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Editorial

Environmental epigenetics and the loneliness epidemic

Editorial

From a biological perspective, epigenetics relies on the ability of cells to regulate gene expression without altering the underlying deoxyribonucleic acid (DNA) sequence [1, 2]. This regulation is vital for enabling cellular diversity, adaptability, and functional specialization within organisms. Moreover, epigenetics explores the regulation of gene expression through molecular mechanisms that are modulated by environmental factors. This framework provides insight into how diverse experiential factors, such as stress [3], natural disasters [4], environmental toxicants [5], and positive experiences like lifestyle enrichment [6], change genetic expression through modifications such as DNA methylation, histone acetylation, and microRNA actions. Thus, epigenetic regulation of gene expression allows organisms to develop a molecular memory and rapidly adapt to dynamically changing environments.

Epigenetic mechanisms also readily respond to social experiences [7, 8]. This is noteworthy because social stressors, such as loneliness, have become pressing global health threats [9]. In Canada, more than 1 in 10 people report frequent loneliness, with young women reporting the highest levels of loneliness [10]. Loneliness and social isolation (SI) have serious physical and mental health risks with a mortality rate that is potentially similar to smoking [11]. Physiological changes driven by adverse social experiences may indeed influence susceptibility to all-cause mortality [12], psychological complications [13], non-communicable diseases [14], and severe infectious complications [15], possibly through epigenetic mechanisms.

SI has been shown to affect epigenetic processes through the stress response via hypothalamic–pituitary–adrenal (HPA) axis activation, inflammatory responses, and profound metabolic changes. Fundamentally, social stresses such as SI trigger a heightened stress response, predominantly through regulation of the HPA axis [16]. SI may also further increase stress vulnerability in lineages exposed to ancestral stress [17]. Possible pathological changes resulting from long-term SI may be a direct result of increased glucocorticoid levels and associated epigenetic modifications, particularly DNA methylation changes in glucocorticoid receptor genes such as nuclear receptor subfamily 3 group C member 1 (Nr3c1) [18, 19] and the mineralocorticoid receptor gene (Nr3c2) [20]. Chronic SI, therefore, may impair the regulatory efficacy of glucocorticoid feedback mechanisms, contributing to long-term stress sensitivity and the development of anxiety or depression, or psychosomatic disorders, such as metabolic or cardiovascular disease.

The epigenetic mechanisms through which loneliness and SI may impact disease risk are still poorly understood. SI may induce rapid and lasting changes in brain plasticity, potentially through methylation of the gene encoding brain-derived neurotrophic factor (BDNF). These modifications influence emotional regulation and the brain's processing of ongoing experiences, such as stress [21]. Through methylation of the BDNF gene, SI may reduce BDNF production and impair synaptic plasticity and augment the risk of mood disorders and cognitive deficits [22]. In parallel to metabolic shifts associated with stress [23], social experiences may also closely regulate the function of immune cells. SI is expected to impact the epigenetic regulation of genes involved in inflammatory responses [24]. SI and chronic social stress are known to upregulate pro-inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) through epigenetic modifications, including DNA methylation and histone acetylation changes in immune-related genes [25, 26]. Even short-term SI leads to changes in HPA axis activity and increased neuroinflammation [27]. It can also be postulated that these changes in the IL-6/CRP axis occur in tandem with the silencing anti-inflammatory pathways, thus upregulating the expression of genes that promote inflammation, such as nuclear factor kappa-light-chain-enhancer of activated B cells and Toll-like receptors [28]. Via these inflammatory cascades, SI may lead to a prolonged inflammatory state that is associated with a range of adverse health outcomes, including depression [29], cardiovascular diseases [30], and accelerated cellular aging [31]. The compounding impact of SI on immune-related gene expression highlights a complex epigenetic mechanism through which social factors can modulate inflammatory responses and overall health. In addition to its role in the lifetime health trajectory, SI can also impact the health of future generations through transgenerational epigenetic inheritance [32]. Thus, it can be expected that loneliness and SI can exert multigenerational impacts on the risk of stress-related disorders. Notably, environmental interventions, such as physical and social enrichment, may mitigate SI-induced elevated stress sensitivity through epigenetic regulators, such as microRNAs, across generations [33].

Together, the social environment is influential and pervasive; it may shape new characteristics, alter existing traits, and drive diverse behavioural patterns [34, 35]. While loneliness and SI not only impair individual stress resilience but also perpetuate these effects intergenerationally and transgenerationally [36, 37], social

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enrichment and support programs can mitigate these adverse consequences at any stage of life [6, 35, 38, 39]. The recent loneliness epidemic emphasizes the need for research focused on the epigenetic mechanisms and translating this knowledge into interventions that effectively mitigate the long-term health impacts of social stress.

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