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Robert C. Roach
Peter D. Wagner
Peter H. Hackett *Editors*

Hypoxia

Translation in Progress

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Part I
Epigenetic Alterations in Hypoxia

Chapter 1
Epigenetic Mechanisms as an Interface Between the Environment and Genome

Zdenko Herceg

Abstract Recent advances in epigenetics have had tremendous impact on our thinking and understanding of biological phenomena and the impact of environmental stressors on complex diseases, notably cancer. Environmental and lifestyle factors are thought to be implicated in the development of a wide range of human cancers by eliciting epigenetic changes, however, the underlying mechanisms remain poorly understood. Epigenetic mechanisms can be viewed as an interface between the genome and environmental influence, therefore aberrant epigenetic events associated with environmental stressors and factors in the cell microenvironment are likely to play an important role in the onset and progression of different human malignancies. At the cellular level, aberrant epigenetic events influence critical cellular events (such as gene expression, carcinogen detoxification, DNA repair, and cell cycle), which are further modulated by risk factor exposures and thus may define the severity/subtype of cancer. This review summarizes recent progress in our understanding of the epigenetic mechanisms through which environmental stressors and endogenous factors may promote tumor development and progression.

Keywords Epigenome • Environment • DNA methylation • Histone modifications • Noncoding RNAs • Cancer

1.1 Introduction

Epigenetics represents a rapidly expanding field of cancer research, as epigenetic changes have emerged as key mechanisms in cancer development. The term "epigenetic" refers to all heritable changes in gene expression and chromatin organization that are independent of the DNA sequence itself and that can be propagated over cell divisions [4]. The key events associated with cancer development and progression can be caused not only by genetic changes but also by epigenetic deregulation. The ubiquity and intrinsic reversibility of epigenetic changes, as well as their

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early appearance in virtually all types of human cancer, makes them attractive subjects for biomarker discovery and strategies for cancer treatment and prevention.

All critical changes in cancer cells, such as silencing of tumor suppressor genes, activation of oncogenes, and defects in DNA repair, can be induced by deregulated epigenetic mechanisms. Therefore, understanding epigenetic mechanisms that promote cancer onset, progression, and metastasis is fundamental to improving our ability to successfully prevent and treat cancer.

1.2 Epigenetic Mechanisms

There are three distinct classes of epigenetic information that can be inherited over cell generations: DNA methylation, histone modifications, and RNA-mediated gene silencing (Fig. 1).

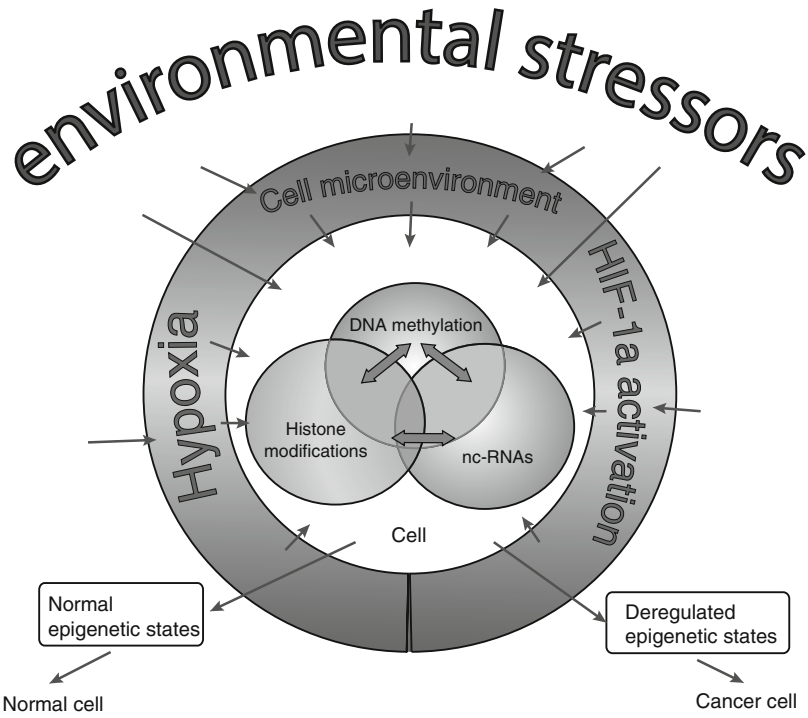

Fig. 1 Signals that trigger epigenetic events and mechanisms of initiation and maintenance of epigenetic states. Theoretically, epigenetic initiators and maintainers respond to epigenators (external and endogenous signals) resulting in initiation and maintenance of a change in epigenetic state. This cascade of events may dictate cellular outcomes by regulating cellular processes such as gene transcription, proliferation, and DNA repair. Deregulation of epigenetic mechanisms may promote the development of abnormal phenotypes and diseases including cancer

