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Epigenomic biomonitors: global DNA hypomethylation as a biodosimeter of life-long environmental exposures

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Epigenomics refers to the study of genome-wide heritable changes in gene activity and expression in the progeny of cells or individuals, without a change in nucleotide sequence, and its contribution to cellular growth and differentiation, disease and aging. Epigenomics provides a window through which we can understand the exposome [1], that is the life-course impact of environment, nutrition and lifestyle choices on health and disease susceptibility, as well as risk [2]. Epigenomic processes, a whole-genome concert of heritable epigenetic changes acting with choreographed precision, behave in a cell-specific, temporally regulated fashion to direct normal development, differentiation, organogenesis, tissue formation, tissue maintenance and aging [3]. While genetic processes rely on the nucleotide sequence of the DNA, epigenomic processes depend on reversible biochemical alterations of the DNA strands or higher order chromatin packaging to regulate gene activity and expression. As such, epigenomic processes can be both appealing and elusive targets for biomonitoring environmental exposures.

Epigenomic mechanisms are linked to gene activation, gene silencing and chromosomal instability, but questions still remain regarding the timing, maintenance and stability of epigenomic marks. Additional knowledge of how critical epigenomic patterns are inherited and maintained is needed to understand the role of the human epigenome in health and disease. For example, little is known regarding how normal growth and development are impacted by the epigenome, which is not a stable entity but rather highly dynamic, as it responds to micro- and macro-environments throughout the life course [4].

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Epigenomic changes are tissue, exposure or disease specific and seem to be in a dynamic flux during the cell cycle and in mitotic divisions [5]. The epigenome is linked to circadian rhythms, is highly dependent on lifestyle and context and may be associated with maternal and grand-maternal exposures. As such, it is a magnificent molecular tapestry of ourselves, providing a record of where we come from and a roadmap of who we will become – invaluable information pending our ability to decipher it. Furthermore, because of its potentially modifiable, yet fundamentally stable nature, there in lies the possibility that we might learn how to manipulate the epigenome to nurture and promote health, as well as to prevent or treat disease [6].

One genome, several epigenomes

The epigenome is an interface between the dynamic environment and the inherited static genome, and is configured during development to shape the diversity of gene-expression programs for different cell types by a highly organized process. Physical, biological and chemical, as well as social factors modify the epigenome at critical time points. Normal development hinges on precise temporal and tissue-specific regulation of gene expression to determine cell fate and function. Epigenomic regulation of gene transcription directs normal development through dynamic transcriptional activities from gametogenesis in the course of embryonic and neonatal stages, and continuing throughout childhood, adolescence, adulthood and old age. Transient and fixed epigenetic modifications occur throughout the life course in response not only to endogenous stimuli, but also in response to exogenous factors in the environment.

DNA methylation, the addition of a methyl group to the 5 position of the cytosine pyrimidine ring (5mC), is the best understood epigenomic mark. Global DNA hypomethylation, a loss of methylation across the genome, mostly in repetitive elements regions, is an early epigenomic mark of the initial transition from a normal to a diseased cell or from a pluripotent cell to a differentiated one. Approximately 90% of DNA methylation occurs in noncoding areas of the genome in normal cells. A loss of methylation in noncoding areas of the genome is associated with the normal aging processes. A sudden dramatic loss of methylated cytosine content across the genome is seen in the transition from normal to diseased cells in several human diseases and under different environmental stimuli. The global loss of methylation is mainly due to the hypomethylation of repetitive DNA sequences and demethylation of coding regions and introns – thus allowing for alternative transcription events. The global loss of methylation continues to occur as disease progresses, sometimes concurrently with an increase in methylation at gene promoters.

DNA methylation patterns change dynamically in early embryogenesis, when CpG methylation is essential for X-inactivation and the selective expression of imprinted genes. 5mC constitutes approximately 1% of all DNA bases and is found almost exclusively as methylation of the dinucleotide CpG. The majority of methylated CpGs are found in repetitive DNA elements, suggesting that cytosine methylation evolved as a defense against transposons and other parasitic elements. This evidence has led some to theorize that global DNA methylation may be the first line of defense of the genome against environmental insult. In somatic cells, promoter hypermethylation often shows a correlation with

downregulated gene expression. Two scenarios have been proposed to describe how gene silencing can result from promoter hypermethylation: CpG promoter methylation either directly interferes with the binding of transcriptional regulators to their DNA sequences or enables recruitment of methyl-CpG binding proteins which create a repressed chromatin environment.

Cellular differentiation is dependent on 5mC motifs, the alteration of which leads to phenotypic variation, pathway alterations and physiological effects. Because the cells of a given individual are genetically homogeneous, epigenetic processes are critical to regulate the phenotype of a given cell according to its specific role at a particular stage of development. Consequently, exposures to different environmental agents *in utero* and in childhood may influence life-course susceptibility to chronic disease via epigenomic alterations, without having any effect on genomic sequence whatsoever. Some epigenomic alterations will be fixed and maintained from birth to death, while others will be transient adaptive changes to a variety of environmental stressors and personal lifestyle, and still other alterations will be the result of age-related epigenomic reprogramming.

