Review

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Epigenomics

# Epigenetic mechanisms activated by childhood adversity

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Adverse childhood experiences (ACE) impair health and life expectancy and may result in an epigenetic signature that drives increased morbidity primed during early stages of life. This literature review focuses on the current evidence for epigenetic-mediated programming of brain and immune function resulting from ACE. To address this aim, a total of 88 articles indexed in PubMed before August 2019 concerning ACE and epigenetics were surveyed. Current evidence partially supports epigenetic programming of the hypothalamic–pituitary–adrenal axis, but convincingly shows that ACE impairs immune function. Additionally, the needs and challenges that face this area are discussed in order to provide a framework that may help to clarify the role of epigenetics in the long-lasting effects of ACE.

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**Keywords:** abuse • adversity • childhood trauma • chronic diseases • epigenetics

The prevalence of mood and other mental disorders is approximately 20% globally in the adult population [1], increasing during the life course from approximately 15% in children [2] up to approximately 40% in aged subjects [3]. The risk for these conditions can be only partially explained by genetic influences [4], suggesting the contribution of other factors, such as life history [5]. Compelling data from humans and animal models show that negative stimuli during fetal and early infancy (i.e., early-life stress, ELS) may confer protection in early life, but affect negatively health at the long term. The original concept of 'fetal programming' has evolved into a more wide-ranging model that includes the whole life-cycle (Developmental Origins of Health and Disease) [6]. Evidence for Developmental Origins of Health and Disease includes a comprehensive understanding that any type of stressor will impact health and well-being during life course [7]. In this context, ELS resulting from the interaction among the environment, the mother (or caregiver) and the offspring will translate into an epigenetic signature that programs the behavior and the responses to stress during the life course [5,7].

The physiologic and molecular changes that explain the impact of ELS are related to the timing and stage of development when the stressor takes place, in other words, the earlier the exposure, the stronger the long-term effects [8]. For instance, maternal stress during pregnancy, as well as neonatal neglect or maltreatment have profound effects on mental health [8], while cumulative adversity (i.e., the additive effect of different adverse events) during childhood has a dose–response effect on the well-being of people at medium- and long-term [9]. These long-term consequences of ELS suggest the involvement of epigenetic mechanisms as priming agents for an altered 'programming' of key molecular pathways [10]. Considering the impact of epigenetic processes on nervous system development, physiology and pathophysiology, research efforts during the last decade have been focused on achieving a comprehensive understanding of the contribution of these mechanisms of the long-life consequences of ELS.

Adverse childhood experiences (ACE), resulting from childhood abuse (physical, sexual or emotional) and neglect (physical or emotional), household dysfunction (e.g., intrafamilial violence) and hostile social environment [11], may result in a distinctive epigenetic signature of genes whose potential expression has been previously primed

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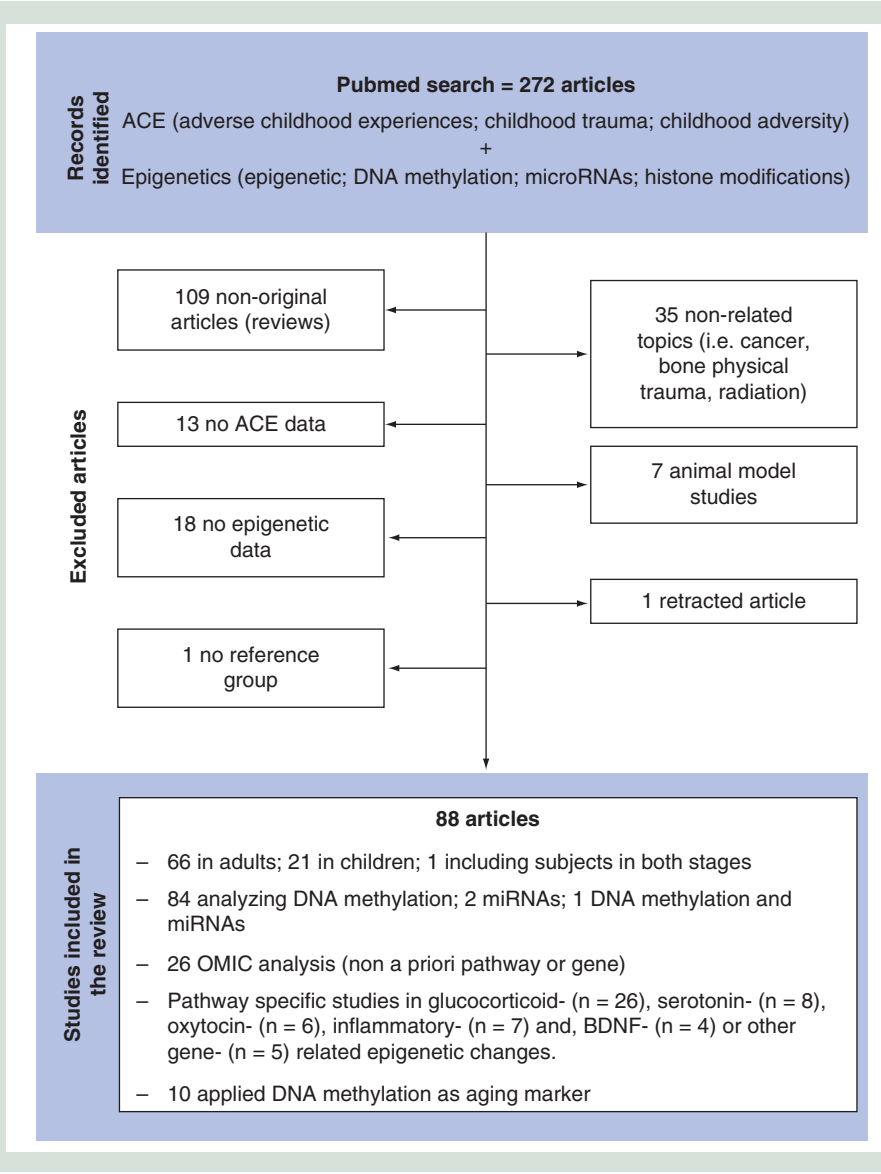


