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Epigenetic code and potential epigenetic-based therapies against chronic diseases in developmental origins

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Accumulated findings have demonstrated that the epigenetic code provides a potential link between prenatal stress and changes in gene expression that could be involved in the developmental programming of various chronic diseases in later life. Meanwhile, based on the fact that epigenetic modifications are reversible and can be manipulated, this provides a unique chance to develop multiple novel epigenetic-based therapeutic strategies against many chronic diseases in early developmental periods. This article will give a short review of recent findings of prenatal insult-induced epigenetic changes in developmental origins of several chronic diseases, and will attempt to provide an overview of the current epigenetic-based strategies applied in the early prevention, diagnosis and possible therapies for human chronic diseases.

Introduction

Increasing epidemiological evidence suggests that maternal nutrition and environmental factors in early development periods play an important part in susceptibility of disease in later life [1,2]. In the mid-1990s, Barker *et al.* coined the hypothesis of 'fetal origins of adult diseases' [3], indicating that intrauterine factors and/or maternal nutritional status have long-term programming effects on fetal development, ultimately leading to increased susceptibility of chronic diseases. This concept has been supported by a growing body of studies on low birth weight (LBW) [4,34], intrauterine growth retardation (IUGR) [5], premature birth [6] and maternal malnutrition [7] associated with increased risks of chronic diseases later in life in humans.

Although underlying mechanisms involved in molecular pathogenesis of chronic diseases in developmental origins are under investigation, it is accepted that changes in epigenetic modifications or code are early significant events in the pathogenesis of chronic diseases. Epigenetics, an emerging subject in the field of genetics, means heritable changes in cellular phenotype and gene expression that are not involved in DNA sequences [8]. During the past decade, the epigenetic code has been identified as a key

regulator of gene expression [9], and therefore is likely to play major parts in transcriptional regulations, genome stability, cell proliferation and embryonic development, among others. Classically, major epigenetic marks contain DNA methylation, histone modifications, genomic imprinting and noncoding RNA.

DNA methylation is a characterized chemical modification of chromatin in all unicellular and multicellular organisms. In mammals, DNA methylation predominantly occurs at cytosine-C5 in the context of CpG dinucleotides, and is established and maintained by three active DNA methyltransferases [10,11]. DNA methylation is a dynamic biological process and undergoes dynamic reprogramming during gametogenesis and early embryogenesis in mammals [12]. As a key regulatory mechanism in epigenetics, DNA methylation has regulatory roles in normal and abnormal cellular processes, and is essential for embryonic development, genomic imprinting, X-inactivation and gene repression.

In eukaryotes, the nucleosome is the basic repeating unit of chromatin, which is an octamer comprising four histones: H2A, H2B, H3, H4, and 146 bp of DNA wrapped around the histones [13]. Typically, each histone harbors an amino-terminal 20–40 residue 'tail'. These histone tails provide sites for an enormous number of reversible post-translational modifications, including methylation, acetylation and phosphorylation [14].

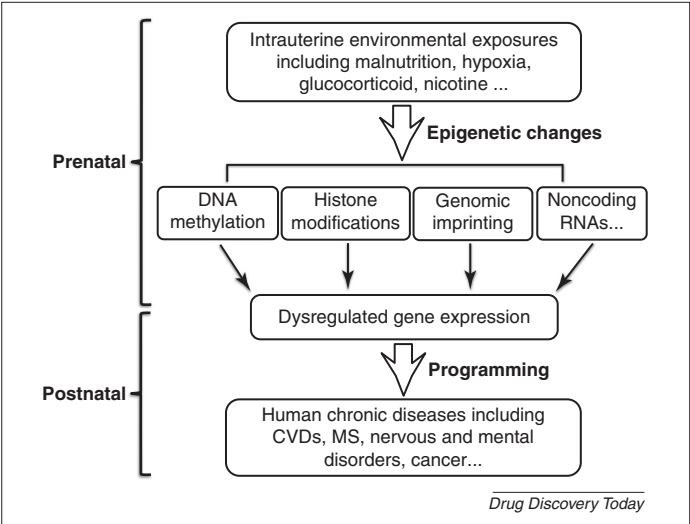Corresponding author:. Xu, Z. (xuzhice@suda.edu.cn)

Epigenetic changes in the developmental programming of human chronic diseases. *Abbreviations*: CVDs, cardiovascular diseases; MS, metabolic syndrome.

