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Perspectives

Environmental epigenomics and the human imprintome

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Abstract

Genomic imprinting is a phenomenon in which one parental allele is silenced epigenetically. My research has focused on the role of epigenetics in human health and disease since 1995 when we identified the first tumor suppressor gene that is also imprinted, the *IGF2R*. Subsequently, by using the agouti viable yellow (A^{vy}) mouse model, we demonstrated that increased maternal dietary exposure to methyl donors *in utero* altered offspring phenotype in adulthood by modifying the epigenome, providing a plausible mechanism for the developmental origins of health and disease (DOHaD). Consequently, the field of epigenetics can be thought of as the "science of hope," since personal changes in diet and physical activity can potentially alter the epigenome to prevent chronic disease formation, and potentially, even ameliorate the negative effects of environmental exposures to chemical and physical toxicants. In this perspectives article, I address a series of questions posed about the field of environmental epigenetics, and discuss the role that the environmentally labile *cis*-acting, imprint regulatory elements in the human genome (i.e. the human imprintome) and the correlated regions of systemic interindividual variation (CoRSIVs) play in disease formation and behavioral development.

Keywords: chronic diseases; CoRSIVs; DOHaD; epigenetics; genomic imprinting; imprintome; radiation hormesis

Introduction

At the turn of the millennium, three epigenetic papers were particularly instrumental in ushering in the era of environmental epigenomics [1]. Firstly, in 2003, the agouti mouse study demonstrated that maternal dietary methyl supplementation (i.e. folic acid, vitamin B12, choline, and betaine) significantly increased the number of healthy, brown offspring by altering the epigenome at the A^{vy} locus [2]. This finding provided a plausible mechanism to explain how environmental exposures of the developing embryo could alter disease susceptibility in adulthood. Secondly, in 2004, postnatal maternal licking and grooming behavior in rats was shown to produce in the offspring stable DNA methylation and chromatin structure alterations in the promoter of the glucocorticoid receptor, *Nr3c1*, in the hippocampus of the brain [3]. This provided a mechanism for the long-term effects of postnatal maternal care on gene expression and behavior in the offspring. Thirdly, in 2005, evidence was provided that the endocrine-disrupting agents vinclozolin and methoxychlor induce transgenerationally inherited alterations that lead to decreased male fertility and spermatogenic capacity by reprogramming the male germ line epigenetically [4].

The results of these pioneering investigations demonstrated, for the first time, that both prenatal and postnatal exposures to environmental factors can alter offspring phenotype and adult disease susceptibility through alterations in the epigenome, and potentially, result in epigenetic transgenerational germline inheritance. Thus, two decades ago, the era of "environmental epigenomics" was ushered into the consciousness of both scientists and the general public.

The first time this term was used was at a joint NIEHS/Duke University conference that Fred Tyson and I co-organized at the Washington Duke Inn in Durham, NC in November of 2005 (Fig. 1). Collin Murphy (https://fineartamerica.com/profiles/collin-murphy?tab=artwork&page=1) painted the poster entitled, *Origins*, that was used for the conference (Fig. 1A). It shows that different environmental exposures in the womb can result in genetically identical twins developing different phenotypes as adults. Over 400 scientists and reporters from 14 countries attended the meeting (Fig. 1B), and I think of this event as being the "Woodstock" gathering for this field of research. Fortunately, the scientific presentations from this historically important conference can still be viewed at https://www.geneimprint.com/site/meetings/2005-durham.

I became interested in epigenetics research in the early 1990s after our discovery that *IGF2R* functions as a human tumor suppressor gene [5, 6]. Interestingly, the mouse *Igf2r* is also imprinted and expressed only from the maternal allele; the paternal copy being silenced epigenetically [7]. As a consequence, we had identified the first imprinted tumor suppressor gene, although imprinting of this gene is not as clearly defined in humans as in mice [8]. The startling discovery that genes involved in suppressing tumor formation could be functionally haploid due to parental dependent, epigenetic silencing initiated my research career in the field of epigenetics and genomic imprinting. Because of my historical