**Figure 1. Flowchart of reference selection.**
ACE: Adverse childhood experiences; OMIC: Epigenetic profiling.

during early stages of life, and this epigenetic signature may differ from that impinged by pregnancy or neonatal stress. Evidence on the neurodevelopment under physiological conditions show that psychosocial maturation occurs after the consolidation of primary behavioral responses [7,12]. Consequently, this review focuses on the evidence for epigenetic-mediated programming of mental health and well-being that results from adversity after infancy and during childhood. This is a period in which the biopsychosocial development is strongly influenced by personal experiences. To address this aim, articles indexed in PubMed until November 2019 concerning ACE and epigenetics written in English were qualitatively assayed. Reports were browsed using the following terms: 'adverse childhood experiences', 'childhood adversity', 'childhood trauma', 'epigenetics', 'DNA methylation', 'histone modifications' and 'miRNAs', excluding those related with the impact of stress during gestation and infancy. From a total of 272 articles, 88 met the criteria of presenting epigenetic data in subjects exposed to ACE (Figure 1 & Table 1). Complementary data from systematic reviews, meta-analyses and animal models (references not listed in Table 1) were used to provide further evidence for this literature review. As primary results, we found no consensus data for epigenetic programming of genes related to the glucocorticoid-mediated stress response, neither an genes-related

Table 1. General description of references discussed in the review.

| Epigenetic mechanism/process | Gene-targeted/OMIC | Subjects age | Gene variants data | Evidence | Author (year) (list number) | Ref. |
|---|---|---|---|---|---|---|
| DNA methylation | *NR3C1* | 18–30 | None | Supportive | Alexander *et al.* (2018) | [59] |
| DNA methylation | OMIC/Horvath's clock | 15–55 | None | Supportive | Austin *et al.* (2018) | [132] |
| DNA methylation | *5HTTPLR* | 19 | *5HTTPLR* | Supportive | Beach *et al.* (2014) | [150] |
| DNA methylation | OMIC | Children† | None | Supportive | Bearer & Mulligan (2018) | [114] |
| DNA methylation | *SSRT4* | 32–54‡ | *SSRT4* | None | Berent *et al.* (2017) | [89] |
| DNA methylation | *SKA2* | 18–50‡ | None | Supportive | Boks *et al.* (2016) | [83] |
| DNA methylation | *5HTTPLR* | 18–65 | None | Supportive | Booij *et al.* (2015) | [151] |
| DNA methylation | OMIC | 4–6 | None | Supportive | Bush *et al.* (2018) | [55] |
| DNA methylation | *FKBP5* | 35–65‡ | None | None | Bustamante *et al.* (2018) | [68] |
| miRNAs | - | 45–52‡ | None | Supportive | Cattane *et al.* (2019) | [99] |
| DNA methylation | OMIC | 45–48‡ | None | Supportive | Chu *et al.* (2018) | [138] |
| DNA methylation | *SKA2* | Adults† | None | Supportive | Clive *et al.* (2016) | [84] |
| miRNAs | - | 26–46‡ | None | Supportive | Dickson *et al.* (2018) | [119] |
| DNA methylation | OMIC | 7 | None | Supportive | Dunn *et al.* (2019) | [109] |
| DNA methylation | OMIC | 12–18 | None | Partial | Esposito *et al.* (2016) | [106] |
| DNA methylation | OMIC | 14–15 | None | Partial | Essex *et al.* (2013) | [56] |
| DNA methylation | *NR3C1, FKBP5* | 20–37‡ | None | Supportive | Farrell *et al.* (2018) | [48] |
| DNA methylation | OMIC/Horvath's clock | 46–70‡ | None | Supportive | Fiorito *et al.* (2017) | [131] |
| DNA methylation | OMIC | 5–8 | Multiple SNPs | Partial | Garg *et al.* (2018) | [107] |
| DNA methylation | *OXTR* | 27 | None | Partial | Gouin *et al.* (2017) | [77] |
| DNA methylation | OMIC | 23–26 | None | Supportive | Guillemin *et al.* (2014) | [60] |
| DNA methylation | OMIC/Horvath's clock | 18–65 | None | Supportive | Han *et al.* (2018) | [136] |
| DNA methylation | *FKBP5* | 19–24 | None | Supportive | Harms *et al.* (2017) | [51] |
| DNA methylation | *KITLG* | 18–55‡ | None | Partial | He *et al.* (2018) | [87] |
| DNA methylation | OMIC | 19 -77 | None | Partial | Houtepen *et al.* (2016) | [86] |
| DNA methylation | OMIC | 43–54‡ | None | Partial | Houtepen *et al.* (2018) | [121] |
| DNA methylation | *IL-6* | 18–25 | None | Supportive | Janusek *et al.* (2017) | [96] |
| DNA methylation | OMIC/Horvath's clock | 6–13 | None | Supportive | Jovanovic *et al.* (2017) | [130] |
| DNA methylation | *5HTTPLR* | Adults† | None | Supportive | Kang *et al.* (2013) | [73] |
| DNA methylation | OMIC | 8–15 | None | Supportive | Kaufman *et al.* (2018) | [137] |
| DNA methylation | *OXTR* | 24–37‡ | None | Partial | Kimmel *et al.* (2016) | [76] |
| DNA methylation | *FKBP5* | 30–53‡ | *FKBP5* | Supportive | Klengel *et al.* (2013) | [61] |
| DNA methylation | *OXTR* | 19–22 | None | None | Kogan *et al.* (2018) | [79] |
| DNA methylation | *OXTR* | 19–22 | None | None | Kogan *et al.* (2019) | [80] |
| DNA methylation | OMIC | Children† | None | Partial | Kumsta *et al.* (2016) | [110] |
| DNA methylation | OMIC | Adults† | None | Supportive | Labonte *et al.* (2012) | [103] |
| DNA methylation | *MTND6* | 18–47‡ | *FKBP5* | Supportive | Lapp *et al.* (2019) | [154] |
| DNA methylation | OMIC/Horvath's clock | 23–53‡ | None | Supportive | Lawn *et al.* (2018) | [128] |
| DNA methylation | OMIC/Horvath's clock | 7.5 | None | Partial | Marini *et al.* (2020) | [126] |
| DNA methylation | OMIC | 67–80‡ | None | Supportive | Marinova *et al.* (2017) | [113] |
| DNA methylation | *NR3C1* | 22–36 | None | Supportive | Martin-Blanco *et al.* (2014) | [50] |
| DNA methylation | OMIC | 37–45‡ | None | Supportive | Mehta *et al.* (2013) | [118] |
| DNA methylation | *NR3C1, MAOA* | 29–74 | *MAOA* | Partial | Melas *et al.* (2013) | [155] |
| DNA methylation | *LINE-1* | 20–30‡ | None | Supportive | Misiak *et al.* (2015) | [135] |
| DNA methylation | OMIC | 7–10 | None | Supportive | Naumova *et al.* (2012) | [104] |
| DNA methylation | OMIC | 17–29 | None | Supportive | Naumova *et al.* (2016) | [112] |