These covalent modifications in nucleosomes are known as histone modifications with well-known roles in alteration of chromatin structures to influence patterns of gene expression [15].

In recent years, increasing evidence indicates that noncoding RNAs (ncRNAs) are important in controlling multiple epigenetic phenomena and regulating differentiation and development in eukaryotes [16]. MicroRNAs (miRNAs), a class of small ncRNAs, are ~22 nucleotides long and crucial regulators in the epigenetic control of gene expression and cell differentiation [17]. Commonly, miRNAs, as relatively negative regulators of gene expression,

have been associated with a variety of diseases, including coronary disease [18,19].

Genomic imprinting, a classic epigenetic mark by which certain genes can be expressed in a parent-specific manner, is acquired during gametogenesis and maintained during pre-implantation development [20]. Genomic imprinting has a crucial influence on the regulation of mammalian development and correlates with pathophysiologic mechanisms in many human diseases [21,52]. In eukaryotes, interactions and crosstalk among various epigenetic marks are essential in regulating chromatin structures and gene expression.

As mentioned above, early embryogenesis *in utero* is a crucial event for the establishment of epigenetic information, especially DNA methylation. However, it also provides a chance for prenatal stress that could affect the establishment of DNA methylation during crucial developmental periods. Indeed, the changes of epigenetic modifications caused by prenatal stress, including prenatal malnutrition [25], and hypoxia [22], as well as other intrauterine insults [23], have crucial programming roles in the postnatal pathological processes of chronic diseases (Fig. 1). In this article, we give a short review of recent findings of epigenetic mechanisms on developmental origins of several human chronic diseases, and try to provide an overview of the current epigenetic-based strategies applied in early prevention, diagnosis and possible therapies against chronic diseases (Table 1).

Epigenetic code and the developmental programming of cardiovascular and metabolic diseases

Starting 20 years ago, there has been a steady growth in the number of laboratories and investigators involved in the investigation on developmental origin of cardiovascular diseases (CVDs) and metabolic syndrome (MS). And considerable evidence demonstrates that the epigenetic regulation of gene expression is crucial

TABLE 1

Epigenetic changes in response to various prenatal stresses and related to chronic diseases

Prenatal stress	Gene expression	Epigenetic mechanisms	Chronic diseases	Refs
Antibiotic exposure during pregnancy	Methylation at imprinted genes (H19/IGF2)(aberrant)	DNA methylation	Chronic diseases (CVDs, T2D)	[23]
		Genomic imprinting		
Maternal dietary protein restriction	Angiotensin II type I receptor (AT1bR)	DNA methylation	Hypertension	[28]
Maternal nutrient restriction	Endothelin-1 (ET-1)	Histone acetylation	Hypertension	[30]
Low-density lipoprotein diets	Endothelial Kruppel-like factor 2 (KLF2)	DNA methylation	Coronary heart disease	[40]
		Histone modifications		
Maternal under-nutrition	Glucocorticoid receptor (GR)	DNA methylation H3K27me3 and H3K9ac	Obesity	[25]
Maternal obesity	Zinc finger protein 423 isoform 2 (Zfp423)	DNA methylation H3K27me3	Obesity	[51]
Utero-placental insufficiency	Pancreatic and duodenal homeobox 1 (Pdx1)	DNA methylation H3/H4ac and H3K4me3 H3K9me3	Type 2 diabetes	[57]
Maternal stress	miR-103 and miR-323	Noncoding RNAs	Nervous and mental disorders	[62]
	miR-151 and miR-145	MicroRNAs		
***In utero* exposure to diethylstilbestrol**	Enhancer Zeste homolog 2 (EZH2)	DNA methylation	Breast cancer	[72]
		Histone modifications		
***In utero* exposure to high-fat or ethinyl-estradiol 2 (EE2)**	Dnmt1, Dnmt3a and Dnmt3b	DNA methylation	Breast cancer	[73]
		Histone modifications		

in prenatal-stress-induced fetal programming of CVDs [22,24]. MS is the name for a group of health problems that occur when hormones or other chemicals fail to interact properly in the body. Obesity and diabetes mellitus type 2 (T2D) are the most common health problems. Recently, the notion that prenatal-insult-induced epigenetic changes play important parts in the etiology of MS has been supported by a growing body of evidence that shows that maternal malnutrition [25], or exposures to adverse environmental factors [26,27], can increase risks for MS in later life. This section focuses on the progress of changes in epigenetic regulations of gene expression in response to intrauterine adverse factors, in association with the pathological process of cardiovascular and metabolic diseases, including hypertension, stroke, coronary heart disease, obesity and T2D.

