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].

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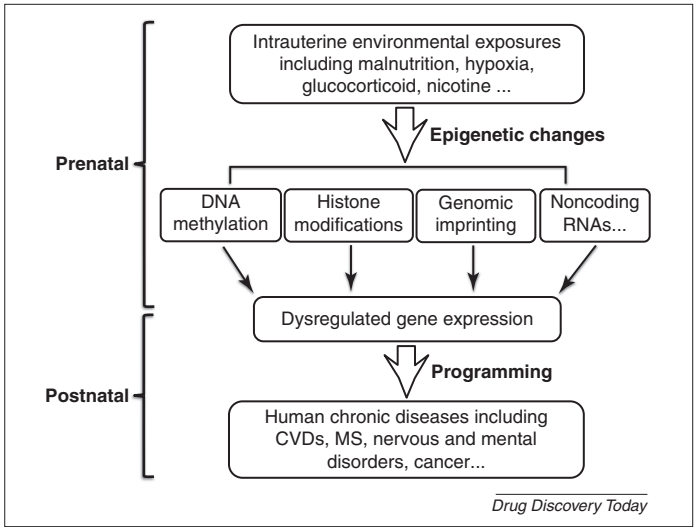

FIGURE 1

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 Genomic imprinting	Chronic diseases (CVDs, T2D)	[23]
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 Histone modifications	Coronary heart disease	[40]
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 miR-151 and miR-145	Noncoding RNAs MicroRNAs	Nervous and mental disorders	[62]
***In utero* exposure to diethylstilbestrol**	Enhancer Zeste homolog 2 (EZH2)	DNA methylation Histone modifications	Breast cancer	[72]
***In utero* exposure to high-fat or ethinyl-estradiol 2 (EE2)**	Dnmt1, Dnmt3a and Dnmt3b	DNA methylation Histone modifications	Breast cancer	[73]