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The role of DNA methylation in the association between childhood adversity and cardiometabolic disease

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ABSTRACT

Growing evidence suggests that adverse environmental stimuli, especially during sensitive periods in early life, may lead to cardiometabolic disease in later life. However, the underlying biological mechanisms remain a mystery. Recent studies inferred that epigenetic modifications are likely involved. We review recent studies, primarily focused on the findings from human studies, to indicate the role of DNA methylation in the associations between childhood adversity and cardiometabolic disease in adulthood. In particular, we focused on DNA methylation modifications in genes regulating the hypothalamus–pituitary–adrenal axis as well as the immune system.

1. Introduction

Childhood adversity, including verbal, physical, or sexual abuse, neglect, as well as family dysfunction (e.g., an incarcerated, mentally ill, or substance-abusing family member; domestic violence; absence of a parent because of divorce or separation etc.), is a global problem, and exerts substantial burden on the children themselves and on society [1]. A mounting body of evidence suggests that adverse experiences in childhood are associated with cardiometabolic disease in later life [2,3]. However, little is known about the underlying biological mechanisms. In the past decade, the search for these mechanisms has progressed rapidly and therein found that epigenetic modifications are likely involved. Emerging evidence from human and animal research suggests that early life stress could lead to lasting, broad, and functionally organized signatures in DNA methylation [4]. For example, mice that were exposed to chronic and unpredictable maternal separation from postnatal day 1 to 14 showed differential methylation in several candidate genes [5]. Subsequent studies in humans also identified differential methylation of *NR3C1* gene promoter not only in postmortem hippocampal tissue among adult suicide victims with a history of childhood abuse, but also in peripheral blood from adults with exposure to childhood maltreatment [6–8]. Several reviews have described the association between childhood adversity and DNA methylation [9,10], and the association between DNA methylation and cardiometabolic disease [11,12]. The present review, however, is primarily focused on the findings from human studies to indicate the role of DNA methylation in the relationship between childhood adversity and cardiometabolic disease in adulthood. While cardiometabolic diseases are caused by a combination of genetic and environmental factors, in this review, we focus on childhood adversity.

Epigenetic modifications are molecular mechanisms that regulate gene expression without changing DNA sequences, including DNA methylation, posttranslational histone modification, small RNA signaling and chromatin conformation changes [13]. Previous studies have demonstrated that the epigenetic modifications take place from the early embryo stage, and could persist across the life course, thereby leading to disease in adulthood [14]. DNA methylation is one of best-studied epigenetic modifications and is essential to mammalian development and cell differentiation. The best-known DNA methylation mechanism is the attachment of a methyl group to cytosine, typically at the fifth carbon position. The primary target of cytosine methylation in mammals is the C-phosphate-G (CpG) dinucleotide [15]. These sites are relatively rare in the genome but more common at promoter regions of genes, also referred to as CpG islands. Generally, increased methylation of CpG islands is associated with gene repression [16]. In addition, methylation at enhancers, insulators and gene bodies were also observed, but the mechanisms by which these influence the binding and function of regulatory proteins are not completely understood [17]. Three active DNA methyltransferases (DNMT1, DNMT3A and DNMT3B) that are responsible for methylation deposition and maintenance have been identified in mammals [18].

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Most data concerning DNA methylation of various pathologies have been obtained from animal models. However, comparable human epigenetic studies are still limited. DNA methylation may hold potential to identify new etiology through which childhood adversity becomes biologically embedded and leads to cardiometabolic disease in adulthood. This knowledge may aid in developing novel prevention and intervention strategies to reduce the burden associated with stress-related health problems. Candidate gene studies and recent preliminary epigenome-wide association studies (EWAS) in early life stress have identified multiple genes involved in the development of obesity, fatty acid synthase, hypothalamus–pituitary–adrenal (HPA) axis, immune system, cellular and neuronal projection etc.(Supplementary Table 1) [19–21]. In particular, DNA methylation alterations in genes HPA axis as well as the immune system in human studies are of most interest. Here we first review the DNA methylation involved in the HPA axis and immune system caused by childhood adversity, then explore the associations of those genes with cardiometabolic disease. Fig. 1 displays the schematic model showing how DNA methylation modifications in some genes related to the HPA axis and immune system could mediate the effect of childhood adversity on cardiometabolic disease in later life.

2. Methods

In the first-stage, we performed a systematic search of PubMed, Embase, and PsycINFO databases through Oct 2017 for relevant studies of the association between childhood adversity and DNA methylation. The following key words were used: ('child abuse' OR 'physical abuse' OR 'sexual abuse' OR 'psychological abuse' OR 'emotional abuse' OR 'neglect*' OR 'trauma*' OR 'advers*' OR 'maltreat*' OR 'bully*' OR 'bullied' OR 'victim*' OR 'expressed emotion' OR 'communication deviance' OR 'parental loss' OR 'separate*' OR 'discrimination') AND 'child*' AND 'methylation'. The titles, abstracts and full-texts were reviewed respectively. After excluding 242 duplicated records, we initially retrieved 1576 abstracts (517 from PubMed, 1171 from Embase, and 130 form PsycINFO) (Supplementary Fig. 1). A majority of those references were excluded after reviewing the abstracts or titles and 42 articles were identified. Of those 33 articles identified genes in the HPA axis or immune system (Supplementary Table 1). The following information from each study is presented in Supplementary Table 1: first author, years of publication, country of origin, definition of childhood adversity, research design, sample size, age of sample size, and main results.