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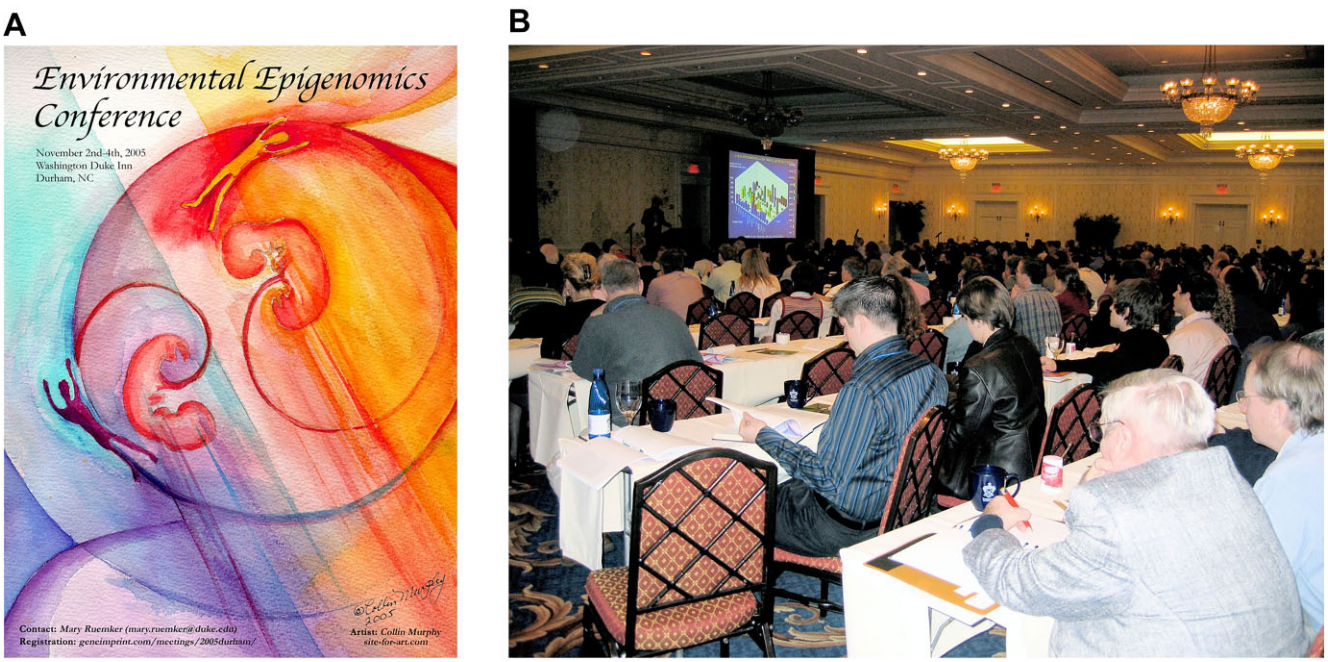

Figure 1. Environmental Epigenomics Conference, Washington Duke Inn, Durham, NC: (A) conference poster; (B) attendees.

perspective on the field of epigenetics and the importance of our research discoveries in this field of research, I was asked to address the following questions.

What major observations have been made by you or others that have helped establish the field of epigenetics and environmental epigenetics?

Since over 17 000 papers were published last year alone in the field of epigenetics, I am only going to describe our research in answering this question. We have made major contributions to the field of environmental epigenomics using two epigenetically labile subsets of genes that link embryonic environmental exposures with adult disease susceptibility—metastable epialleles and imprinted genes (see review [8]).

Metastable epiallele studies

Nutritional exposure

The *agouti* gene in A^{vy} mice is a metastable epiallele, and its expression is highly variable between individuals, but uniform in tissues within an individual since the marks are established early before the initiation of cellular differentiation. We used the A^{vy} mouse to determine if maternal exposure to methyl donor supplements (i.e. folic acid, choline, vitamin B_{12}, and betaine) during embryogenesis significantly increased the incidence of brown healthy offspring by altering the epigenome (Fig. 2). This study provided the first plausible molecular mechanism for the developmental origins of health and disease hypothesis (DOHaD), and has been cited over 2600 times since its publication in 2003 (https://scholar.google.com/citations?user=4MlaQoAAAAAJ&hl=en&oi=ao).

