Journal of Physical Chemistry & Biophysics

Vinci et al. J Physic Chem Biophysic 2011, S:3
DOI: 10.4172/2161-0398.S3-001

Review Article Open Access

Sensing the Environment: Epigenetic Regulation of Gene Expression

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Abstract

The genomic era has just scratched the surface of the complex mechanisms responsible for bringing the organism phenotype into their being. In light of the recent discoveries, it is becoming clear that "other genetic" and environmental factors tightly interplay to provide information and instructions for the use of genetic material. Under this point of view, the DNA represents "the hardware", the first ancestral genetic layer of cell information that is identical in all tissues of the individual; another layer of information differently distributed across the genome, continuously written, read and erased in response to both physical and social environmental signals, represents the cell "software", the network connection with the changing world around us. Conrad H. Waddington (1942) termed this concept epigenetics to describe the hypothetical interaction among genes and their immediate surroundings during development and phenotype determination. Epigenetics is referred as the ensemble of functionally relevant modifications that regulate gene expression without altering the underlying DNA sequence. This article will examine the interaction between the genome, epigenome and environment with reference to how and when external signals affect long-term regulation of transcriptional programs.

Keywords: Epigenetics; Environment; Epigenetic programming; Developmental plasticity

Introduction

Are we the mere result of our genes? The decoding of the human genome at the turn of the millennium has opened the hope of discovering the most hidden mechanisms responsible for the organism phenotype. This is just the beginning, the genomic era has only scratched the surface of the complex mechanisms responsible for bringing the organism phenotype into their being. For a long time, the genome has been considered as immutable master plan lain down with the inception of our lives. However, in light of the recent discoveries, it is becoming clear that "other genetic" and environmental factors tightly interplay to provide information and instructions for the use of genetic material. Under this point of view, the DNA represents "the hardware", the first ancestral genetic layer of cell information that is identical in all tissues of the individual; a second layer of information differently distributed across the genome, continuously written, read and erased in response to both physical and social environmental signals, represents the cell "software", the network connection with the changing world around us [1]. This concept has been summarized by the term epigenetics coined by Conrad H. Waddington in 1942 to describe the hypothetical interaction among genes and their immediate surroundings during development and phenotype determination [2]. Epigenetics is defined as changes in gene expression in the absence of underlying changes in DNA sequence. The language of epigenetic program is encoded by specific DNA and chromatin covalent modifications (epigenetic marks) that regulate the accessibility of the DNA to the transcription machinery [3]. Epigenetic marks are the result of complex enzymes/chromatin interactions that establish and maintain different gene expression programs in specific cell types, leading to phenotypically different tissues despite the same genetic information, and ensure short and/or long lasting-heritable response of the organism to the changing environment [4]. Thus, epigenetics not only orchestrates constitutive gene expression during stem cell differentiation, embryonic development and organogenesis but coordinates the adaptive alteration of gene expression in response to the extracellular environment. Epigenetic mechanisms include several gene expression regulation pathways: 1) the DNA methylation, 2) the histone tail post translational modifications and 3) the noncoding RNA-based mechanisms [5]. All together these modifications represent the apparatus that, controlling access to DNA, constitute the main interface between environmental signals and the activation/repression of genomic response. This article will examine the interaction between the genome, epigenome and environment with reference to how and when external signals affect the long-term regulation of transcriptional programs.

Epigenetic modifications: the interface between transient gene regulation and stable gene expression

Histone modifications: In the eukaryotic cells, the DNA is organized in a highly conserved structural polymer termed chromatin. The basic building block of chromatin is the nucleosome which consists of 146 bp of DNA wrapped around an octamer constituted of dimers of core histone proteins H2A, H2B, H3, and H4 held together by an H1 linker [6]. Core histones are evolutionarily conserved proteins consisting of globular domain with a covalently modifiable N-terminal tail at level of lysine and/or arginine residues. Each modification constitute a signal that is read alone or in combinations with other marks or neighboring histones constituting a "histone code". At least 9 different types of posttranslational modifications (e.g acetylation, phosphorylation, methylation, biotinylation, SUMOylation, ADP ribosylation and ubiquitination) influence chromatin condensation and coordinate protein and enzyme complexes accessibility to the DNA [7]. Histone acetylation on lysine (K) residues has been linked to transcriptional activation. The addition of an acetyl group neutralizes the positive charge of K ε-amino group of histone tail reducing the electrostatic