†The study does not provide the precise age ranges.
‡Age ranges were estimated from Mean ± SD.
Supportive: epigenetic marks are consistently associated/related/altered in ACE versus non-ACE subjects.
Partial: epigenetic marks have a weak correlation/association with ACE or, differences are lost after correcting by FDR <0.05, sex effect, gene polymorphisms or other factors.
None: epigenetic marks are not associated with ACE history.
ACE: Adverse childhood experiences; FDR: False discovery rate; OMIC: Epigenetic profiling; SD: Standard deviation.


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Table 1. General description of references discussed in the review (cont.).

| Epigenetic mechanism/process | Gene-targeted/OMIC | Subjects age | Gene variants data | Evidence | Author (year) (list number) | Ref. |
|---|---|---|---|---|---|---|
| DNA methylation | OMIC | 1–3 | None | Supportive | Naumova *et al.* (2019) | [53] |
| DNA methylation | *5HTTPLR* | 10 | None | Supportive | Ouellet-Morin *et al.* (2013) | [71] |
| DNA methylation | OMIC | 9–12 | None | Supportive | Papale *et al.* (2018) | [108] |
| DNA methylation | *NR3C1* | 3–5 | None | Supportive | Parade *et al.* (2016) | [43] |
| DNA methylation | *FKBP5* | 3–5 | *FKBP5* | Partial | Parade *et al.* (2017) | [47] |
| DNA methylation | *NR3C1,BDNF,5HTTPLR* | 20–57‡ | None | Partial | Peng *et al.* (2018) | [69] |
| DNA methylation | *NR3C1* | 20–54‡ | None | Supportive | Perroud *et al.* (2011) | [49] |
| DNA methylation | *BDNF* | 20–53‡ | None | Supportive | Perroud *et al.* (2013) | [141] |
| DNA meth/miRNA | OMIC | 31–44‡ | None | Supportive | Prados *et al.* (2015) | [115] |
| DNA methylation | OMIC | 22–28‡ | None | Supportive | Provencal *et al.* (2013) | [98] |
| DNA methylation | OMIC | 22–28‡ | None | Supportive | Provencal *et al.* (2014) | [97] |
| DNA methylation | OMIC | 24–29 | None | Supportive | Roberts *et al.* (2018) | [120] |
| DNA methylation | *NR3C1* | 11–14 | None | Supportive | Romens *et al.* (2015) | [44] |
| DNA methylation | *NR3C1* | 20–63‡ | None | None | Schur *et al.* (2018) | [66] |
| DNA methylation | OMIC/Horvath's clock | 38–58‡ | None | None | Simons *et al.* (2016) | [133] |
| DNA methylation | *OXTR* | 38–58‡ | None | None | Simons *et al.* (2017) | [78] |
| DNA methylation | *NR3C1* | Adults† | None | Supportive | Suderman *et al.* (2012) | [52] |
| DNA methylation | OMIC | 45 | None | Supportive | Suderman *et al.* (2014) | [117] |
| DNA methylation | OMIC | 42–45 | None | Partial | Suderman *et al.* (2015) | [116] |
| DNA methylation | OMIC | 46–47 | None | Supportive | Sugden *et al.* (2019) | [122] |
| DNA methylation | *BDNF* | 17–48 | None | Supportive | Thaler *et al.* (2014) | [85] |
| DNA methylation | *FKBP5* | 18–65 | *FKBP5* | Partial | Tozzi *et al.* (2018) | [153] |
| DNA methylation | *NR3C1* | 18–59 | None | Supportive | Tyrka *et al.* (2012) | [57] |
| DNA methylation | *NR3C1* | 3–5 | None | Partial | Tyrka *et al.* (2015) | [45] |
| DNA methylation | *FKBP5* | 3–5 | *FKBP5* | Supportive | Tyrka *et al.* (2016) | [46] |
| DNA methylation | *5HTTPLR* | 12–15 | *5HTTPLR* | Partial | van der Knaap *et al.* (2015) | [72] |
| DNA methylation | *NR3C1* | 36–52‡ | None | None | Vangeel *et al.* (2015) | [64] |
| DNA methylation | *NR3C1* | 30–52‡ | None | Partial | Vangeel *et al.* (2018) | [65] |
| DNA methylation | OMIC/Horvath's clock | 24–40‡ | None | None | Verhoeven *et al.* (2018) | [134] |
| DNA methylation | *5HTTPLR* | 38–54‡ | *5HTTPLR* | Partial | Vijayendran *et al.* (2012) | [74] |
| DNA methylation | *NR3C1* | 28–41 | None | Supportive | Wang *et al.* (2017) | [67] |
| DNA methylation | *HTR1A, HTR1B* | 18–70 | *HTR1A, HTR1B* | Supportive | Wang *et al.* (2018a) | [143] |
| DNA methylation | *BDNF* | 18–70 | *BDNF* | Supportive | Wang *et al.* (2018b) | [142] |
| DNA methylation | *OXTR* | 24–47 | *OXTR* | None | Womersley *et al.* (2019) | [81] |
| DNA methylation | *KITLG* | 66–72‡ | None | None | Wrigglesworth *et al.* (2019) | [88] |
| DNA methylation | OMIC | 18–50 | None | Supportive | Xu *et al.* (2018) | [139] |
| DNA methylation | OMIC | 5–14 | None | Supportive | Yang *et al.* (2013) | [105] |
| DNA methylation | *FKBP5* | 65–82‡ | None | Supportive | Yehuda *et al.* (2016) | [63] |
| DNA methylation | *FKBP5* | 24–50‡ | *FKBP5* | Partial | Yeo *et al.* (2017) | [62] |
| DNA methylation | OMIC/Horvath's clock | 18–77 | None | Supportive | Zannas *et al.* (2015) | [127] |
| DNA methylation | *FKBP5* | 18–81 | None | Supportive | Zannas *et al.* (2019) | [95] |
| DNA methylation | OMIC | 23–54‡ | None | Supportive | Zhang *et al.* (2013) | [111] |