Genistein is a major phytoestrogen in soy linked to the chemoprevention of cancer, neurodegenerative disorders, cardiovascular diseases, and obesity [9]. Maternal A^{vy} mouse dietary genistein supplementation during gestation also shifted the coat color of the A^{vy}/a offspring toward the healthy brown by increasing DNA methylation at the A^{vy} locus (Fig. 2) [10]. This was the first evidence that *in utero* dietary genistein affects gene expression, and alters susceptibility to obesity in adulthood by permanently altering the epigenome, even though it does not contain a methyl group.

Endocrine disruptor exposure

Bisphenol A (BPA) is a chemical used in the manufacture of polycarbonate plastic, epoxy resin, and other polymer materials. It is an endocrine disruptor associated with higher body weight, increased breast and prostate cancer, and altered reproductive function [11]. Maternal exposure of A^{vy} mice to BPA shifted the coat color in the offspring to the unhealthy yellow, obese animals by decreasing DNA methylation at the IAP of the A^{vy} locus, providing evidence that BPA causes negative epigenetic patterning during early stem cell development (Fig. 2) [12]. Moreover, maternal dietary supplementation, with either methyl donors or the phytoestrogen genistein, blocked the negative DNA hypomethylating effect of BPA. These results indicate that early developmental exposure of A^{vy} mice to BPA increases offspring disease susceptibility by altering the epigenome, an effect that can be counteracted by maternal dietary supplements. Thus, as Hippocrates emphasized over two millennia ago, food is medicine!

Ionizing radiation exposure

The majority of human exposures occur in the low-dose range (i.e. <10 cGy). We demonstrated that maternal low-dose ionizing radiation (LDIR) exposure of the A^{vy} mouse at the time of implantation (i.e. gestational day 4.5) causes positive adaptive changes in the offspring by significantly increasing DNA methylation at the A^{vy} locus [13]. Maximum adaptive effects occurred at 3 cGy, and the offspring coat color was shifted toward the healthy brown

