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Epigenetic memory of environmental organisms: A reflection of lifetime stressor exposures

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ABSTRACT

Both genetic and epigenetic responses of organisms to environmental factors, including chemical exposures, influence adaptation, susceptibility to toxicity and biodiversity. In model organisms, it is established that epigenetic alterations, including changes to the methylome, can create a memory of the received signal. This is partly evidenced through the analysis of epigenetic differences that develop between identical twins throughout their lifetime. The epigenetic marks induce alterations to the gene expression profile, which, in addition to mediating homeostatic responses, have the potential to promote an abnormal physiology either immediately or at a later stage of development, for example leading to an adult onset of disease. Although this has been well established, epigenetic mechanisms are not considered in chemical risk assessment or utilised in the monitoring of the exposure and effects of chemicals and environmental change. In this review, epigenetic factors, specifically DNA methylation, are highlighted as mechanisms of adaptation and response to environmental factors and which, if persistent, have the potential, retrospectively, to reflect previous stress exposures. Thus, it is proposed that epigenetic "foot-printing" of organisms could identify classes of chemical contaminants to which they have been exposed throughout their lifetime. In some cases, the potential for persistent transgenerational modification of the epigenome may also inform on parental germ cell exposures. It is recommended that epigenetic mechanisms, alongside genetic mechanisms, should eventually be considered in environmental toxicity safety assessments and in biomonitoring studies. This will assist in determining the mode of action of toxicants, no observed adverse effect level and identification of biomarkers of toxicity for early detection and risk assessment in toxicology but there are critical areas that remain to be explored before this can be achieved.

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1. Introduction

Organisms have the ability to respond to environmental stressors such as toxic chemicals and adapt beneficially to new environments. This is accomplished, in part, by altering their epigenomes and subsequently their transcription profiles. Thus, overlaid on the genome are epigenetic marks, particularly methylation and hydroxymethylation of CpG sites that determine, in part, how the genome responds through regulation of transcription [1–3]. It is well established that various environmental stressors, including dietary deficiencies and exposure to a wide range of chemical pollutants, can modulate the epigenome [4–7]. The changes in response to environmental stressors may contribute to an adaptive survival advantage to local populations of organisms through advantageous gene expression [8,9]. However, in some cases these changes are associated with marked phenotypic endpoints that can be detrimental [10,11]. Such accumulated modifications of DNA, and the consequent changes in gene expression, have important implications in diseases, including cancer [12] and may, in some situations, be persistent through subsequent generations. Furthermore, it is becoming more evident that epigenetic mechanisms are involved not only in adaptive responses in individuals; they also have a significant role in host-pathogen interactions as reviewed by Gomez-Diaz et al. [13]. This demonstrates the role of epigenetic mechanisms in multiple species interactions.

In this review, we explore the epigenetic responses of organisms to environmental stressors with a particular focus on the persistence or "memory" of such modifications and the ways in which this memory can usefully reflect the status of the environment in which humans and other organisms reside. Epigenetic factors, specifically DNA methylation, are introduced as an interface between the genome and the environment, providing partial mechanistic explanations for the sensitivity of organisms to environmental factors. We argue that epigenetic mechanisms such as DNA methylation are essential in determining how organisms respond to environmental agents and we present examples of studies in a

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range of species showing how exposure to chemicals can promote persistent changes in the epigenome with phenotypic outcomes. Furthermore, these studies lead to the concept of "epigenetic footprinting" for retrospective assessment of chemical exposures. The relevance and significance of epigenetic mechanisms in environmental risk assessment and the potential for establishment of suitable biomarkers is discussed in this review. These insights may shape the future of regulatory toxicology and environmental monitoring, especially where there are chronic exposures to pollutants.