DNA methylation. Methylation of DNA refers to the covalent addition of a methyl group (-CH3) on the cytosine pyrimidine ring in DNA by a number of DNA methyltransferases. It occurs almost exclusively at cytosines that are located 5′ to a guanine in a CpG dinucleotide [3], although there is growing evidence for the presence of methylated cytosine which is not in a CpG configuration [3, 10, 15, 39, 42, 54]. DNA methylation is a physiological process that participates in the maintenance of gene activity states (imprinting, differentiation) and cell identity as well as in genome defence mechanisms, acting against potentially deleterious mobile genetic elements. However, unscheduled hypermethylation of small stretches of DNA, known as CpG islands, that are often located within the promoter regions of human genes and frequently free of DNA methylation in normal cells, tend to be associated with aberrant transcriptional inactivation in cancer cells. However, the precise molecular mechanism by which DNA methylation brings about gene silencing is not fully understood.

Histone modifications. Histone modifications include a variety of posttranslational modifications of the histones (specialized proteins associated with genomic DNA forming the chromatin, a DNA–protein complex). Histone modifications include acetylation, phosphorylation, ubuiquitination, and methylation of histone proteins at specific amino-acid residues. Previous studies have suggested that different histone marks may act in a combinatorial fashion to regulate cellular processes and consistently dictate the outcome, a concept known as the "histone code" [25].

Noncoding RNAs. Noncoding RNAs, found in the form of small RNAs (microRNAs) or long noncoding RNAs (lncRNAs), represent the most recent epigenetic mechanism playing an important role in the regulation of the gene transcription [7]. Deregulation of noncoding RNA expression has been associated with human diseases, including cancer [34].

Recent studies have provided evidence that different epigenetic mechanisms work together to establish and maintain gene activity states over many cell generations and that deregulation of one may cross-influence other epigenetic mechanism [66] (Fig. 1).

1.3 Epigenetic Changes in Cancer

A wealth of evidence indicates that all three classes of epigenetic modifications are profoundly altered in human malignancies. Deregulation of DNA methylation is found in two distinct forms: global hypomethylation and promoter-specific hypermethylation. Global hypomethylation refers to a total loss of 5-methyl cytosine that is found in virtually all human cancers [29]. This consistent, although relatively moderate, demethylation is caused by the loss of methyl-cytosine in the regions of the genome containing transposons and repetitive sequences. Although it has been proposed that global hypomethylation may act through the induction of chromosomal instability and activation of cellular proto-oncogenes, the precise mechanism

by which the global loss of DNA methylation contributes to the oncogenic transformation and tumor development remains unknown [14].

DNA hypermethylation occurs at CpG islands in the promoter regions of large numbers of genes and is usually associated with gene inactivation [14, 30]. A large number of human genes, including tumor suppressor genes and other cancer-associated genes, have been found hypermethylated and epigenetically silenced in most, if not all, human malignancies. However, with the advent of new epigenomic tools that allow high-resolution and cost-effective profiling of DNA methylation the list of genes targeted by aberrant hypermethylation is likely to grow steadily. Although it is well established that the predominant consequence of methylation is transcriptional silencing, it is less clear whether this is mediated through a direct or indirect mechanism [66]. Direct inhibition of transcription may be through blocking transcription factors from binding to promoters containing methylated CpG sites, while indirect repression may involve proteins that bind to methylated DNA via a methyl-CpG-binding domain.