Hypertension

Hypertension is a major health problem worldwide with approximately one in three adults suffering from this disease. A large body of literature suggests that the epigenetic code provides a potential link between the prenatal stress and changes in gene expression that can lead to hypertension [28–31]. For example, offspring whose pregnant mothers fed on low protein diets showed hypomethylated AT1bR gene promoters along with an increased adrenal expression of AT1bR [28]. AT1bR is a major subtype of angiotensin II (Ang II) receptors. Ang II is the most active peptide of the renin–angiotensin system (RAS) in cardiovascular systems. Major classical actions of Ang II include regulation of blood pressure and blood volume mediated by AT1R [29]. Therefore, a suboptimal intrauterine environment induces adult hypertension, probably because of an alteration of expression of AT1bR via changing DNA methylation at the promoter of the AT1bR gene. Other studies also reported that maternal nutrient restriction led to an increase in levels of histone acetylation in the endothelin 1 (ET-1) gene promoter of pulmonary vascular endothelial cells in newborn rats with in utero growth restriction [30]. This epigenetic change could result in IUGR rats highly sensitive to stress such as hypoxia later in life, causing pulmonary arterial hypertension (PAH) or pulmonary vascular remodeling.

Like low-protein diets during pregnancy, a high-salt diet is another adverse intrauterine factor. Ding et al. [31] reported that the protein of AT1R, not AT2R, in the fetal heart was selectively changed following exposure to a high-salt diet, and this change was linked to DNA methylation. The results indicated high-salt diet during pregnancy influenced development of the fetal RAS associated with fetal cardiac cellular changes, probably involved in programming of hypertension. Together, those studies demonstrated a link between environmental-insult-induced epigenetic changes in the genes and resultant alteration of gene expression in adult life, ultimately leading to pathogenesis of hypertension.

Stroke

In general, stroke is usually caused by interruption of blood supply to the brain as a result of blood vessel damage or clots. In recent years, numerous research works have explored pathogenesis of stroke at developmental levels. Some achievements, including the roles of epigenetic marks in pathobiology of stroke, have attracted significant attention.

As the main part of the epigenetic modifications, the levels of DNA methylation were markedly altered in the cerebral cortex following ischemia in rats [32]. DNA methylation of long interspersed nucleotide element 1 (LINE-1) was correlated with ischemic heart disease and stroke. Meanwhile, individuals with lower LINE-1 methylation have a higher risk in developing ischemic heart disease and/or stroke in longitudinal analyses [32,33]. Li et al. [34] reported that perinatal nicotine increased vulnerability of hypoxic–ischemic brain injury in neonatal rats through aberrant expression patterns of central AT2R. Meanwhile, increased methylation of CpG locus 3 bases upstream of the TATA box at the AT2R gene promoter could be a mechanism of nicotine-mediated AT2R gene changes.

Histone modifications and noncoding RNAs were also involved in the pathological process of stroke. For example, the evidence from animal models of stroke suggests a significant increase in H3K4me3 and H3K3 acetylation, as well as a decrease in H3K9me3 in the kidney of rats suffering stroke [35]. Moreover, noncoding RNAs [36] such as microRNA and long ncRNAs were involved in regulating the development of nervous systems and homeostatic functions, showing their roles in correlation with all kinds of cellular processes under normal conditions, as well as various disease statuses, including stroke.