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Received October 20, 2012; **Accepted** October 27, 2012; **Published** October 29, 2012

Citation: Vinci MC (2012) Sensing the Environment: Epigenetic Regulation of Gene Expression. J Physic Chem Biophysic S3:001. doi:10.4172/2161-0398.S3-001

bonding of histone with negatively charged DNA and decreasing chromatin condensation [8]. The enzymes involved in regulating this process are the histone acetyltransferases (HATs) and histone deacetylases (HDACs). Four classes of HDACs have been described. Class I: HDAC 1, 2, 3, and 8 (exclusively in the nucleus); class II: HDAC 4, 5, 6, 7, 9, and 10 (predominantly residing in the cytoplasm and shuttling in and out of the nucleus); class III: Sirtuin-related enzymes (SIRT) 1, 2, 3, 4, 5, 6, and 7 (localized in either nucleus, cytoplasm, or mitochondria); class IV: HDAC-11 [9,10]. Histone methylation occurs on both K and arginine residues (R). These histone modifications are catalyzed by three families of histonemethyl transferase (HMT) enzymes: the protein arginineN-methyltransferase (PRMT) family, the lysine methyltransferase such as the protein complexes of the polycomb (PcG) and the trithorax groups (TRXG) containing a SET domain, and the disruptor of telomere silencing 1 (DOT1) family 8 [11,12]. Histone H3 arginine methylation (H3Rme) is usually associated with active gene expression, whereas histone lysine methylation (Hkme) has bivalent function as can be associated with both active and silenced genes depending on the modified lysine [13,14]. H3K9me and H3K27 are usually repressive marks, while H3K4 is generally an active mark. The contemporary presence of repressive H3K27me3 and active H3K4me3, termed "bivalent domain", is particularly frequent in undifferentiated embryonic and progenitor cells, where the genes aremaintaine drepressed but ready to sense extracellular signaling and "poised" for transcription. In this case, the extracellular environment is determinant for cell commitment. Moreover, R and K methylation degrees (e.g. mono-, di- and trimethylation) provide different patterns of regulation of gene transcription, most likely because effector proteins such as transcriptional coactivators or inhibitors recognize mono-, di- and trimethylated epitopes with different affinity. For example, H3K4me is associated with both repressed and active genes whereas H3K4 is considered associated with active genes [15]. Finally, the same modifications in different regions of the gene can determinate opposite effect on gene transcription regulation. The presence of H3K9 methylation on coding region is associated with gene transcription, whereas its presence on the promoter leads to gene silencing. Histone methylation has for a long time been considered an irreversible epigenetic marker, as its removal was thought to be the histone turnover. Recent studies have described the existence of multiple histonedemethylases able to remove methyl group from lysine histonetails. These enzymes encompass lysine-specific demethylase1 (LSD1), which removes mono- or di-methyl groups from H3K4, and JumomnjiC (JmjC) specific for trimethylated modification [16].

The phosphorylation of serine (S), threonine (T), and tyrosine (Y) residues in the histones induces repulsive forces between the negatively charged histones and DNA leading to chromatin distention, enhanced accessibility to DNA and transcriptional activation [17]. These modifications, mediated by protein kinases (PKs) and protein phosphatases (PPs), are the most intriguing histone modifications as epigenetic machinery is directly connected to PK and PP dependent intracellular signaling pathways [18,19].