†The study does not provide the precise age ranges.
‡Age ranges were estimated from Mean ± SD.
Supportive: epigenetic marks are consistently associated/related/altered in ACE versus non-ACE subjects.
Partial: epigenetic marks have a weak correlation/association with ACE or, differences are lost after correcting by FDR <0.05, sex effect, gene polymorphisms or other factors.
None: epigenetic marks are not associated with ACE history.
ACE: Adverse childhood experiences; FDR: False discovery rate; OMIC: Epigenetic profiling; SD: Standard deviation.

epigenetic biomarkers for ACE. In contrast, growing data show that ACE results in accelerated epigenetic aging and programming of the immune function, supporting a role for epigenetics as a mediator of the consequences of childhood trauma. Furthermore, the need for additional studies considering the current limitations is discussed.

## General aspects of epigenetics

The first description of epigenetic effects came from Conrad Waddington studies in animal development, as an explanation for gene–environment interaction that leads to a phenotype [13]. With the advantages in molecular biology, it has been proposed that epigenetic mechanisms involve the mitotically or meiotically transmission of traits without affecting DNA sequence. However, both definitions have different consequences concerning the process that they explain and some efforts to have a definitive concept of epigenetics are still pending [14]. Nonetheless, epigenetics can be considered as a stable phenotype resulting from changes in a chromosome without alterations in the DNA sequence (Banbury Conference Center and Cold Spring Harbor Laboratory Consensus 2008) [15]. In this regard, development is controlled by epigenetic mechanisms, regulating the differentiation and recording the environmental signals under physiologic and pathologic conditions [16]. These mechanisms contribute across the whole life span to shape cellular and physiological functions, providing or limiting their plasticity, with more prominent effects during the embryo and fetal development that decrease as aging proceeds [6]. Epigenetic mechanisms include DNA methylation, histone post-translational modifications (HPTM; e.g., acetylation, methylation, phosphorylation and others), ATP-dependent chromatin modifications and noncoding RNAs (ncRNAs) [17]. To provide context for this review, a brief description of DNA methylation, HPTM and ncRNA is presented below.

### DNA methylation

In mammals, DNA is methylated in CpG dinucleotides via enzymatic activity that transfers a methyl group to the 5′ position of cytosine ring generating 5-methylcytosine. This reaction can be catalyzed by DNA methyltransferases (DNMTs), with the contribution of DNMT1 and the isoforms DNMT3a and DNMT3b being the best understood. DNMT1 activity has been classically associated with preserving the DNA methylation pattern after DNA replication during mitotic cell division as well as after fertilization [18,19]. This process is guided by the occurrence of hemimethylated CpGs, which are recognized by DNMT1 in dsDNA [20]. Meanwhile, DNMT3a and DNMT3b enzymes contribute to the establishment of *de novo* DNA methylation patterns during gametogenesis, embryonic development and cell differentiation [18,19]. In contrast, DNA demethylation mechanisms remain elusive. However, it has been proposed that they may result from the oxidation and repairing of CpG, mediated by two enzymes; ten-eleven translocation (TET) family enzymes that oxidize 5-methylcytosine, leading to and passive demethylation after DNA replication, or to a cytosine replacement by a thymine DNA glycosylase-mediated base excision repair [21].

It is worth noting that different cell types in the same person share most of the DNA methylation patterns throughout the genome. Nonetheless, major differences take place in the promoter regions of genes, representing less than 5% of the total genomic DNA methylation [22]. These subtle differences are controlling most of the cell-specific protein expression in the whole organism [23]. Furthermore, it is commonly accepted that increased DNA methylation in promoter regions represents a hallmark of reduced gene expression and long-term gene silencing [24].

### Histone post-translational modifications

The nucleosome, the protein unit of the chromosomes, is formed by two copies of four histones proteins named H2A, H2B, H3 and H4. Post-translational modifications (PTMs) occur mainly on the flexible tail of histones, regulating the interaction of these proteins with DNA [25]. HPTMs are dynamic and not easily related to a transcriptional outcome (i.e., gene silencing or activation). The effects of HPTMs are context-dependent and interrelated with other nearby PTMs, suggesting the existence of a 'histone code' or 'language' [26]. HPTMs are controlled by a plethora of enzymes named histone acetyltransferases (HAT), histone deacetylases (HDAC), lysine methyltransferases (KMT) and lysine demethylases (KDM). HAT and HDAC control positively and negatively, respectively, the acetylation of lysine (K) residues 9 and 14 in H3, and 5, 8, 12 and 16 in H4. It is normally assumed that the presence of acetylation is associated with increased chromatin accessibility and gene expression. In contrast, single or multiple histone methylations occur in K residues of H3 (K4, 9, 27, 36 and 79) and H4 (K20), a reaction that involves KMT (adding) and KDM (removing) activities. Methylation on histone H3K4, H3K36 and H3K79 is linked to gene activation, while di- and tri-methylation on H3K9, H3K27 and H4K20 are related to gene silencing [25,26].


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### Noncoding RNAs

Less than 5% of the transcribed RNAs encode for proteins. Most RNA corresponds to ncRNAs, which are involved in regulatory mechanisms of gene expression [27,28]. Among the main regulatory ncRNAs are 'long' ncRNA (lncRNA), small interfering RNA (siRNA) and miRNA. The lncRNAs regulate the expression of a complementary specific gene either through chromatin remodeling, alternative mRNA processing (splicing) or siRNA [27] generation. Conversely, siRNA and miRNAs are interference RNA-based epigenetic mechanisms, which silence genes via noncoding RNAs of approximately 21 bp. To date, more than a thousand miRNAs have been reported, which are transcribed by the RNA polymerase II and encoded by specific genes (~70%) or, in lesser amounts, within the intronic regions of genes encoding proteins. Subsequently, they are exported to the cytoplasm for miRNA maturation by the action of the complex formed by the DICER1 protein and RNase IIIa–IIIb [29]. This processing leads to a single-strand RNA that is incorporated into the 'protein-induced silencing complex miRNA' (miRISC), which binds to a complementary region in a target mRNA. It has been proposed that a full complementarity between the miRNA and mRNA leads to degradation of the mRNA, while partial complementarity represses translation [30]. Notably, a single miRNA can regulate the expression of multiple mRNAs often associated signaling pathways or metabolic processes, while several miRNAs may converge to regulate a single mRNA constituting a complex mechanism for gene expression regulation [29,30].