1.4 Epigenators, Initiators, and Maintainers

The vast majority of epigenetics and epigenomics studies have focused on the analysis of epigenetic states in different cell types (including normal and tumor tissues) and pathophysiologic conditions. While these studies have provided important information on the maintenance and heritability of epigenetic patterns, they have had a limited impact on our understanding of the mechanisms involved in the initiation of epigenetic changes. Also, little is known on the agents and conditions that trigger epigenetic events. Three types of signals (known as epigenators, initiators, and maintainers) are thought to participate in triggering and establishing epigenetic states that are transmitted over cell generations [2]. Epigenators are defined as the signals originating from the cell's external environment that trigger an intracellular pathway leading to epigenetic change. In contrast to plants, the role of epigenators in human tissues and how their deregulation promotes human diseases is largely unknown [2, 57]. For example, cell–cell and cell–extracellular matrix changes induced by environmental exposures and endogenous cues could be considered as epigenators. However, further studies are needed to determine the identity of epigenators and elucidate the mechanisms involved in the initiation of epigenetic states. Application of new epigenomics tools combined with appropriate experimental models may prove valuable in providing important information on epigenators and their mode of action.

It has been proposed that an epigenetic initiator responds to an epigenator signal and defines the location of the epigenetic change on the chromosome [2]. DNA binding proteins and noncoding RNAs (ncRNAs) can be considered epigenetic initiators. In this respect, lncRNAs have been shown to play an important role in determining how chromatin modifications are distributed along chromosomes. For example, HOTAIR (a long noncoding RNA) was shown to participate in silencing a

chromosomal region by binding to the RNA binding domain of Polycomb repressive complex, thereby dictating epigenetic silencing through Polycomb-mediated deposition of repressive histone marks [17]. Because ncRNAs have been implicated in the mechanisms underlying silencing of large chromatin regions (heterochromatin) this class of epigenetic modifications may be a bridge between initiator signals and epigenetic maintainers. lncRNAs are currently under intensive research and the near future is likely to provide information on the role of ncRNAs as epigenetic initiators.

In contrast to epigenators and epigenetic initiators, a great deal is known about the molecules involved in maintaining epigenetic states. This is particularly true for DNA methylation and histone modifications. Epigenetic maintainers are defined as molecules and complexes that respond to initiators and ensure the maintenance of epigenetic states [2]. DNA methylation and histone modifications are carriers of epigenetic signals through cell division, and can thus be considered epigenetic maintainers. Deregulation of epigenetic maintainers has been found in complex human diseases, notably cancer; however, the identity of the epigenators and initiator signals that presumably precede and promote maintaining aberrant epigenetic states remains to be established. Screening for potential epigenators, initiators, and maintainers in parallel in the same model system combined with focused functional studies may prove informative in identifying possible interactions and interdependencies between epigenators, initiators, and maintainers in physiological and pathological conditions.

1.5 Epigenome as an Interface Between the Environment and Genetic Code

Epigenetic modifications are considered an interface between genotype and phenotype [4, 13, 20, 24]; however, the epigenome could also be viewed as an interface between the environment and the genome (Fig. 1). This epigenetic interface may "buffer" the impact of environmental exposures on the genome. It also modulates the response of the genome to environmental cues. The implications of this concept are twofold: first, defects in the epigenetic interface components may deregulate key cellular processes (such as gene transcription or DNA repair and replication) following environmental exposure, which may result in cell death or oncogenic transformation. Second, environmental factors may leave "exposure sequelae" on the epigenetic interface that could be exploited in biomarker discovery.

A number of agents in the environment have been suggested to alter epigenetic states [20]. Evidence is accumulating that environmental agents may affect cellular functions through their impact on DNA methylation, histone modifications and noncoding RNAs. Several recent studies suggest that the hypermethylation and unscheduled silencing of several key cellular genes in lung cancer are associated with exposure to tobacco smoke [1, 48, 65]. Therefore, tobacco smoke may, in addition

to inducing gene mutations, contribute to oncogenic transformation by inactivating key cancer-associated genes through epigenetic disruption. Environmental toxins, such as arsenic and nickel, may also deregulate epigenetic states (including chromatin modifications and DNA methylation) [9, 33, 59, 60, 73, 74], and promote cancer development through epigenetic mechanisms.