DNA methylation: DNA methylation has been the first described and best-understood DNA modification associated with gene inactivation. In eukaryotes DNA methylation specifically occurs on cytosine at the 5th C position of the pyridine ring, primarily in the context of CpG dinucleotides on double stranded DNA [20]. The methylation of CpG enriched regions, termed CpG island and mainly located in the gene promoter, are sensed by proteins that turn gene expression on or off, through histone modifying complex recruitment [21]. The central mechanism by which DNA methylation inhibits DNA expression is through methyl-CpG binding proteins, such as MeCP2, and MBDs, which recruit histone modification enzymes to the methylated DNA modulating chromatin structure [22]. DNA methylation at CpG dinucleotides occurs upon transfer of S-adenosylmethionine (SAM) on cytosine by DNA methylases (DNMTs). Mammalian genome encodes three DNMTs: DNMT1, DNMT3a, DNMT3b and DNMT3L. DNMT3a and DNMT3b methylases play the lead role in de novo DNA methylation [23], DNMT3L, although belonging to DNMT3 family and lacking in methyltransferase activity, it is crucial for DNMT3a and DNMT3b function as revealed colocalization and co-immunoprecipitation studies [24]. The *de novo* methylation is then transmitted to the cell progeny by DNMT1 as long as methylation processes takes place; indeed, consistent with its role, DNMT1 shows preference for hemimethylated DNA *in vitro* [25]. DNA methylation and histones modifications act in concert in an epigenetic program that integrate gene silencing/transcription networks within the cells. In fact, specific histone modifications have been shown to be associated with DNA hypermethylation of CpG island, including deacethylation of histone H3 and H4, loss of H3K4me, and gain of H3K9me3 and H3K27me3 [26,27]. DNA methylation is heritable during cell division, and typically underpins processes that demand sustained control of gene expression as exemplified by long-term and /or selective gene silencing during cell differentiation [28,29], X chromosome inactivation [30], parentorigin specific silencing (genomic imprinting) and suppression of transposable mobile elements [31,32]. Together these properties make DNA methylation an attractive mechanism to stably record past life experience.

Noncoding RNAs: A wide body of literature is demonstrating that also noncoding RNAs regulate chromatin structure [33-37]. The term noncoding RNA (ncRNA) is commonly used for RNA that does not encode a protein. It was assumed that most of the genome was translated into proteins, only recently it has become apparent that the majority of the genetic material of mammals and other complex organisms is transcribed into ncRNAs. These RNA species, together with the constitutively expressed infrastructural RNAs (e.g. ribosomal, transfer RNA) constitute the 90% of mammalian transcriptome. The family of ncRNAsen compass long-noncoding RNAs (lncRNAs), micro RNAs (miRNAs), tinyRNAs (tiRNAs) (when alternatively spliced and/or processed into smaller products), as well as other classes of small regulatory RNAs, such as snoRNAs or yet-to-be-discovered molecules [34,38]. These RNA molecules represent a deep layer of internal signals that control gene expression both during development and physiological cell processes [39]. Moreover, ncRNAs are, at the same time, in charge of multi-level control of gene expression of epigenetic machinery (DNMT, HDAC, sirtuin (SIRT), polycomb (Pc) proteins, etc.). For example, miRNAs and/or long ncRNAs and tiRNAs are involved in gene regulation by posttranscriptional and transcriptional mechanisms respectively [36,40,41]. The latter regulate gene expression and/or DNA methylation by promoter association [34,42] showing that DNA-methylation can also be RNA-directed [33,43].

Shaping the phenotype: environmental sculpture of epigenome

During evolution, all organisms had to face changing environment, and adapting to it, to ensure their survival. These responses imply mechanisms based on gene-environment interaction, such as chromatin modification, that results in long-lasting adaptation of gene expression without altering genome integrity. In order to maintaining adaptation, epigenetic changes must be heritable from cell to cell, hence through cell lineage development or even transgenerationally from parent to

offspring to grand offspring (the so called "epigenetic memory") [44]. The environment is a strong predictor of phenotype and is accountable for the developmental origin of adult disease. However, the question is: when and how does the environment alter life outcomes?