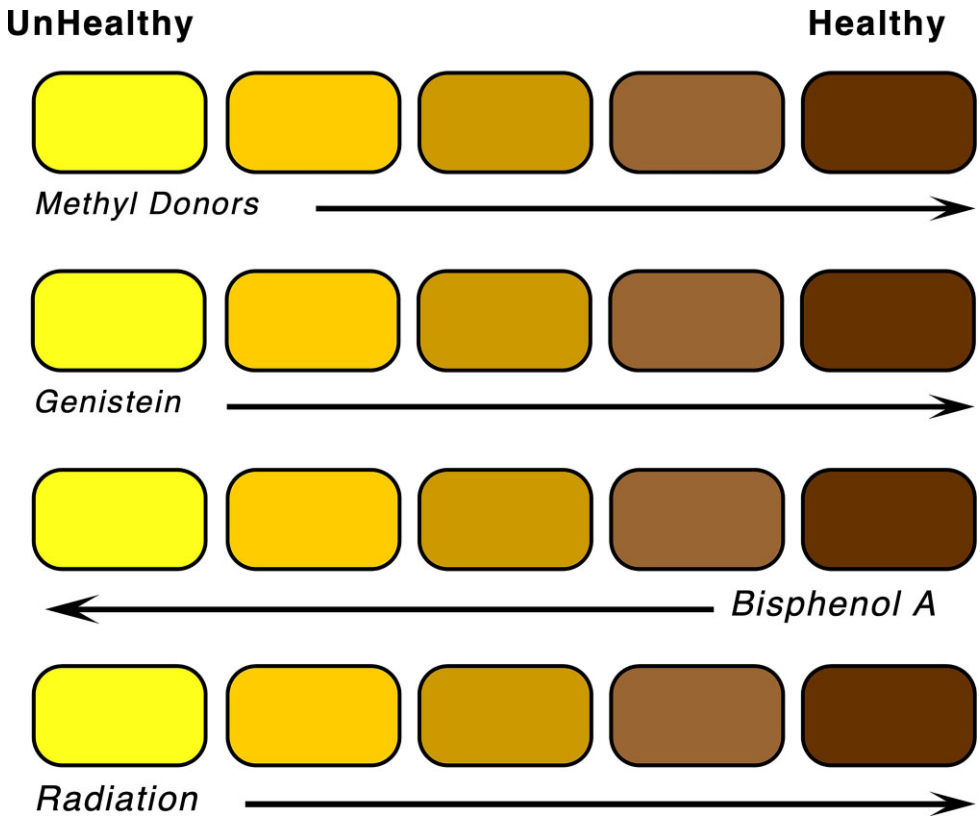

Figure 2. Agouti mouse studies. Average coat color of A^{vy} mouse offspring range from yellow (unhealthy) to brown (healthy) after *in utero* exposure to methyl donors, genistein, bisphenol A, and ionizing radiation. The arrow depicts whether the environmental exposure results in the offspring being more or less healthy.

(Fig. 2). This phenotypic coat color response is linked to reduced obesity, diabetes, and cancer in the A^{vy} mouse. Interestingly, maternal dietary antioxidant supplementation mitigates both the DNA methylation changes and coat color shift induced in the offspring exposed to LDIR, indicating that these positive adaptive effects are mediated, in part, by oxidative stress. Thus, LDIR exposure of A^{vy} mice *in utero* results in the offspring being healthier than those that are not exposed to radiation.

The phenomenon that occurs when an environmental factor that is toxic at high doses stimulates a beneficial adaptive response in an organism at low doses is called hormesis, a Greek word meaning "to excite" (see reviews [8, 14]). Our A^{vy} mouse study used low-energy transfer (LET) radiation (i.e. X-rays); however, there is evidence that this natural protective system may be dependent on the LET of the radiation modality [15, 16].

The beneficial health effects of LDIR have been successfully exploited for centuries in the use of radon springs to treat arthritis and other diseases [17]. In the first half of the twentieth century, LDIR was also successfully used in the treatment of a large range of diseases, including arthritis, asthma, boils, cancer, carbuncles, deafness, gas gangrene, inflamed adenoids, inner ear infections, pertussis, pneumonia, sinusitis, and tendonitis (see reviews [17, 18]).

LDIR therapeutic studies have since been curtailed following the US National Academy of Sciences' recommendation of the linear no threshold (LNT) model for radiation risk assessment that postulates there is no safe dose of radiation [19]. If ionizing radiation only caused genetic mutations, the LNT model and its postulates would be correct; however, LDIR also modifies the epigenome—the cellular programs that tell the genes when, where, and how to work—resulting in the positive adaptive biological responses observed by us [13] and others (see reviews [14, 16, 20]). Consequently, scientists are now attempting to use the biological phenomenon of hormesis to enhance biological performance, resilience, and health by leveraging the body's natural adaptive responses to mild stressors [21].

Imprinted gene studies

Genomic imprinting is a unique species-dependent, epigenetic form of gene regulation that evolved ~150 million years ago in a common ancestor to Therian mammals (see review [8]). It results in monoallelic, parent-of-origin dependent gene silencing. Thus, imprinted genes are functionally haploid disease susceptibility loci, since only a single genetic or epigenetic event is required to alter their function. Expression of imprinted genes in the human genome is regulated by *cis*-acting, differentially methylated imprint control regions (ICRs) in the human imprintome [22, 23]. Furthermore, the dysregulation of DNA methylation in ICRs associated with chronic diseases (e.g. cancer, diabetes, and obesity) and behavioral disorders (e.g. autism, bipolar disorder, psychopathy, and schizophrenia) can now be determined using the human imprintome array [24]. The potential importance of the ICRs that control imprinted genes and the correlated regions of systemic interindividual variation (CoRSIVs) that regulate metastable epialleles [25] in the genesis of environmentally induced human chronic diseases and behavioral disorders are discussed in greater detail previously [1, 8].