Coronary heart disease

Coronary heart disease (CHD), also known as coronary artery disease (CAD), has been demonstrated to be linked to a number of well-defined risk factors. One of the confirmed major risks for the development of CHD is low birth weight or in utero growth restriction, which can either induce or be associated with alterations of epigenetic features in developing tissues and organs [37]. In fact, various epigenetic processes can be involved in the pathophysiology of CHD. Using a DNA methylation-sensitive restriction enzyme assay to evaluate methylation status of the genome, the researchers found that the genomic DNA methylation in the CHD patients was significantly higher than that in the control [38]. At a single gene level, the level of methylation at a lot of gene promoters was shown to be associated with progression of CHD. For example, DNA methylation levels at the p15INK4b gene [39] were found to be significantly increased in the CAD patients compared with the control, and the changes in methylation and expression of the p15INK4b gene could be involved in the mechanisms of chromosome 9p21 on the development of CHD.

Similarly, histone modifications are crucial in the underlying mechanisms for the development of CHD. For instance, a previous study demonstrated that low-density lipoprotein (LDL), a major modifiable risk factor for CHD, repressed the expression of endothelial Kruppel-like factor 2 (KLF2) via altering histone- and DNA-methylation-mediated epigenetic modifications [40]. LDL could stimulate binding of the DNA methyl-CpG-binding protein 2 and histone methyltransferase enhancer, whereas it decreased binding of the KLF2 transcriptional activator to the KLF2 promoter in endothelial cells. In this case, downregulation of KLF2 by LDL could lead to a dysfunctional endothelium and the increased susceptibility of CHD. In addition, a number of investigations in the past decade have shown epigenetic abnormalities in other CVDs, including cardiac hypertrophy [41] and heart failure [42]. Taken together, abnormal changes in epigenetic marks are surely involved in developmental programming of CVDs.

The prospects of epigenetic code for therapies against CVDs
Given the reversible characteristic of the epigenetic code, it is a unique opportunity to offer a great potential for unlocking the door to multiple novel diagnostic, prognostic and therapeutic strategies against CVDs. Indeed, many laboratories and investigators are involved in studying new epigenetics-based therapies and agents targeting CVDs. Significant progress has been made in preclinical epigenetics-based therapies of a variety of CVDs. For example, many chromatin regulatory factors and their identified inhibitors can serve as therapeutic agents for CVDs [43–47]. These factors primarily contain members of the repressor element-1 silencing transcription factor, such as lysine-specific demethylase 1 (LSD1) [43], and polycomb group (PcG) proteins [44], which have been found to be linked to the pathophysiology of CVDs. Among them, the most common example is histone deacetylase (HDAC) enzyme inhibitors, which are chromatin-modifying factors that have already been demonstrated to have great promise as therapeutic agents against CVDs and other diseases [45,47]. A HDAC inhibitor trichostatin A (TSA) [46] was shown to be able to protect wild-type mice from ischemic brain injury, and could induce bone-marrow-derived multipotent progenitor cells to differentiate into endothelial cells.

In addition, microRNAs also offer promising therapeutic strategies for stroke, and that could be another kind of effective approach against CVDs [48]. Taken together, along with investigation of epigenetic roles in the development of CVDs, studies have already demonstrated great promise and offered reasonable potentials for therapeutic approaches against CVDs using single or multiple agents that can alter and/or reverse the pathological epigenetic processes.

Obesity
Obesity is a global epidemic and medical condition in which the natural energy reserves are over stored in the fatty tissue. In the past few years, a large number of studies have shown that gestational diabetes, maternal overweight and other prenatal insults [49,50] could increase risks of obesity and its complications in offspring in later life. And epigenetic marks such as DNA methylation, histone modifications and genomic imprinting [25,51,52] have been shown to be involved in the pathological changes in obesity. For example, Begum and colleagues found the evidence of decreased methylation at the glucocorticoid receptor promoter and H3K27 trimethylation, as well as increased H3K9 acetylation in hypothalamic neurons from the adult offspring exposed to undernutrition during their mothers' pregnancy in sheep [46], suggesting that maternal undernutrition in gestation could lead to specific epigenetic changes in the hypothalamic neurons in regulating energy balance in the adult offspring.