Therefore, while we have one genome, we have several dynamic epigenomic profiles, as our epigenome is reprogrammed repeatedly beginning *in utero*, influenced by environmental exposures and endogenous factors. The gatekeeper for this life-long epigenome–environment interaction may be global DNA methylation changes, because they are thought to be the first nontransient tissue- and exposure-specific epigenomic changes to occur in response to outside stimuli. Therefore, it appears that global DNA methylation levels undergo adaptive changes throughout the life course in response to environmental stressors, lifestyle impacts and age-related effects – all of which may impact disease susceptibility in tandem with or independent of genetic susceptibility to disease [7].

Global DNA methylation profiles: a footprint of health & disease pathways

DNA hypomethylation is associated with genomic instability and subsequent tumor development through the deregulation of transposable elements, pericentromeric regions, or activation of endoparasitic sequences [8]. To a lesser extent, DNA hypomethylation also impacts growth regulatory genes, imprinted genes, developmentally critical genes, genes regulated by transposable elements and tissue-specific genes, such as germline-specific tumor antigen genes [9]. DNA hypomethylation patterns represent footprints of transcription factor activities, and therefore are indicative of active cellular pathways. Global DNA hypomethylation profiles can thus be used as prognostic indicators of disease, or as predictive markers of sensitivity or resistance to particular therapies or environmental exposures [10].

Alterations in both global and gene-specific DNA methylation have been linked to exposure to metals, peroxisome proliferators, air pollutants, endocrine-disrupting/reproductive toxicants, diet, maternal behavior, viruses, bacteria, simulated-microgravity exposure, metabolic imprinting and stress [11]. Most of these changes are associated with global DNA hypomethylation changes in separate body compartments or biofluids, in some cases, passed down to future generations [12].

More closely associated with the early onset of disease hypothesis, global DNA hypomethylation in cord blood DNA has been linked to *in utero* exposure to cigarette smoke, polycyclic aromatic hydrocarbons, lead and polyfluoroalkyl compounds [13]. These initial findings are laying the groundwork for future life-course epigenomic monitoring projects that will eventually provide us with the molecular footprints of health and disease using global DNA methylation as a biodosimeter of environmental exposures. However, until we are able to use deep and single molecule sequencing technologies to map tissue- and exposure-specific genomic locations of methylation loss, global DNA methylation signatures by themselves will remain nonspecific footprints of cellular disruption and varied exposure scenarios.

Global DNA methylation: both mechanism & phenotype in health & disease

Global DNA methylation can be either an epigenomic driver of phenotypic variation or an epigenomic passenger mark of adaptive responses to the micro- and macro-environment [14]. Gene-expression alterations and signaling pathway disruptions linked to global DNA hypomethylation changes, induced by prenatal exposures, may underlie some of the currently observed fetal and neonatal conditions. Global DNA methylation alterations, acting as a mechanistic driver, may in turn set the stage for a life course of predisposition to and increased risk of disease under the influence of environmental triggers and stressors.

Global DNA hypomethylation occurs mostly as the loss of methylation in CpG rich areas of the genome, such as satellites SAT2 and SAT3, and interspersed repeat sequences, such as long interspersed elements (LINEs), short interspersed elements and long-terminal containing repeats. Approximately 30% of the transcriptome is controlled by CpG rich areas outside of the gene promoter regions: the repetitive elements LINEs, short interspersed elements and long-terminal containing repeats [15]. More importantly, hypomethylation of retrotransposons was recently demonstrated for the first time to cause altered gene expression in humans and induce alternative transcripts in cancer [16]. Thus, it now seems that differential methylation of repetitive elements, once referred to as junk DNA or noncoding areas of the genome, can alter the functional transcriptome and could play a role in driving pathogenesis and disease predisposition.

Global DNA methylation changes may also be evolution-conserved adaptive responses that maintain homeostasis and assure cell survival in the face of threatening and noxious environmental stimuli. Adaptive changes in global patterns of differential DNA methylation variability at specific genetic loci can also result from inherited genetic variants that predispose demethylating phenotypes with selective advantages [17]. Global DNA methylation, as a passenger mark now, may be a phenotype of the stochastic adaptation to repeated exposures to environmental stressors, which would select for epigenetic heterogeneity, and thus the ability of cells to grow outside of their normal milieu [18]. Therefore, changes in global DNA methylation content may explain the phenotypic variation described by both Darwinian selection forces and Lamarckian evolution development [19].