What major obstacles have slowed or hindered the development of the field of epigenetics or environmental epigenetics?

A major limitation for environmental epigenetic studies initially was not knowing the human ICRs [22] and CoRSIVs [25] that control the expression of imprinted genes and metastable epialleles, respectively. CoRSIVs have been identified not only in mice (e.g. A^{vy} locus [26], the *Axin*^{Fu} gene [27], and *Cabp*^{IAP} gene [28]), but also in cattle [29] and human [25, 30, 31], indicating that these systemic epigenetic variants are common in mammals. ICRs and CoRSIVs are regulatory regions influenced by DNA methylation that mediate how early-life environments (e.g. maternal nutrition, toxins, and stress) can influence stable methylation patterns in the offspring that persist throughout life, affecting phenotypic variation and disease risk. Moreover, the DNA methylation of the CpG sites in both of these two sets of gene regulatory regions does not vary significantly between tissues in an individual, even though CoRSIVs expression can vary greatly between individuals, since they are established early in development before cellular differentiation. This results in both ICRs and CoRSIVs being useful in assessing epigenetic changes in tissues that are not accessible for epidemiological studies (e.g. brain) by using samples that are accessible (e.g. blood white cells, buccal cells, etc.).

Another obstacle to performing environmental epigenetic studies is the limited availability of human prospective epidemiological data sets designed specifically to identify early exposures associated with stable epigenetic alterations that may alter chronic disease susceptibility later in life. To address this limitation in our research group, Cathrine Hoyo has established two novel human prospective cohort studies. The Newborn Epigenetic Study (NEST) is a prospective study of women and their children designed to identify early exposures associated with stable epigenetic alterations in infants that may alter chronic disease susceptibility later in life [32]. The Southern Liver Health Study (STRIVE) is an ongoing multi-center prospective longitudinal observational study investigating the role of environmental exposures on liver disease formation [33]. More human cohort studies like NEST and STRIVE are needed, especially those that take into account that environmentally induced epigenetic changes can potentially be inherited transgenerationally [34].

Determining the role of genomic imprinting in metabolic diseases and developmental and behavioral disorders ultimately required that the complete repertoire of human imprinted genes and their ICRs to be defined. The gICRs refer to DNA methylation marks established in the germline (i.e. sperm and oocyte) that are parent-of-origin specific. They are maintained post-fertilization and throughout development, and regulate monoallelic expression of imprinted genes across various cell types and tissues in healthy individuals [35]. In contrast, somatic ICRs (sICRs) are parent-of-origin specific DNA methylation marks that are established after fertilization, and can vary across different tissues. A significant problem in environmental epigenomic studies is the inherent variability of epigenetic marks involved in cell-type differentiation, complicating the interpretation of findings when using the cell types normally available in human population studies (i.e. peripheral blood lymphocytes, umbilical cord blood, and buccal epithelial cells). Thus, the gICRs—which are ~50% methylated unless altered by environmental factors during gamete formation and/or during early development when the gICRs are normally protected from the global demethylation that occurs soon after fertilization—can be used as biosensors for early epigenetic changes in inaccessible tissues of interest (e.g. brain) with the use of cell types available in human environmental epigenomics studies [36].

Characterizing a gene as being monoallelically expressed in a parent-of-origin dependent manner, while doable with next generation RNA-seq techniques [37], is still a daunting task, particularly in humans. Not only do imprinted genes vary between species [38, 39], but the monoallelic expression of imprinted genes is often sex, tissue, and developmental stage specific [40–42]. This requires sampling of the correct tissue or cell type at the right developmental stage, which is especially difficult in humans. Moreover, the development of species-specific ICRs during mammalian evolution may have influenced neurodevelopment, potentially making it difficult to use animal models to investigate the role of imprinted gene dysregulation in the pathogenesis of human behavioral disorders [39, 43, 44].

What recent observations have been made that you feel are critical and help facilitate the development of the field?