Biological agents, such as viruses, like Human papillomavirus (HPV), Epstein-Barr virus (EBV), and Human hepatitis virus (HBV), and bacteria may also alter the expression of host genes via an epigenetic strategy [11, 20, 37, 41, 67]. Epigenetic mechanisms including DNA methylation, chromatin modifications, and RNA-mediated gene silencing are believed to be important in protecting against viral genomes [3, 20, 24]. However, viruses also use epigenetic mechanisms to regulate expression of their own genes [75]. Importantly, previous studies have shown that HBV infection and integration of viral genomes may lead to epigenetic changes at the level of both viral and host genomes [20]. Therefore, epigenetic changes associated with viral infection and integration of viral genomes may trigger aberrant events that lead to oncogenic transformation and cancer development. In other words, different viruses may abrogate cellular defence systems and induce silencing of host genes through epigenetic deregulation; however, the role of epigenetic events associated with viral infection and their role in cancer remains largely unknown. In particular, it is unclear whether viral infections promote carcinogenesis directly through deregulation of key genes and pathways or indirectly, through inflammatory processes. For example, chronic production of cytokines during inflammation may alter epigenetic states in affected cells. Alternatively, low oxygenation (hypoxia) that commonly occurs in inflamed tissue may induce Hypoxia-Induced Factors (HIFs) that may have an impact on histone modifications [5, 51] (Fig. 1).

In addition to viruses, bacterial infection (such as that induced by *H. pylori*) has been associated with aberrant epigenetic states (DNA methylation) in human gastric cancer. *H. pylori* infection appears to induce DNA methylation changes in promoters of many key genes in gastric mucosa, thus promoting the development and progression of gastric cancer [41]. Although, the mechanism by which *H. pylori* infection induces changes in DNA methylation remains poorly understood, chronic inflammation and cell proliferation associated with bacterial infection, rather than the presence of bacterial agents, may trigger aberrant hypermethylation [23, 61, 68]. For example, the suppression of gene expression in the host genome, a phenomenon frequently observed in tissues affected by inflammation, may promote aberrant DNA methylation [12, 22, 45, 58].

1.6 Dietary Factors and One-Carbon Metabolism

Diet influences DNA methylation levels in cells in several ways, but mainly via the one-carbon metabolism pathway. The DNA methylation reaction involves the use of methyl groups, therefore the establishing and maintaining of DNA methylation

relies on dietary methyl donors [63]. In a DNA methylation reaction, the final methyl donor produced by one-carbon metabolism, S-adenosylmethionine (SAM), is used. The primary methyl donors and key mediators of one-carbon metabolic pathways are dietary folates, although choline and other cofactors such as vitamins B6 and B12 represent important methyl donors [72]. For the production of tetrahydrofolate (THF), a precursor for homocysteine conversion to methionine, cells use methyl-THF which serves as a methyl group donor. In cells, methionine is converted to SAM by methionine adenosyltransferase, whereas SAM serves as the principal methyl donor [35]. Therefore, conversion of SAM to S-adenosylhomocysteine (SAH) is critical for the methylation process. Because SAH is a potent competitive inhibitor of methylation reactions, disruption of the SAH/SAM ratio, through an increase in SAH or a decrease in SAM, leads to inhibition of methylation reactions. The SAM:SAH ratio is regulated via inhibition of SAM by 5,10-methylene-THF reductase (MTHFR), and of GNMT by folate compounds [16]. Therefore, intake of dietary folates is important for reactions in one-carbon metabolism, and low dietary intake of folate and choline may decrease concentrations of SAM, potentially triggering DNA hypomethylation.

Consistent with the essential role of dietary folate in DNA methylation, deficiencies in folate, methionine, and vitamin B6 have been associated with an increased risk of cancer at different sites. Recent studies suggested that serum levels of one-carbon metabolites are associated with cancer risk [28] and DNA methylation states in blood cells [69]. These results support the notion that dietary intake of folates, and subsequently plasma levels of one-carbon metabolites and B vitamins, could influence the methylation level of key cellular genes; however, the precise mechanism underlying the modulation of DNA methylation levels by one-carbon metabolites and B vitamins remains to be established.