## Life-course epigenetic mechanisms modeling behavior

During the last two decades, numerous studies have addressed the immediate and long-lasting deleterious effects of pre- and postnatal adversity on health and well-being in the offspring [7]. Considering the diverse neurophysiological processes that take place during fetal, neonatal and childhood stages, it is possible to argue a differential effect of stressors in each one of these stages, which may lead to dissimilar long-term consequences [12]. In this regard, several reports have shown that during intrauterine development and neonatal period, maternal stress and caregiver behavior result in epigenetic changes in the offspring that programs anxiety, stress and immune function, among other responses [31]. These effects are related to the critical developmental stage in which stress response mechanisms are being established, especially those that involve the hypothalamic–pituitary–adrenal (HPA) axis [32,33]. It is worth noting that there is no consensus on whether the degree or type of adversity results in an increased or blunted cortisol secretion in basal conditions or response to stress [34–36]. Therefore, the long-term effect of ACE on the HPA-axis may not be comparable to that resulting from stress during pregnancy or infancy.

## Epigenetic mechanisms & ACE

Since a pioneer study by Weaver *et al.* in rats [37] showing that epigenetic changes resulting from differences in neonate maternal care are related to the glucocorticoid receptor (GR, NR3C1) expression in the hippocampus, several reports have aimed to replicate this potential programming of the HPA-axis in humans. In addition, increased expression of DICER1, a crucial regulator of miRNAs biosynthesis, has been shown to be associated with increased fear-dependent activation of the amygdala as well as altered circulating levels of miRNA. These findings are related to a higher risk of developing post-traumatic stress disorder (PTSD) and depression in humans [38]. Thus, it is possible to argue a role for epigenetic mechanisms in the life-course origins of mental disorders. Nonetheless, as it will be discussed later, most of the epigenetic studies in humans have been performed using saliva or blood samples, while epigenetic markers are supposed to be cell-specific, therefore epigenetic patterns derived from nonbrain tissues might be not representative of neural programming. This issue has been partially addressed by studies in animal models comparing the methylome patterns in brain and blood samples, suggesting a potential, but limited, relationship in the epigenomic pattern between these cell types [39,40]. Furthermore, concordance between brain and blood DNA methylation patterns in human samples is low (<10%), with comparable CpG sites mainly located within intergenic regions [41], and very few of them located in regions related with gene expression [42]. Altogether, these data suggest that epigenomic markers of ACE must be interpreted considering the methodology by which they have been described, meanwhile the relationships between peripheral biomarkers, derived from nonbrain tissues, and the brain function must be interpreted with caution.

### ACE & epigenetic markers on stress-related pathways

#### *Glucocorticoid signaling*

Studies using peripheral blood samples of maltreated children have shown increased [43,44] or no changes [45,46] in CpG-specific methylation levels of *NR3C1* exon 1F associated with maltreatment. However, other studies have

shown a positive association between cumulative adversity and increased *NR3C1* exon 1F methylation, as well as maltreatment and increased *NR3C1* exon 1D methylation and decreased methylation of FKBP5, a co-chaperone that regulates GR sensitivity [45–47]. These changes have been partially found in adults with an ACE history [48–52]. An epigenomic study comparing children raised in orphanages and those from biological families showed a significant epigenetic effect in pathways associated with cellular responses to stress [53]. Similarly, in children from Tanzania, a comprehensive epigenetic characterization of genes involved in the HPA-axis (i.e., *AVP, CRH, NR3C1* and *POMC*) shows that high exposure to adversity results in increased DNA methylation in *CRH* and *POMC* genes, but not in *AVP* and *NR3C1* [54]. Meanwhile, early-life low socioeconomic status results in subtle epigenomic changes affecting a small proportion of genes [55]. Furthermore, sex differences in response to adversity have been found in *NR3C1* [46] DNA methylation and at epigenomic level [56], likely reflecting the sexual dimorphism in response to stress [32].

In adults, diverse types of ACE have been associated with either increased basal cortisol levels and in response to additional traumatic events, as well as a decreased cortisol stress reactivity, an effect that is potentially mediated by a differential methylation pattern in *NR3C1* exon 1F [57–59]. *NR3C1* methylation levels are positively associated with maltreatment and parental loss, but negatively associated with deficient parental care [57]. Additional studies have focused on the potential programming of genes that mediate the cortisol response. Data from a DNA methylation array comparing adult females with or without a history of physical aggression during childhood showed a decreased methylation in corticotrophin-releasing hormone-binding protein and NR3C1 [60]. Also, *FKBP5* DNA methylation has been associated with ACE, as well as the *in vitro* response of immune cells to glucocorticoids [61,62]. Notably, the latter effect may be also intergenerational, as is suggested in a study of offspring from survivors of the Jewish Holocaust [63]. These data may support the notion that childhood adversity imposes epigenetic changes in genes related to cortisol-mediated stress response; however, a definitive cortisol-related marker for ACE in children and adults remains elusive. A considerable number of studies have reported no changes in DNA methylation, neither in *NR3C1* nor in *FKBP5* genes in association with ACE [64–68], including a study in monozygotic twins [69] in which the potential genetic-background effect can be controlled.

Whether ACE leads to epigenetic programming of key genes involved in the glucocorticoid-mediated stress response still unsolved, similarly as the lack of consensus regarding the ACE effect on HPA-axis response [34–36]. However, several issues need to be addressed before drawn conlcusions regarding the contribution of DNA methylation changes in *NR3C1* gene on the programming of the stress response in humans. For instance, most studies have focused exon 1F, which is among the less expressed transcript variant in hippocampus and other brain tissues, while no clear correlation between these epigenetic changes and glucocorticoid plasma levels have been found (for further information, see [70]). Similarly, a high dependency on gene polymorphisms and the DNA methylation status has been proved for the epigenetic changes associated with ACE in the *FBKP5* gene [61], raising some clues regarding the epigenetic specificity of this effect.