A range of critical windows throughout life has been identified. These include the periconceptional period, embryonic stage, mid and late gestation, postnatal/post weaning period, and puberty [45]. The developmental plasticity, that characterizes these phases, enables an organism to develop under various environmental conditions. Recently, compelling data from epidemiological and extensive clinical and experimental studies indicate that early-life events influence later susceptibility to diabetes, cardiovascular and psychiatric disorders [46,47]. During prenatal and postnatal mammalian development, environmental factors such as nutrition (caloric intake, specific nutrient level), behavior (maternal care deficiency, stress), chemicals (toxins, drugs) or unknown (stochastic, random events) can affects cell differentiation and developmental pathways. The underlying epigenetic modifications responsible for these effects can induce regulatory and permanent changes in gene expression driving to alteration of the adult phenotype or predisposing organism to disease susceptibility. These findings demonstrate that environmental signals through still poorly understood biological mechanisms, can generate inheritable epigenetic modifications during early development with potential long term consequences [48]. Histone modifications and DNA methylation are the stable and heritable epigenetic modifications mediating, at least in part, the developmental plasticity.

The time points of epigenetic lability

Environmental factors affect the epigenome mainly during embryogenesis because of high synthetic rate of DNA and the establishment of methylation pattern (programming) required for normal tissue development. In mammals, this process occurs naturally only at two specific times during development: at the onset of embryogenesis, when the genome of the zygote and subsequently of the early blastomeres acquires totipotency, and during the course of primordial germ cells development [49]. During these phases, the mammalian genome undergoes two waves of global DNA demethylation followed by de novo methylation (Figure 1). Within the pregnant mother (G_0), the F1 embryo generates a group of cells, primordial germ cells, destined to migrate and differentiate into gamete precursors that will generate F2 offspring. By convention, the first wave of demethylation (epigenetic reprogramming) occurs in primordial germ cells, whereas the second wave of demethylation happens shortly after zygote formation. After fertilization, the paternal genome is rapidly demethylated except for imprinted genes, retrotrasposons, heterochromatin around centromeres and some repetitive elements [50], whereas maternal follows a relatively slower demethylation pattern. In this phase, DNMT1 is responsible for maintaining methylation of imprinted genes [50]. At embryonic stage, primordial germ cells undergo demethylation during migration into genital ridge; afterwards somatic methylation pattern occurs and, for imprinted genes, the gender specific methylation pattern matches the genotype of the individual in which they reside. In males, methylation pattern of primordial germ cells is fully reestablished during embryonic development, whereas in females, the primordial germ cells remain largely unmethylated until maturation in the F1 adult during each estrous cycle. Immediately after F2 gametes combination a new and more complete demethylation wave takes place to establish a new somatic methylation patterns (excluding F3 primordial germ cells) restarting life cycle [51,52] (Figure 1). It is evident that exposure of the pregnant mother (G0) to any environmental factors can dramatically affect methylation status of both F1 (post-fertilized F1 pluripotent somatic cells) and F2 (F2 primordial germ cells) generation, with important relapses throughout postnatal life on adult phenotype and disease susceptibility in cardiovascular, reproductive function as well as behavior [53].

Nutrition, behavior, stress and toxicants: the change of epigenetic karma

There is a wide body of literature demonstrating that nutritional conditions affect epigenetic patterns of gene transcription or silencing during the embryonic and fetal life in utero. This concept has been supported by epidemiological evidences, as well as by animal studies, that have associated maternal diet with susceptibility to develop metabolic and psychiatric disorders (obesity, glucose intolerance, hypercholesterolemia, type II diabetes, schizophrenia) during adulthood, [54-57]. These studies have highlighted that the epigenetic alterations, as mentioned above, may be also permanently passed transgenerationally from mother (G0) to F1 and F2 progeny [58-60]. In mice, folate deficiency during pregnancy and lactation is associated with whole genome hypomethylation in offspring [61], where as a low methyl donor diet regime, at early postnatalphase, decrease methylation of imprinted gene *Igf2* [62]. In utero, malnutrition of rodents directly alters the expression and methylation of several genes such as glucocorticoid receptors (GRs), *Nr3c1, Pparα*, and the neonatal response to leptin; these epigenetic effects persist later in the life ending in adipose phenotype [63]. Humans are also affected by nutritional status: epidemiological studies demonstrated that DNA methylation was changed in IGF2 gene of subjects exposed to the Dutch hunger winter [64], whereas human longevity of grandchildren was associated to food abundance during prepubertal growth of their grandparents [65].