1.7 DNA Demethylation

DNA methylation has long been considered as a highly stable epigenetic modification. However, recent studies suggest that cycles of DNA methylation and demethylation may take place during the life of a cell, arguing that DNA methylation mark may be more dynamic than previously thought. For example, Kangaspeska et al. reported a cyclical pattern of DNA methylation and demethylation at a set of promoters during the initial cycle of transcription, and again after the second cycle of productive transcription [32]. Another study also demonstrated that cyclical DNA methylation occurs at several CpG sites and that this process may be strand specific, with only the transcribed strand being demethylated after the first cycle of transcription [43]. Consistent with these observations, DNMT enzymes were found at the active promoter and their recruitment coincides with both phases of DNA methylation and demethylation. These intriguing results argue that DNMTs may be involved in both the addition and removal of methyl groups. Furthermore, DNA methyltransferases DNMT3A and DNMT3B were found capable of deaminating

methylated cytosines, thereby generating mismatches that are cleaved by a glycosylase and repaired by machinery involved in the base-excision repair [43].

These studies, together with those showing a rapid wave of DNA demethylation of the paternal genome after fertilization [36], argue that the mechanism of DNA demethylation is operational in mammalian cells. One of the proposed mechanisms involves passive DNA demethylation through rounds of DNA replication, brought about by inhibition of DNMT1. This process can be chemically induced by 5-Aza-2′-deoxycytidine, an inhibitor of DNMT, which blocks DNMT1 activity, compromising the maintenance of the DNA methylation mark through cell division [49, 71]. However, a passive mechanism for DNA demethylation may not be the only mechanism and active DNA demethylation might exist. There are several possible active mechanisms of DNA demethylation that may operate in mammalian cells. These include the direct removal of the methyl group via hydrolytic attack, oxidation, or a DNA demethylase enzyme [55]. Removal of methyl groups from cytosines is considered unlikely, arguing that alternative pathways involving DNA glycosylases and deaminases may operate in mammalian cells [38, 56, 64], although many reported DNA demethylase activities have been challenged [19, 26, 47] and it is not clear which protein(s) may function as an active DNA demethylase in mammals [6].

Recent studies suggested that the Tet family of proteins may be involved in active DNA demethylation. The capacity of Tet proteins to hydrolyse methyl cytosines (producing 5-hydroxymethylcytosine, 5hmC) and to act on fully methylated or hemi-methylated DNA has been reported [62]. Moreover, Tet1 blocks DNMTs and DNA demethylation is followed by chromatin remodelling including loss of H1 and H2Az [18, 62]. Other potential players such as GADD45 and ELP3 have been investigated in the context of DNA demethylation [40, 46, 47, 52, 70]. Together, these results provide compelling evidence that DNA methylation mark is more dynamic than previously thought. These observations may also suggest that establishing and maintaining DNA methylation may be highly susceptible to modulation by environmental and extracellular influences.

1.8 Environmental Exposure and Transgenerational Epigenetic Inheritance

Exposure to environmental and dietary factors during embryonic life as well as during childhood and adolescence is associated with a change in risk of developing specific human cancers in adulthood. Epigenetic deregulation during this critical period of growth and development might explain such observations. This notion is supported by recent studies showing an association between early life energy restriction and DNA methylation states in adult colorectal cancer [21]. Therefore, exposure to a transient environmental factor during early life may result in persistent epigenetic changes that later influence cancer development. Furthermore, it is possible that epigenetic changes induced by environmental exposures might be

transmitted to future generations. It is widely believed that epigenetic states are cleared on passage through the germ line in mammals and that only genetic features are passed on to subsequent generations. However, accumulating evidence argues that in both animals and plants epigenetic modifications are not completely erased between generations. The phenomenon of incomplete erasure of epigenetic marks between generations resulting in a detectable phenotype is known as transgenerational epigenetic inheritance [27].

Perhaps surprisingly, recent studies indicate that epigenetic states can be inherited transgenerationally after not only maternal but also paternal transmission [8, 53]. Epigenomic screening revealed that paternal diet may induce changes in DNA methylation and consequently expression of specific genes and pathways in offspring of inbred mice and that carriers of epigenetic information that reside in sperm may respond to environmental exposures [8]. In addition, epigenetic intergenerational transmission of metabolic changes from father to offspring in rats have also been described [44]. Therefore, epigenetic changes induced by environmental exposures may be inherited through the germline and this could be a plausible transgenerational carrier of environmental "memory", although future studies are required to substantiate these observations and to define their underlying mechanism.