Recent research showed that DNA methylation in the Zfp423 promoter was lower and the Zfp423 expression was higher in fetal mice whose pregnant mothers were fed obesogenic diets. Zfp423 is a key transcription factor and regulates adipogenic differentiation in fetal progenitor cells [51]. Those findings suggested that maternal obesity can enhance adipogenic differentiation in fetal mice through reducing DNA methylation at the Zfp423 promoter, and elevating its gene expression, which could be involved in programming adiposity and metabolic dysfunctions later in life. In addition, the percentage of methylation levels at different CpG sites of CLOCK, BMAL1 and PER2 genes were shown to be associated with monounsaturated and polyunsaturated fatty acid intake and obesity and MS characteristics [53], indicating a close link between obesity and epigenetic modifications.

Diabetes
Like studies on obesity, numerous works on humans and animals have highlighted the relationship between a variety of expositions to adverse environmental factors *in utero* and T2D in later life [54,55]. In general, occurrence of T2D is attributable to functional β cells failing to compensate for insulin resistance in animals and humans. Recent discoveries raise the hypothesis that epigenetic changes in response to various environmental insults play important parts in regulating β cell functions and development during developmental stages, ultimately leading to increased risk of T2D [56,57]. For example, under normal conditions, the proximal promoter of Pdx1 gene is found in an unmethylated open chromatin state marked by H3 and H4 acetylation as well as H3K4me3, which is essential for transcription. However, pancreatic islets isolated from IUGR fetuses show a significant decrease in H3/H4 acetylation and H3K4me3 at the proximal promoter of Pdx1, whereas there was a significant increase in H3K9me2 and extensive DNA methylation, which led to locking the Pdx1 gene in a transcriptionally silent state [57,58]. Pdx1, a pancreatic and duodenal homeobox 1 transcription factor, is a crucial regulator of β cell growth and functions in the body. A relatively modest decrease in Pdx1 expression can alter β cell functions and cellular developments, ultimately impairing compensatory responses to insulin resistance [58]. Recently, these molecular mechanisms were validated by mounting evidence from studies on patients with T2D. By assessing the methylation status of proximal promoter of Pdx1 in islets, Yang and colleagues [58] verified that Pdx1 methylation was reliably increased, whereas Pdx1 expression was significantly decreased in patients with T2D, indicating that epigenetic modifications of Pdx1 play a crucial part in the development of T2D.

Taken together, more and more evidence has shown that a myriad of epigenetic changes, including aberrant DNA methylation and histone modifications, are associated with obesity, T2D and other metabolic syndromes. This defective condition provides the basis for the clinical use of the DNA methyltransferases and/or histone modifying enzyme inhibitors for treatments of metabolic syndrome [59,60]. A widely investigated example is HDAC4, which represents a potential therapeutic target for the management of obesity and insulin resistance [60]. Using epigenetics marks could be an emerging field in translational medicine, and may provide a window of opportunity for early detection, intervention and therapy against metabolic syndrome.

Epigenetic code and the developmental programming of neural and mental disorders and cancer
Neural and mental disorders
Neural and mental disorders are diseases of the nervous system, including Parkinson's disease, schizophrenia, autism spectrum disorders (ASDs) and other disorders affecting the central and peripheral nervous system. Recent studies have shown that neural and mental disorders are linked with early life stress

Reviews • GENE TO SCREEN

in utero, including insufficient nutrition, maternal use of psychiatric drugs and mental stress during pregnancy [61–63]. For example, accumulated evidence indicates that methyl CpG binding protein 2 (MeCP2) has crucial roles in the brain development and pathogenesis of various ASDs, such as in Rett syndrome [64]. In addition, prenatal exposure to valproate, a drug used in the treatment of epilepsy, increased susceptibility to autism spectrum disorders in the offspring [65]. Maternal use of valproate during pregnancy [66] could induce demethylation in the promoter regions of specific genes such as wnt1 and wnt2 in the Wnt/β-catenin pathway in the rat brain, resulting in the increased expression of its target genes and susceptibility to autism spectrum disorders in the offspring.