### *Other stress mediators*

In addition to the potential programming of genes related to glucocorticoid signaling, a considerable number of studies have addressed the effects of ACE on other genes that modulate the response to stress. Serotonin transporter (SCL6A4) variants have been proposed as a biological base of resilience, suggesting a crucial role in the responses to ACE [5]. A remarkable study in monozygotic twins showed that a discordant exposure to bullying increases the DNA methylation in SCL6A4 promoter in peripheral blood cells [71], an effect that can be almost exclusively attributed to social adversity. Similarly, a positive correlation between the number of ACE and DNA methylation of the serotonin transporter gene has been reported in depressed youth [72] and adults [73]. Furthermore, methylation of two CpG sites is associated with SLC6A4 expression in women, depending on their sexual abuse history [74]. Further studies replicating these findings may help to confirm this relationship between higher *SCL6A4* DNA methylation and ACE, with potential consequences on treatment for ACE-related mood disorders [75].

Oxytocin also plays a key role in controlling the stress response, as a mediator of attachment. An initial report based on global DNA methylation changes in females with postpartum depression showed that DNA methylation in the oxytocin receptor (*OXTR*) gene is moderately associated with the risk of depression [76]. Also, this methylation change, which occurs in an intronic region of the gene in response to estrogens, is associated with their ACE history. However, further studies show controversial data. One study shows that ACE is associated with an increased *OXTR* DNA methylation in females but not males [77]. However, other reports have shown no changes in *OXTR* DNA methylation either in adult women or men [78–81].


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Other studies have focused on additional stress-related genes. For instance, a history of childhood abuse is associated with decreased expression of the kappa opioid receptor in the anterior insula of the adult, moderated by a decreased DNA methylation in the second intron of the Kappa gene that alters the regulation of this gene by the GR [82]. A similar association of ACE severity and DNA methylation in adults has been reported for *SKA2* [83,84] and *BDNF* [85]. A comprehensive study suggests that cortisol stress reactivity in adults is associated with CpG-specific increased methylation in the *KITLG* [86], a protein whose expression correlates with GR expression. This increased *KITLG* DNA methylation may be ACE-specific and unrelated to other conditions, such as bipolar disorders [87]. However, this relationship between *KITLG* DNA methylation and childhood trauma is absent in aged subjects, despite the correlation between this epigenetic mark with cortisol levels [88]. In contrast, DNA methylation of SSTR4 is unaffected by ACE [89]. Altogether, these data suggest a subtle or absent effect of ACE on *OXTR* DNA methylation, with some support for the potential programming of serotonin receptors and other stress-related genes. In this regard, activation of epigenetic mechanisms in response to ACE remains a hypothesis, without convincing evidence for a causal role in the long-term effects of early adversity on anxiety and stress.

## ACE & epigenetic effects on immune function

As has been previously commented, most of the studies identifying epigenetic markers resulting from ACE have been performed on blood samples, and specifically in monocytic and lymphoid cells. Based on the substantial evidence for an epigenetic signature related to ACE in these cell types, it may be proposed that early adversity has long-lasting effects on the immune function. In this regard, compelling evidence consolidated in meta-analyses shows that ACE is associated with increased systemic levels of proinflammatory mediators such as CRP and IL-6 [90,91]. Diverse conditions of childhood adversity are associated with a proinflammatory transcriptional profile in monocytes and T cells [92–94] and a differential distribution of monocytic and lymphoid cell subsets [93].

A low parental socioeconomic status is associated with an increased basal expression of proinflammatory genes regulated by NF-κB and CREB transcription factors, and a decreased expression of genes that respond to glucocorticoids in adults, despite an improved current family income [92]. In this regard, decreased methylation of the *FKBP5* gene in immune cells may mediate the increased inflammatory response resulting from ACE [95]. Furthermore, exposure to an acute stressful situation induces an enhanced proinflammatory response in adult subjects exposed to ACE [94]. This increased acute inflammatory response may result from some hypomethylated cytokine gene promoters, such as the *IL-6* gene, characteristic of subjects with high exposure to ACE [96]. Further evidence suggests that this epigenetic effect is occurring at genome level differentially affecting pro- and anti-inflammatory genes as well as transcription factors that mediate their expression via DNA methylation [97,98] or the regulation of multiple miRNAs [99].

Taken together, these data support the contribution of epigenetic mechanisms mediating the immune effects of ACE detectable during early childhood, with long-lasting consequences in one of the main systems involved in the development of impaired neurological health and psychological well-being [100–102].

## Epigenetic biomarkers for ACE

One of the major challenges in the ACE research is to provide markers of early stress for diverse interest, from a mechanistic understanding of experience-based emotional maturation to biomarkers for diagnostic and prognosis applications. Hippocampal tissue from adults with a history of childhood abuse shows an epigenetic signature affecting pathways involved in neuronal plasticity [103]. Genome-wide epigenetic studies show that early neglects or impaired attachment results in diverse changes in DNA methylation in children [104–110]. Despite the reported changes, these studies are not completely comparable, although potential effects on genes involved in neurodevelopment and immune function have been suggested [105–108].

Additionally, an increased 'epigenetic susceptibility' may be present in early infancy compared with later life [109]. Meanwhile, in adults, ACE is associated with a relatively limited number of differentially methylated CpGs [111–117]. Studies in peripheral blood samples show that PTSD in individuals with a history of childhood maltreatment is associated with a transcriptomic and epigenetic (DNA methylation) profile that differs from nonabused PTSD subjects [118]. Furthermore, an epigenetic effect resulting from ACE can be observed in the miRNA [119] and DNA methylation [120] profiles of sperm. Similarly, childhood trauma is associated with differential expression of circulating miRNA involved in the regulation of neurodevelopment and inflammation [99]. Notably, validation in an animal model suggests that ACE-induced altered miRNA expression, at least in sperm, contributes to a heritable stress response on nonadversity-exposed progeny [119]. In contrast, some recent studies have not found the

epigenetic signature of ACE in circulating cells from adult subjects [121,122]. According to the above, further studies are required to define the utility of global epigenetic changes as markers of ACE.