IGF2 is imprinted and expressed exclusively from the paternal allele in both mouse [45] and human [46]. It is also the first imprinted gene shown to display loss of imprinting (LOI) in human cancer [47, 48]. LOI occurred not only in colon cancer tissues, but importantly, also in matched normal tissues and peripheral blood cells [48]. Furthermore, LOI at the *Igf2* locus in the Apc$^{Min/+}$ mouse, which contains a mutation found in human colorectal cancers [49], significantly increased the incidence of intestinal tumors [50]. This demonstrates that *IGF2* functions as a tumor oncogene.

LOI at a number of imprinted loci has been identified in both juvenile [51] and adult cancers [48, 52], with it most commonly occurring at the *H19/IGF2* locus [48]. The human imprintome [22] can now be used to readily screen any tumor type and its surrounding normal tissue for LOI in gICRs. Such studies are further facilitated with the development of the human imprintome array [24]. The detection of additional ICRs that have LOI in a number of tumor types and their surrounding normal tissues could provide novel epigenetic targets for both cancer detection and treatment.

What major unanswered questions or topics need to be addressed to provide major advances in the fields of epigenetics and environmental epigenetics?

Environmental factors such as alcohol, assisted reproduction, endocrine disruptors, exposure to smoking, heavy metals, maternal nutrition, and stress, and perinatal complications can all alter imprinted gene expression (see reviews [53–57]). Since imprinted genes control pathways in stress regulation, emotional bonding, and social behavior (see reviews [58, 59]), their dysregulation potentially provides a mechanistic link between the environment and neurobehavioral disorders, such as psychopathy.

Psychopathy is an antisocial behavioral condition characterized by grandiosity, callousness, and manipulativeness, coupled with a lack of remorse, guilt, and empathy (see reviews [60–62]). The presence of these psychopathic behaviors in people often results in poor academic achievement, criminality, and significant behavioral problems. Psychopathy prevalence is ~1% in the general population [63, 64], 3% in the forensic population [65], 4% among corporate managers [66], and 20% in the prison population [67]. Psychopathy occurs in both males and females, but it is more prevalent in males [68]. Psychopaths have higher rates of

crime, recidivism, and resistance to treatment [62]. The estimated annual cost associated with psychopathy in the USA in 2009 was ~$460 billion [62]; and in 2023, it was estimated to approach a staggering $1.6 trillion annually [69]. Thus, psychopathy represents a formidable therapeutic challenge for the mental health and criminal justice systems [61].

A landmark fMRI study by Kent Kiehl [70] demonstrated that the affective abnormalities observed in psychopaths are linked to deficient input from the limbic structures in the brain; however, the molecular changes responsible for these neural response deficits remain largely unknown. Twin studies demonstrate that psychopathy is highly heritable [71–75], but genetic variation in only a few genes has been linked to psychopathy, including *MAOA*, *5HTT*, *COMT*, *SLC6A4*, and *DRD4* [22, 76–78]. More recently, *HTR1B*, a gene we predict to be imprinted [22], was also associated with psychopathic behavior [79].

Thus, it is important to screen the human imprintome for additional ICRs that are significantly epigenetically dysregulated in psychopaths to facilitate their identification and improve their treatment. Such studies may also help identify imprinted genes involved in the development of human empathy. This fundamental behavioral characteristic is postulated to enable humans to possess the unique ability to share extensively between unrelated individuals [80, 81], potentially allowing *Homo sapiens* to become the last surviving hominin on Earth [82].

What is your perspective on the future of the field of environmental epigenetics in biology, medicine, and molecular sciences?

With the identification of the human imprintome [22] and CoRSIVs [25], the development of the human imprintome array [24], and the ability to now perform superior high-throughput DNA methylation sequencing [83–85], I believe we are, as Winston Churchill stated, at the "end of the beginning" of the era of environmental epigenetics research. In the future, we should quite readily be able to determine the importance of ICRs and CoRSIVs in the pathogenesis of all chronic diseases and behavioral disorders that plague humans.

Author contributions

Randy Jirtle (Conceptualization [lead], Funding acquisition [lead], Validation [lead], Visualization [lead], Writing—original draft [lead], Writing—review & editing [lead])

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Data availability

NA.

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