piece of the puzzle in understanding the development of psychiatric and other disorders. Other factors, such as genetic predisposition, nutrition, and social support, also play a crucial role in shaping an individual's future physical and mental health outcomes. Additionally, intergenerational trauma, such as prenatal maternal stress, might affect the development of the corticolimbic circuit in the brain[9] and result in the development of mental illnesses in offspring later in life,[10] which can confound the relationship between childhood adversity and epigenetic

changes. Although epigenetic changes associated with childhood adversity might offer valuable insights into the mechanisms underlying the development of psychiatric disorders, a comprehensive evaluation of the interplay between multiple risk factors is needed to inform targeted interventions aimed at mitigating the effects of childhood adversity on mental health.

In conclusion, the study by Lussier and colleagues[1] provides valuable insights into the relationship between early childhood adversity and epigenetic modifications. Their findings on the relationship between age-dependent epigenetic changes and childhood adversity and the identification of a crucial developmental period have imperative clinical implications. Research is warranted to clarify causality, understand the intricate mechanisms underlying these associations, and develop effective interventions accordingly.

We declare no competing interests.

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