Compelling evidence studying the telomere length supports the notion that ACE results in accelerated aging [123], an effect that may mediate the increased risk for obesity-associated with ACE [124]. In this context, aging is related to a DNA methylation signature that can be determined at the epigenomic level defined as DNAm age (Horvath's clock) [125]. ELS (before 7 years) may results in a age-, sex- and adversity- specific accelerated aging, suggesting that this epigenetic mark of ACE are heightened during specific life stages [126]. Adversity during childhood is also associated with a moderate increase in DNAm age in adulthood [127,128], an effect that may result from the fact that several CpG sites whose methylation contributes to the Horvath's clock colocalize with binding sites for the GR [129]. Furthermore, this epigenetic effect on DNAm age is associated with an epigenetic upregulation of FKBP5 [95]. A comparable effect on Horvath's clock has been reported to occur in children directly or indirectly exposed to violence [130], or adults raised under adverse social conditions [131,132]. However, some controversy on the epigenetic signature of early social adversity has been reported [133,134]. In contrast, subjects with first schizophrenia episode and ACE history have lower methylation of LINE-1, a surrogate of DNAm and aging, compared with the first schizophrenia episode without ACE and healthy controls [135]. Similarly, an additive effect of ACE and aging has been reported in patients with major depression [136]. Nevertheless, a limited number of studies suggest that ACE-related epigenetic marks mediate the increased risk for obesity in children [137] and adults [138,139]. Altogether these data support that ACE exposure, like other environmental stimuli that conditionate long-term health, is associated with accelerated aging evidenced at the epigenetic level.

## Epigenetic marks as a predictor of treatment outcomes in ACE

Epigenetic marks might be associated with response to treatment or therapies in mental disorders associated with ACE exposure. A critical review of the effect of broadly used drugs suggests that CpG-specific methylation levels in *SLC6A4*, *BDNF* and *IL-11* genes have a potential prognostic value for antidepressant response [140]. In this regard, mean *BDNF* exons DNA methylation is increased in subjects with borderline personality disorder and a history of childhood maltreatment. Those levels decrease in subjects that respond to dialectical behavior therapy, while nonresponders maintain the increased BDNF methylation [141]. Similarly, lower BDNF DNA methylation is associated with the impaired antidepressant response, an effect mediated by age, cumulative life stress and *BDNF* genotype [142]. Furthermore, *BDNF* DNA methylation at baseline is significantly lower than after 8 weeks of successful treatment with escitalopram. Altered DNA methylation in serotonin receptor *HTR1A* and *1B* predicts the response to treatment and it is modified after 8 weeks of antidepressant treatment [143]. Notably, *HTR1A/1B* methylation at the beginning of the treatment differs between responders and nonresponders. Further studies analyzing the epigenomic effect of diverse mood stabilizers and psychotic drugs (e.g., lithium, valproic acid, carbamazepine, quetiapine) have reported heterogeneous changes in the DNA methylation profile in peripheral blood mononuclear cells [144,145] and these effects can be modified by the coadministration of these drugs [146].

In summary, this evidence reviewed shows that epigenetic changes resulting from ACE can be used as biomarkers of the impact of adversity in a given individual as well as in predicting and evaluating the effects of treatment. However, their use as signatures of the exposure to specific patterns of adversity is still unsolved. This may be the result of the lack of standardized methods to evaluate epigenetic markers, such as DNA methylation, a crucial factor to generate valid biomarkers. Studies in this review consider several approaches and data analyses to determine the level of DNA methylation, and some of them are poorly informative regarding the actual methylation level. Therefore, additional efforts are required to provide evidence potentially validate by different groups, an aim that may be addressed by applying quantitative and reliable DNA methylation procedures and analysis methods [147–149].

## Implications & challenges

This article seeks to provide an overview of the evidence regarding the role of epigenetics as a biomarker and mechanism involved in the origins of diseases resulting from ACE (Figure 2). Along with the contribution of epigenetic mechanisms to modulate the effects of ACE, genetic background plays a major role in providing the basis for a biological resilience [5]. In this regard, several studies suggest that gene variants of the serotonin transporter (*5HTTLPR/SCL6A4*) [72,74,150–152] or its receptors (*HTR1A* & *1B*) [143], the glucocorticoid regulator *FKBP5* [45,61,62,153,154], *MAOA* [155] and *BDNF* [142] have a significant impact on the epigenetic marks resulting from ACE. Thus, it is strongly recommended to consider these gene variants, as well as others that remain to be discovered, that modify the risk of ACE-negative consequences for epigenetic studies. Nonetheless, the role


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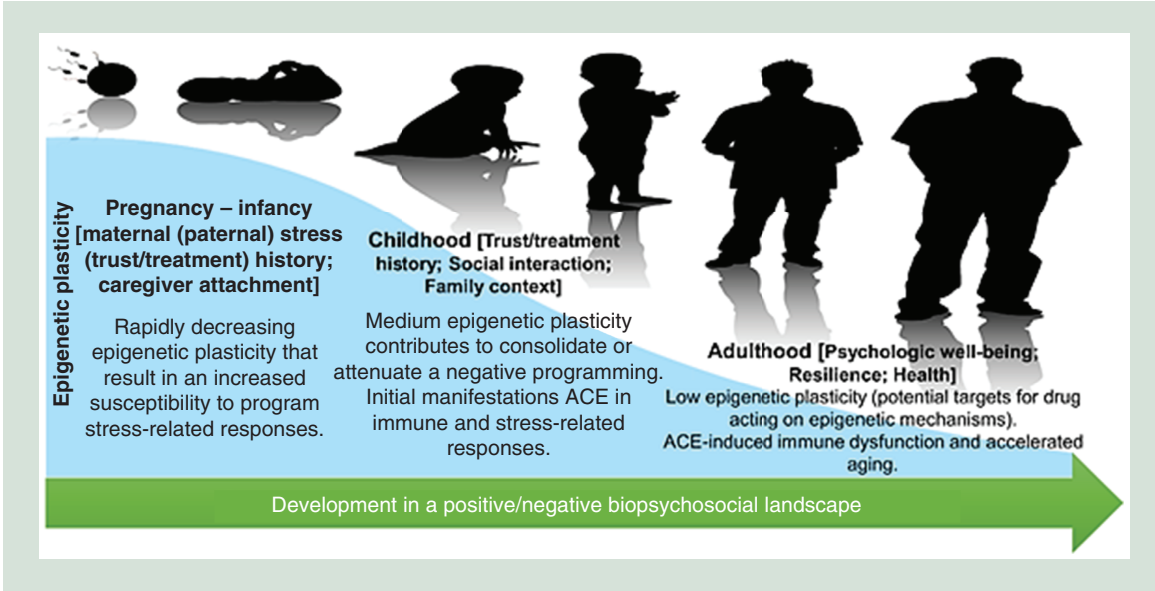