This intriguing concept, derived from experimental studies, is further supported by epidemiological observations suggesting that environmental and dietary exposures in men may influence health and susceptibility to diseases in following generations [31, 50]. However, to what extent the parental environmental exposures contribute to cancer risk through transgenerational epigenetic inheritance remains to be establishes and warrants further study.

1.9 Conclusions and Perspectives

The field of cancer epigenetics has been expanding rapidly over the past decade and numerous conceptual advances have dramatically accelerated research in this and related fields. Both the scientific and medical communities now recognize the key role of epigenetic mechanisms in the development and control of normal cellular processes as well as abnormal events associated with disease development, notably human cancer. Epigenetic modifications can be viewed as an interface between the environment and the genome, the deregulation of which may disrupt key cellular processes, leading to disease. This interface may also be a memory system that "records" and transmits information about past exposures to the subsequent generations of cells, and could thus be exploited in biomarker discovery. Recent studies also indicated that epigenetic states may be more dynamic than previously thought, and that establishing and maintaining them may be influenced by environmental and dietary factors and endogenous cues. However, further studies are needed to elucidate the molecular mechanisms by which the environmental and extracellular signals impair initiation, establishment, and maintenance of normal patterns of epigenetic modifications as well as aberrant epigenetic states associated with cancer

development. The almost spectacular advances in epigenomics and the emergence of powerful technologies that allow the analysis of epigenetic events in high-throughput and genome-wide settings should facilitate this task.

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Chapter 2
Developmental Origins of Hypoxic Pulmonary Hypertension and Systemic Vascular Dysfunction: Evidence from Humans

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Abstract Epidemiological studies have shown an association between pathologic events occurring during fetal/perinatal life and the development of cardiovascular and metabolic disease in adulthood. These observations have led to the so-called developmental origin of adult disease hypothesis. More recently, evidence has been provided that the pulmonary circulation is also an important target for the developmental programming of adult disease in both experimental animal models and in humans. Here we will review this evidence and provide insight into mechanisms that may play a pathogenic role.

Keywords Barker hypothesis • Epigenetics • Perinatal insult

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2.1 Introduction

2.1.1 The Barker Hypothesis

The initial observations made by Barker and colleagues [1], that individuals born with a low birth weight present increased cardiovascular mortality in adulthood, gave rise to the "Barker hypothesis." This hypothesis postulated that environmental factors, in particular nutritional, could act during the early phases of life and determine the risk to suffer from metabolic and/or cardiovascular disease later in life. Since then, many epidemiological studies have confirmed the association between impaired fetal growth (deduced from birth weight or body composition) and an increased incidence of cardiovascular diseases, type 2 diabetes mellitus, or their precursors: dyslipidemia, impaired glucose tolerance, or vascular endothelial dysfunction. The terms "fetal programming" and "developmental origin of adult diseases" were coined to describe these associations. Interestingly, this association is not only present in children with extremely low birth weight, since in children with normal birth weight the cardiovascular risk is also inversely related to birth weight. In some conditions, adverse developmental influences could also affect disease risk without birth size affected [12].

Developmental plasticity provides organisms with the ability to change structure and function in response to environmental cues. These changes usually take place during critical time windows, and then become permanent, and thereby permit a range of phenotypes to develop from a single genotype. The predictive developmental adaptive responses are thought to optimize the phenotype for the probable environment of the mature organism. Where there is a match between the predicted and actual mature environment, these predictive adaptive responses are appropriate and assist survival. Conversely, inappropriate predictions increase the risk of disease. Modeling suggests that such lagged responses aid the survival of the species [11].

To explain his observations, Barker postulated that when the fetal environment is low in nutrients, the fetus adapts its metabolism to increase its chances of survival after the birth in presumably similarly poor conditions. However, if the actual environment will be richer in food than predicted, then the adaptations programmed during the pregnancy might be deleterious and predispose to disease in adulthood [15].

In humans, such a situation occurred towards the end of World War II. A Dutch epidemiological study showed that an insufficient caloric intake in pregnant mothers during the period of famine of the winter 1944–1945 increased the risk of the offspring to develop cardiovascular or metabolic diseases in adulthood, and this even in the presence of a normal birth weight [30]. Noteworthily, the girls born from these pregnancies in period of famine gave themselves birth to children of lower than normal weight, suggesting the possibility of a transgenerational transmission of the consequences of a perinatal insult [28].