At the same time, a substantial body of evidence indicates that several neurodevelopmental and neuropsychiatric disorders are partially caused by aberrant epigenetic marks, including histone modifications and microRNA [62,68]. Accumulated evidence supports the thesis that post-translational modifications of histones are not only important for normal neural functions but also for the pathological progression of Huntington's and Parkinson's diseases [67,68]. Recent findings showed that histone H3K27me3 demethylase JMJD3 was able to enhance the polarization of microglia by modifying H3K27me3, and played an important part in the switch of microglia phenotypes that might be involved in the pathogenesis of Parkinson's disease [68]. MicroRNA is also involved in neuroplasticity and physiological processes in response to gestational stress. For instance, gestational stress can regulate expression of miR-219 in controlling expression of gene Dazap1 [62]. miR-219 and Dazap1 are putative markers of bipolar affective disorder and schizophrenia in humans. These findings indicate that gestational stress modifies epigenetic modifications linked to multiple neural and mental disorders during crucial periods in the development of the brain.

Therefore, like the epigenetics-based therapies for CVDs mentioned above, the targeting of important epigenetics regulatory proteins seems to be a reasonable therapeutic strategy for neural and mental disorders. During the past decade, numerous studies have identified HDAC inhibitors that could be candidate drugs for the therapy of neurodegenerative and psychiatric disorders [69,70]. Meanwhile, owing to HDAC inhibitors exhibiting neuroprotective properties in animal models of various brain disease, they have great potential for treatment cognitive impairment resulting from neurodevelopmental and neurodegenerative disorders, and also serve as cognitive enhancers [70,71]. Together, accumulated knowledge from studies on diseases in developmental origins offers a new challenge if we can use epigenetic weapons to prevent those chronic diseases in early life periods, because many epigenetic changes could be reversible.

Cancer

Recently, emerging evidence suggested that some cancer could originate from early life [72,74]. For example, recent studies from animal models showed that maternal exposure to high-fat or ethinyl-estradiol (EE2) [73] during pregnancy could increase mammary cancer risk in several generations of offspring, which was associated with changes in DNA methylation machinery and DNA methylation patterns. In addition, experimental data showed that perinatal exposure to diethylstilbestrol (DES) or bisphenol-A (BPA) induced neoplastic changes in mammary tissue of mice via changing expression and functional activity of enhancer of Zeste homolog 2 (EZH2) [72]. EZH2, a histone methyltransferase, is a novel epigenetic regulatory factor, by which perinatal exposure to DES or BPA could lead to epigenetic changes in development of breast cancer. Meanwhile, recent findings showed that the expression of prostatic phosphodiesterase type 4 variant 4 (PDE4D4) was methylation-regulated by exposure to oestradiol and BPA during pregnancy, which was involved in cell proliferation and neoplastic transformation [74]. Those abnormal changes in a gene-specific manner implicate that the epigenetic code could reveal underlying mechanisms in developmental carcinogenesis.

Since a decade ago, a number of laboratories have shown great interest in the use of epigenetic code in testing of cancer and prenatal diagnosis. Epigenetic marks such as DNA methylation and histone modifications could serve as potential mediators or biomarkers of cancer. Indeed, research literature volumes have significantly increased in the past decade on the application of epigenetics in cancer therapies. For example, the anticancer effect of histone deacetylase inhibitors (HDACi) was supported by a body of evidence [75,76]; HDACi have been shown to inhibit cancer cell growth *in vitro* and *in vivo*. In addition, other histone-modification enzymes have also been demonstrated to play crucial parts in inhibiting cancer cells via multiple pathways, such as SETDB1 (H3K9me3 HMTase) [77], histone demethylase, JMJD1A [78] and KDM1 [79]. Taken together, it is clear that recent findings and accumulated evidence in epigenetic links to developmental origins of cancer will be beneficial to motivate future research against this disease.

Concluding remarks

Along with the studies on molecular pathogenesis of chronic diseases, roles of epigenetic codes in developmental origins of chronic diseases, and more details in epigenetic changes in diseases with developmental origins, are going to be discovered in the near future, because more studies are going on in that field. In addition, clinical and basic science researchers have finally realized that early intervention could be the top strategy in prevention of chronic diseases. Meanwhile, based on the important characteristic that the epigenetic code can be manipulated, a unique chance is to develop multiple novel therapeutic strategies against chronic diseases initiated during early developmental periods, using agents that can alter and/or reverse those pathological epigenetic processes. Of course, it also requires further intensive medical and scientific efforts to introduce these epigenetic-based outcomes into clinical therapy successfully.

Acknowledgments

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Reviews • GENE TO SCREEN

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