**Figure 2. Perspective of epigenetic mechanisms resulting from life-course adversity.** Initial steps of development are characterized by a fast differentiation of cells and tissues, during which subtle alterations, resulting from adverse/positive trust and treatment experiences, can induce strong long-term effects. During childhood, epigenetic mechanisms contribute to consolidate or repair, with a lower plasticity, the effects of an early adversity. In adulthood, life-course experiences led to the establishment of diverse risk/protection for psychological well-being. The potential transition from one state to the others may be possible by intervening the epigenetic effects of adverse experiences. ACE: Adverse childhood experiences.

of epigenetics in the long-term programming of genes related to the glucocorticoid-mediated stress response has controversial support.

It should be noted that most epigenetic studies reviewed have focused on DNA methylation, thus a very important gap in this field need to be solved. In this regard, HPTMs and miRNAs represent interesting targets to address the effects and potential therapeutic tools. The original observation of the long-term effects of maternal care on cortisol stress response in rats shows that direct administration of a histone deacetylase inhibitor into the brain of adult offspring of rats reverts the epigenetic programming of low-grooming care [37]. This is also supported by the effects of valproic acid and other histone deacetylase inhibitor at the epigenomic level, as previously commented. Therefore, clarifying the effects of drugs targeting HPTM may give us insights about their uses under diverse ACE histories [144–146].

Equally, miRNA-associated mechanisms require further attention, especially due to their potential diagnostic and therapeutic applications. Evidence shows that miRNA are identified and quantified by reliable methods [156,157], and their origins can be traced as functions of tissue-specific markers in the vesicles carrying them [157,158]. These analytical traits will provide more direct evidence compared with the evaluation of indirect epigenetic markers (i.e., DNA methylation in peripheral blood cells). Similarly, miRNA- [159] and RNA interference-based [160] therapies are promising approaches that may contribute to the development of targeted therapies addressing ACE-related chronic conditions.

## Conclusion

Based onthe analyzed reports, current evidence partially supports direct epigenetic programming of the hypothalamic–pituitary–adrenal axis, whose functional alterations in ACE subjects also remains elusive. In contrast, there is compelling evidence showing that ACE, since early stages of infancy, impairs immune function and contributes to accelerated aging, and the latter represents one of the most characteristic changes resulting from childhood trauma. However, most studies have focused on DNA methylation, and in some cases using targeted groups with broad age ranges, which could mask age-specific epigenetic biomarkers resulting from ACE. Furthermore, the contribution of other epigenetic mechanisms in the regulation of crucial pathways associated with stress, and other resilience mechanisms may not be ruled out. In this regard, the needs and challenges that face this area

are to gather compelling information about multiple epigenetic markers, considering the complex consequences of childhood trauma and the diverse emotional responses that further, positive and or negative, adult experiences may impact in the long-lasting effects of ACE.

## Future perspective

Research into the various epigenetic mechanisms activated by childhood adversity represents a growing field from which future diagnostic and therapeutic tools could be obtained. Special attention must be put on the multidimensional aspects that involve the establishment of an epigenetic marker for long-term effects. Thus, while compelling evidence supports the gene-background effect as a primer for biological resilience, little is known about how different adverse events will result in epigenetic makers, as well as the reversion of these markers by treatment. Addressing these and other factors mentioned across this article might help in defining the role of epigenetics in the long-lasting effects of ACE (Figure 2).

### Executive summary

**Life-course epigenetic mechanisms modeling behavior**

- Maternal stress and caregiver behavior during early development and neonatal period, result in epigenetic changes in the offspring that programs anxiety, stress and immune function.
- There is no consensus if any kind or degree of adversity results in an increased or blunted cortisol secretion in basal conditions or response to stress.
- Long-term effect of adverse childhood experiences (ACE) on the hypothalamic–pituitary–adrenal axis may not be comparable to that resulting from stress during pregnancy or infancy.

**Epigenetic mechanisms & ACE**

- Most of the epigenetic studies in humans have been focused on DNA metylation, using saliva or blood samples, while epigenetic markers are supposed to be cell-specific.
- Concordance between brain and blood DNA methylation patterns in human samples is less than 10% and very few of these CpG sites are located in regions related with gene expression.
- Altered expression of miRNA-regulating proteins is associated with increased fear-dependent activation of the amygdala as well as altered circulating levels of miRNA in humans.

**ACE & epigenetic markers on stress-related pathways**

- Several reports have addressed the *NR3C1* and *FKBP5* gene DNA methylation as biomarker of the stress response in humans.
- Most studies on NR3C1 have focused exon 1F, which is among the less expressed transcript variant in hippocampus and other brain tissues, while no clear correlation between these epigenetic changes and glucocorticoid plasma levels have been found.
- High dependency on gene polymorphisms and the DNA methylation status has been proved for the epigenetic changes associated with ACE in the *FBKP5* gene.
- Other genes of interest, such as the *SCL6A4*, *OXTR* and *BDNF* have shown poor consistency on their DNA methylation profile and ACE.

**ACE & epigenetic effects on immune function**

- Altered epigenetic markers in peripheral blood cells has been found in young and adult that explain higher risk of chronic inflammatory diseases ACE subjects.
- These epigenomic changes show direct functional relationships with immune alterations.

**Epigenetic biomarkers for ACE**

- Epigenetic marker of aging (i.e., Horvath's clock and LINE1) and metabolic risk are consistent with ACE.
- Many CpGs considered in the Horvath's clock include cortisol-related genes.
- A potential role for miRNA in the transgenerational effects of ACE has been found in human and animal models.

**Epigenetic marks as a predictor of treatment outcomes in ACE**

- Epigenetic changes resulting from ACE can be used as biomarkers of the impact of adversity in a given individual as well as in predicting and evaluating the effects of treatment.
- There is a lack of standardized methods to evaluate epigenetic markers, such as DNA methylation, a crucial factor to generate valid biomarkers.

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