Absence of maternal grooming in rats during the first week of life led to persistent DNA methylation changes of GR receptor and other loci of hippocampus [66]. Humans abused in early life also showed increased DNA methylation at the NR3C1 glucocorticoid receptor

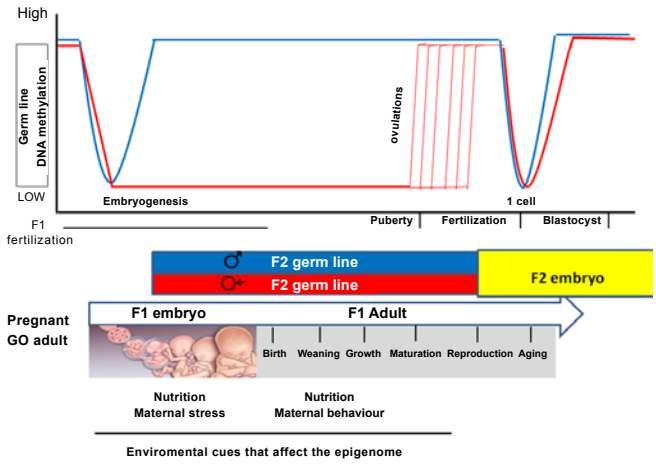

Figure 1: Epigenome sensitivity to external environment throughout life. The graph on the top indicates the epigenetic reprogramming of F2 germ line cells occurring during F1 development (female red line, male blue line). The bottom row indicates the main environmental factors that affect epigenome with late-life consequence, and the stages of life at which they act.

promoter in the hippocampus [67]. Stress from maternal separation led to *Mecp2* and *Cb1* gene methylation, *Crfr2* demethylation; the change of this methylation DNA pattern was responsible for depressive behavior [68]. Noteworthy, this phenotype and epigenetic makeup can be transmitted transgenerationally [68]. In humans, early life stress events are related to changes in gene expression of polymorphic form of serotonin receptor [69].

Bisphenol A, a chemical compound primarily used to make polycarbonate plastic for a variety of common products including baby and water bottles, has been recently declared toxic and harmful for fetuses, infants, and young children. Widely studied as endocrine disruptor, it has shown to affect DNA methylation in multiple rodent tissues such as brain and liver [70,71]. A study of Wu et al. provided evidence that the early exposure to lead (Pb)accounted for Alzheimer disease-like pathology in aged monkeys by reducing DNA methyl transferases activity that persisted even after 23 years [72].

The initial seed

What are the specific settings and mechanisms that allow external stimuli to couple to epigenetic machinery and leave a trace on our genes?

The mechanism involved in the initiation, maintenance and heritability of epigenetic programming is still a debated research field [73,74]. Recent studies have put on the light several molecular pathways underpinning epigenetic transmission. Berger and collaborators proposed a multi-step mechanistic model of control of gene expression, in which such pathways interplay, leading to the establishment of a stable and heritable epigenetic profile [75]. They identified three categories of signaling: a) the "Epigenator", the signal generated by environment that triggers intracellular pathways; b) the "Initiator" that transduces Epigenator signal to chromatin context at precise chromosomal location and c) the "Maintener" that maintain the epigenetic modification over the time. Environmental cues or changes into the cellniche (Epigenator) trigger intracellular pathways that in turn activate the Initiators. Epigenators can be protein-protein interactions or allosteric modulators that unleash the latent activity of Initiators. However, these transient signals that trigger epigenetic phenotype, might be not necessary for the subsequent events. Activated Initiators define the precise location on chromosome where epigenetic modification is required. Initiators can be represented by DNA-binding protein, non-coding RNAs, and any other factors involved in the coordination of chromatin assembly. These signals need to be self-reinforced and self-renewed through positive feedback mechanisms and, unlike Epigenators, might persist with the mainteners. The maintainers ensure the maintenance of epigenetic modification through cell cycle as well as epigenetic transgenerational inheritance, but they are not sufficient to initiate it. They involve many different pathways such as DNA methylation, histone modifications, histone variants, nucleosome positioning and others. Importantly, unlike Initiators, they do not have absolute DNA sequence specificity; therefore they could operate at any chromosomal location to which they are engaged by an Initiator [75]. In this model there is an important distinction between transient and persistent epigenetic modification and its consequent gene expression.