Wireless dashboards for life-course biomonitoring of environmental exposures

The dual nature of global DNA methylation as both a driver and passenger of environmentally-driven phenotypic variation and heterogeneity provides the dynamic functional range needed for a potential life-course epigenomic biodosimeter of the exposome. However, several hurdles still need to be overcome in terms of which technologies are best suited to quantify global DNA methylation and how to best interpret the results provided by them, particularly when measured in different tissues, bodily fluids and body compartments. The importance of standardizing methods to quantify and interpret global DNA hypomethylation data is illustrated by the renewed interest in Alu and LINE-1 quantification. There has been a recent flurry of publications that examine the determinants of global DNA hypomethylation alterations, most using differential methylation in Alu, Sat2 and LINE-1 repetitive elements, as surrogate markers of global methylation status. Although the hypomethylation of centromeric and pericentromeric tandem repeats can be coassociated, sometimes one of these types of repeats is hypomethylated and the other is not [20]. As the body of work on these two markers accumulates, it is becoming apparent that using LINE-1 and Alu as surrogate measure of global DNA methylation across the genome often provides contradictory and confusing information for health studies. Therefore, before measures of global DNA methylation can inform public health in a substantial way, more research is needed to form an evidence-based scientific consensus regarding the interpretation of these measures.

Once validated, epigenomic biomonitors of the exposome have the possibility of transforming medicine and public health. Individual and population epigenomic data streams can be coupled with environmental information to provide a better understanding of the exposome making use of mobile- and web-based technologies to facilitate biomonitor discovery and validation. Devices and applications with which to readily quantify an individual epigenome and remotely compare several epigenomes will allow us to better manage the exposome. Thus, we are moving towards a confluence of epigenomic and telecommunications technologies that can be used to empower both individuals and communities, while providing medical and public health professionals with data that will transform the way in which we experience and manage health and disease.

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Biographies

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Bibliography

1. Wild CP. Complementing the genome with an ‘exposome’: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol. Biomarkers Prev. 2005; 14(8):1847–1850. [PubMed: 16103423]
2. Herceg Z. Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. Mutagenesis. 2007; 22(2):91–103. [PubMed: 17284773]
3. Portela A, Esteller M. Epigenetic modifications and human disease. Nat. Biotechnol. 2010; 28(10): 1057–1068. [PubMed: 20944598]
4. Berdasco M, Esteller M. Aberrant epigenetic landscape in cancer: how cellular identity goes awry. Dev. Cell. 2010; 19(5):698–711. [PubMed: 21074720]
5. Brown SE, Fraga MF, Weaver IC, Berdasco M, Szyf M. Variations in DNA methylation patterns during the cell cycle of HeLa cells. Epigenetics. 2007; 2(1):54–65. [PubMed: 17965591]
6. Gluckman PD, Hanson MA, Mitchell MD. Developmental origins of health and disease: reducing the burden of chronic disease in the next generation. Genome Med. 2010; 2(2):14. [PubMed: 20236494]
7. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of *in utero* and early-life conditions on adult health and disease. N. Engl. J. Med. 2008; 359(1):61–73. [PubMed: 18596274]
8. Ehrlich M. DNA methylation in cancer: too much, but also too little. Oncogene. 2002; 21(35):5400–5413. [PubMed: 12154403]
9. Kulis M, Esteller M. DNA methylation and cancer. Adv. Genet. 2010; 70:27–56. [PubMed: 20920744]
10. De Smet C, Loriot A. DNA hypomethylation in cancer: epigenetic scars of a neoplastic journey. Epigenetics. 2010; 5(3):206–213. [PubMed: 20305381]

11. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Curr. Opin. Pediatr. 2009; 21(2):243–251. [PubMed: 19663042]
12. Hochberg Z, Feil R, Constancia M, et al. Child health, developmental plasticity, and epigenetic programming. Endocr. Rev. 2010 (Epub ahead of print).
13. Guerrero-Preston R, Goldman LR, Brebi-Mieville P, et al. Global DNA hypomethylation is associated with *in utero* exposure to cotinine and perfluorinated alkyl compounds. Epigenetics. 2010; 5(6) (Epub ahead of print).
14. Kalari S, Pfeifer GP. Identification of driver and passenger DNA methylation in cancer by epigenomic analysis. Adv. Genet. 2010; 70:277–308. [PubMed: 20920752]
15. Faulkner GJ, Kimura Y, Daub CO, et al. The regulated retrotransposon transcriptome of mammalian cells. Nat. Genet. 2009; 41(5):563–571. [PubMed: 19377475]
16. Wolff EM, Byun HM, Han HF, et al. Hypomethylation of a LINE-1 promoter activates an alternate transcript of the MET oncogene in bladders with cancer. PLoS Genet. 2010; 6(4):e1000917. [PubMed: 20421991]
17. Feinberg AP, Irizarry RA. Evolution in health and medicine Sackler colloquium: stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease. Proc. Natl Acad. Sci. USA. 2010; 107(Suppl. 1):1757–1764. [PubMed: 20080672]
18. Feinberg AP, Irizarry RA, Fradin D, et al. Personalized epigenomic signatures that are stable over time and covary with body mass index. Sci. Transl. Med. 2010; 2(49):49ra67.
19. Handel AE, Ramagopalan SV. Is Lamarckian evolution relevant to medicine? BMC Med. Genet. 2010; 11:73. [PubMed: 20465829]
20. Ehrlich M. DNA hypomethylation in cancer cells. Epigenomics. 2009; 1(2):239–259. [PubMed: 20495664]