In the second stage, based on the genes identified in the first stage, we searched the databases and identified the genes not only related to childhood adversity, but also associated with cardiometabolic diseases. The following key words for cardiometabolic disease were used: 'cardiovascular diseases' OR 'cardiovascular' OR 'coronary artery disease' OR 'atherosclerosis', 'coronary disease' OR 'coronary heart disease' OR 'ischemic heart disease' OR 'heart failure', 'myocardial infarction' OR 'stroke' OR 'brain vascular accident' OR 'hypertension' OR 'metabolic syndrome' OR 'metabolic cardiovascular syndrome' OR 'diabetes type 2' OR 'diabetes mellitus'.

3. Results

3.1. Hypothalamus–pituitary–adrenal axis

The HPA axis is a biological system particularly affected by early adverse experiences, such as child abuse and neglect [22] or being reared in harsh early environments [23]. The HPA axis is one of the primary stress response systems [24]. Upon exposure to stress, the paraventricular nucleus of the hypothalamus activates and secretes corticotrophin-releasing hormone that promotes the release of adrenocorticotropic hormone from the anterior pituitary to the adrenal glands, which finally stimulates the release of glucocorticoids [25]. The activity and regulation of this system are driven by adrenal cortisol release, which via a negative feedback loop, inhibits the HPA axis activity initiated in the hypothalamus and pituitary. The association between adversity and later health outcomes mediated by HPA axis feedback regulation has been observed not only in childhood [26], but also long after the cessation of the early adverse experience, in adolescence and adulthood [27,28].

3.1.1. Childhood adversity and DNA methylation in HPA axis

Changes in methylation levels of stress reactivity genes can be induced by childhood adversity. Candidate or genome-wide epigenetic studies in humans have found that many HPA axis related genes were affected by childhood adversity through DNA methylation, such as glucocorticoid receptor gene (*GR*) [7], Serotonin transporter gene (*SLC6A4*) [29], proopiomelanocortin gene (*POMC*, encodes a preproprotein) [30], potassium voltage-gated channel subfamily Q member 2 (*KCNQ2*), Ephrin B1 (*EFNB1*) [31], alsin Rho guanine nucleotide exchange factor (*ALS2*, involved in small GTPase regulation) [32], leucine rich glioma inactivated 1 (*LGI1*) [33], brain-derived neurotrophic factor (*BDNF*, a stress and activity-dependent factor involved in many activities modulated by the HPA axis) [34], Kit ligand gene (*KITLG*, encodes the ligand of the tyrosine-kinase receptor) [30], and FK506-binding protein 5 (*FKBP5*, an important regulator of the stress hormone system) gene [35]. One of the most studied is the *GR* gene, also known as *NR3C1* gene, which codes for the glucocorticoid receptor and is located in the reverse strand of

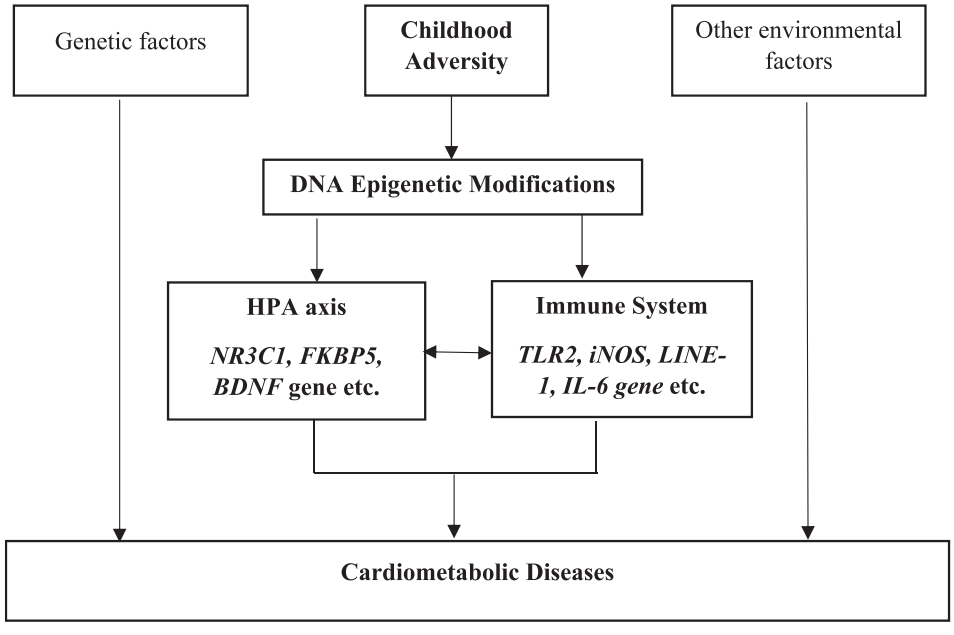

Fig. 1. Childhood adversity associated with later life cardiometabolic disease risk mediated through DNA methylation modifications in HPA axis and immune system.

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