An example of an operational epigenetic change

A compelling example of this model derives from a study of Murgatroyd et al. in which all the steps previously reported can be identified [76]. This work showed a transition of behaviour-dependent epigenetic marks from a preliminary, labile state to a hard-coded, stable state. Early life stress has long lasting effects on the brain, increasing vulnerability to stress related disorders, such as depression and anxiety. In rodents, a similar stress is evocated by periodic infant-mother separation during early postnatal life. These animals are characterized by lifelong increased secretion of glucocorticoids (GC) and disruption of homeostatic mechanisms regulating the activity of the hypothalamus-pituitary-adrenal axis [77]. Two neuropeptides, corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) recently linked to mood and cognitive behavior, represent the neural positive controllers of GC secretion [78]. Murgatroyd showed that early stress in mice (daily 3 hours separation from the mother during postnatal 10 days) caused persistent epigenetic modification (hypomethylation) on the regulatory region (enhancer) of *Avp*gene with sustained AVP mRNA expression. However, unlike increased AVP expression, DNA methylation did not differ from control mice after 10 days of stress exposure. These data demonstrated that adverse experience was not straightforwardly translated into changes of DNA methylation patterns. MeCP2 occupancy at *Avp* enhancer was decreased whereas the active chromatin marks were raised. MeCP2 is an epigenetic platformin which synergistic crosstalk among histone deacetylation, H3K9 methylation and DNA methylation take place to establish transcriptional repression and gene silencing [28]. What are the signals that control MeCP2 occupancy at this step? Sensory experiences induce synaptic activity that causes membrane depolarization, calcium influx and consequent activation of intracellular calcium dependent pathways. Neural depolarization has been recently associated to Ca^{2+}-dependent phosphorylation of MeCP2 at serine 421 (human) mediated by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [79]. Consisting with this finding MeCP2 dissociation from *Avp* enhancer is regulated by depolarization through Ca^{2+}/CaMKII pathway and depend on phosphorylation of serine 438 (in mice) [76]. Analyzing the sequence of events leading to the stable epigenetic modification, it appears that Ca^{2+}/CaMKII pathway and MeCP2-S438 represent epigenator and Initiator respectively as they faded away in adult. By contrast, DNA hypomethylation (Maintainer) increased in stressed mice underpinning the reduced MeCP2 occupancy at level the *Avp* enhancer. Briefly, experience dependent phosphorylation and dissociation of MeCP2 reduce *Avp* enhancer DNA methylation that reinforces dissociation of MeCP2 and consequently primes further demethylation. This vicious loop uncouples MeCP2 from the initial stimulus and ultimately leads to hard-coding of early life experience at level of DNA methylation.

Conclusion

The phenotype of an individual is the result of complex gene-environment interactions that lead to lifelong remodeling of the epigenome. Exposure to chemical, nutritional and behavioral factors alters gene expression and affects health and disease, not only by mutating promoter and sequence regions of the genes but also by altering the epigenome. Actually, environmentally induced alteration of DNA methylation and histone modifications are the best characterized epigenetic modification; however, other mechanisms, such as posttrascritpional modification of chromatin modifying enzymes, require further investigation. Evidence that dietary or pharmacological interventions have the potential to modify epigenetic states, has recently provided additional impetus for elucidating the molecular pathways underlying epigenetic programming and interaction with the environment. Our understanding of how epigenetic mechanisms contribute to the development of disease will continue to be refined for years to come.

Acknowledgments

No acknowledgements to disclose.

Conflict of Interest Statement

The author indicates no potential conflicts of interest.

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This article was originally published in a special issue, **Gene Regulation** handled by Editor(s). Dr. Maumita Mandal, Carnegie Mellon University, USA