2. Epigenetics

Epigenetics is defined as meiotically and mitotically heritable changes in gene expression that cannot be explained by changes in DNA sequence [14,15]. Such modifications include DNA methylation, post-transcriptional chemical modifications of the *N*-tail of histones and amino acids within the globular histone domains, binding of non-histone chromatin proteins to DNA or histone modifications (i.e. transcription factors), non-coding RNA, nucleosome positioning and higher order chromatin organisation [10,14,16–19]. Moreover, these modifications are not isolated events and are closely inter-linked by influencing chromatin structure at various levels and by further interactions with the genome [19]. Under normal conditions, cells of an organism display a finely tuned epigenetic equilibrium [1]. However, disruption of the activity of enzymes regulating the epigenome or changes in the levels of the metabolites required for the action of these enzymes can result in alteration of epigenetic marks and the epigenomic equilibrium [10] leading to inappropriate regulation of transcription and potential disorders [14,19]. Methylation of DNA at CpG dinucleotides is the most studied epigenetic modification [1] and it is the principal focus of this review. DNA methylation is the transfer by DNA methyltransferases (DNMTs) of a methyl group from the universal methyl donor, *S*-adenosylmethionine (SAM), to the 5th carbon position of a cytosine pyridine ring [20,21]. The crosstalk between histone modification and DNA methylation at the transcriptionally active and inactive regions is partly accomplished by a cfp1 (CXXC finger protein 1) and methyl-CpG binding proteins (MeCPs), respectively [22]. These proteins selectively bind to methylation-free and methylated CpG dinucleotides, respectively [22–24], encouraging recruitment of histone acetyltransferases and de-acetyltransferase and other epigenetic and non-epigenetic factors leading to regulation of transcription [23,24]. Although the precise mechanisms of DNA de-methylation are not known, it has been suggested that DNA can also either passively or actively undergo de-methylation. During passive de-methylation, 5-methyl cytosine is removed in a replication-dependent manner by inhibition of DNMTs while active de-methylation depends upon enzymatic removal of 5-methyl cytosine. Recently, methylcytosine dioxygenase 10–11 translocation 1 (TET1) has been found to be involved in regulation of DNA methylation. TET1 protein catalyses the conversion of 5-methyl cytosine to 5-hydroxymethyl cytosine (5-hmC) which is poorly recognised by DNMTs. This results in a passive replication-dependent loss of DNA methylation. Alternatively, 5-hmC can be recognised by the repair machinery and converted to cytosine [25–27]. Thus, although methylation can be removed from CpG islands, this is a highly regulated process and, as discussed below, many such modifications are persistent and "memorised" in cells.

3. Environmental sensitivity of the epigenome throughout life time and retention (memory) of environmentally-induced changes

Adaptive responses and sensitivity of an organism to environmental stimuli (e.g. chemical contaminants, diet and stress) are observed throughout the lifetime of an organism. However, a key question is what are the molecular mechanisms leading to changes in the expression of the genome? For example, why do homozygous twins have different disease susceptibilities in the absence of genetic variation? As introduced above, it is becoming more evident that, although epigenetic marks are stable enough to regulate gene expression, they are also susceptible to change by environmental signals. This means that the epigenome can change as a response to environmental stimuli, which then can lead to alteration in the phenotype [15]. In a way, the epigenome can act as the link between environmental cues (external and internal) to the organism and phenotype by translating the environmental signals to phenotypic responses through altered gene expression profiles. For example, in response to their immediate environment, a fraction of pluripotent stem cells will differentiate and form distinct cell types with a characteristic gene expression profile. The tissue-specific expression patterns are generally maintained throughout the lifetime of the individual. The differences in transcription profiles of the differentiated cells are then attributed to their different heritable epigenetic profiles. Hence, tissue-specific epigenetic profiles provide a method of sustaining the memory of the differentiation process in the absence of the initiating signal [12,28–30]. One of the best examples of the influence of environment on the epigenome and subsequent changes in gene expression is the response of *Arabidopsis* to prolonged exposure to cold weather (vernalisation). Following prolonged exposure to cold weather (an environmental factor), flowering locus C, a repressor of flowering, becomes epigenetically silenced. This results in coordination of flowering time (phenotype) with spring and summer [31–33].

Although the epigenome is sensitive to the environmental stimuli throughout an individual's lifetime, there are critical windows during development that the epigenome is at its most sensitive with lasting transcriptional effects. For example, genes such as oestrogen receptor (ER) and glucocorticoid receptor (GR) are regulated, in part, through DNA methylation of their promoter regions. The methylation and subsequently the transcription levels of these genes are gender- and region-specific. Furthermore, DNA methylation of these genes is substantially influenced by environmental factors, such as maternal care and exposure to chemicals, encountered during embryogenesis and early postnatal stages (reviewed in [34–36]). Another good example of developmental sensitive windows of alterations in the epigenome comes from the studies conducted in fish species looking at the effect of temperature on gender. Sex determination in many fish and reptile species is influenced by many factors including the temperature of the water during early stages of larval development. In European sea bass, high temperatures (21 °C) and low temperatures (15–16 °C) increase the number of male fish and female fish, respectively. It was demonstrated that exposure to high temperature at critical stages of larval development increased the DNA methylation level of the *aromatase* (*cyp19a1*) promoter in female gonads prior to formation of gonadal ridge and differentiation of the gonads. Aromatase converts androgen to oestrogen. A decrease in the expression of this gene as a result of high temperatures and subsequent methylation and suppression of the promoter region of this gene results in increased levels of androgen, differentiation of the gonads, formation of testis and a male-biased sex ratio [37]. Many other studies, demonstrate that environmental agents, independent of inducing mutations, can alter transcription profile and subsequently the phenotype of an individual by altering its epigenome [11,39]. Such changes in the epigenome profile can act as a memory (Fig. 1). However, although gender-dependent DNA methylation of the promoter region of the aromatase gene could explain differential expression of the aromatase gene in brain, liver and gonads of Japanese medaka, this correlation was not apparent following treatment with 17β-estradiol [38].

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