Commentary

Everyday Epigenetics: From Molecular Intervention to Public Health and Lifestyle Medicine

Martha R. Herbert, MD, PhD*

Department of Neurology, Massachusetts General Hospital, Charlestown, MA

Epigenetics, which refers to changes in which genes are turned on or off rather than to the genetic code itself, helps us understand that we have much more power over our health and well-being than we could have imagined when everything was thought to be determined by our genes. Although it is possible to design drugs to impact genetics, the path to truly proving safety and efficacy is long. Meanwhile, right now we can change our epigenetics through everyday choices such as eating high nutrient density food; avoiding junk food, allergens, toxicants and infections; getting plenty of exercise and sleep; minimizing stress; and nurturing each other better. These evolutionarily tried and true approaches have documented impacts on epigenetics. They can help us avoid disease, reduce disease severity and promote recovery. The serious chronic illnesses such as obesity, diabetes, autism and cancer can all be impacted greatly by addressing epigenetics through presently available everyday changes. Public health and economics as well as each person's desire for the best possible life all dictate that we promote these affordable and practical everyday epigenetic interventions.

We are moving from the age of genes into the era of epigenetics. This means that we are recognizing that even with the same set of genes – the same set of genetic coding – there are many different options for how things turn out, because there are many ways that influence how genetic code is expressed, spliced, or not expressed. Now more than ever we know it is not solely our genes that determine our bodies, brains and health – many other factors contribute as well.

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BACKGROUND

The emergence of epigenetics is opening up remarkable new avenues of investigation and insight into disease mechanisms. It is giving us more ways to articulate the specific ways that genes and environment might interact to influence development and health. It is also opening the way to fresh ideas about health promotion.

Indeed we have come a long way from the not-so-long ago days of the "central dogma" of genetics. This was the idea that there is a one-way street from DNA to RNA to protein. , It was accompanied by the expectation that we would find the causes of disease in a small number of genes each of high impact. Now we know that there are hundreds of mostly low impact genes involved in the major chronic illnesses, that there are many different ways of having even single-gene mutation disorders, and that we are dealing with networks where influence runs in many directions.

The term epigenetics refers to alterations in gene expression - from embryo to fetus to infant, child and adult - and it also which genes are turned on and which turned off. Gene expression is different at different phases in development - differs from one tissue type or organ to another. But epigenetics is also modified in further ways, many of which are just being discovered or fleshed out. On this account, epigenetics does not at present have a standard definition, though several processes are prominently associated with it, including DNA methylation, histone modification, non-coding RNAs and microRNAs. Another way that the same DNA code can result in different proteins is alternative splicing, which generates protein diversity by utilizing and omitting different parts of the genetic code in generating proteins; this was previously thought to impact a small percentage of the human genome but today is known to affect the vast bulk of it. It also turns out that non-coding DNA - DNA that does not code for protein, that some call "dark matter," can code for non-coding RNA which is also implicated in epigenetics; embarrassingly non-coding DNA used to be presumptuously called "junk DNA" as if it couldn't possibly be doing anything if it weren't coding for DNA - whereas in fact it increases hugely in evolution as organisms become more complex, and is highly functional.

Does epigenetics bring us closer to treatments that will really make a difference in autism? Actually, the answer is probably yes. But are these novel treatments? At the

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*__Corresponding Author:__ MGH, TRANSCEND/Pediatric Neurology, Room 10.043, 149 13th Street, Charlestown MA 02129. Tel: 617-724-5920. (Email: mherbert1@partners.org)

moment, the main thing about the near-at-hand treatments that can impact health and improve the lives of people with autism is not that they are novel, but that we now have novel explanations for treatments that have been around for a long time. Many of these treatments are inexpensive and widely applicable.

Therefore in this commentary I would like to consider the newly appreciated epigenetic dimensions of some old standby interventions and lifestyle modifications. This leads to the critical translational and transformational question: can this new scientific plausibility allow us to finally get funding and policy support for implementing them in a large scale public health program? They are presently available and could make a large difference to huge numbers of people.

EPIGENETICS: WHEN?

In epigenetic discourse in autism there has been a great deal of emphasis on prenatal contributors to epigenetic change. Prenatal stress, infection during pregnancy, exposure to toxicants, electromagnetic frequencies and prenatal nutrition – these are some of the main factors that may contribute to epigenetic alterations with consequences that may persist far into the lifespan.

However many kinds of postnatal exposures and experiences may also shape the ways that epigenetic modifications occur. This is very important because it means that our personal choices matter, and that opportunities still exist to significantly influence development even after the extremely vulnerable and malleable period of gestation is over.

EVERYDAY EPIGENETICS

Here are some of the levels at which mundane, everyday experiences may influence epigenetics.

Diet

A wealth of literature links diet to epigenetics in the postnatal as well as prenatal and preconceptional periods.

- *Macronutrients:* An imbalance or poor quality of macronutrients can contribute to pressures that may alter epigenetics. Imbalances may include low nutrient density, low quality, high glycemic index carbohydrates such as sugar and high fructose corn syrup. It may also include an excess of trans-fats and an insufficiency of essential fatty acids as well as an overly high omega 6: omega 3 fatty acid ratio. Proteins may not contain an appropriate balance of essential amino acids, or there may be problems or interference with intestinal absorption of critical amino acids such as cysteine.[1]

- *Micronutrients:* Deficiencies or insufficiencies of various critical micronutrients are common in ASDs and many of these are associated with epigenetic change. For example, folate is quite involved in epigenetics,[2] and particularly in the setting of lack of prenatal vitamins or food fortification, can increase autism risk.[3-5] Zinc, often low in ASDs,[6] is necessary for many neurological and systemic processes; its insufficiency can lead to many problems including compromised immune function, problems with wound healing, faulty DNA damage repair, increased oxidative stress and epigenetic regulation of neuronal cells. Vitamin D is also known to have epigenetic influences[7] with improvement when deficiencies are overcome.

- *One-carbon metabolism:* The establishment and maintenance of DNA methylation is critically supported by one-carbon metabolism, which can be impaired by mutations that are fairly common in the general population but more common in ASD and family members of individuals with ASD as well as with various other chronic conditions.[8] It can also be supported by the presence of adequate precursors in the diet such as usable forms of folate, or impaired by the lack thereof.

- *Intermediary metabolites:* Dietary substances can be converted into intermediary metabolites that can modulate HDAC (histone deacetylase) activity. These include short-chain fatty acids, seleno-alpha-keto acids, small molecule thiols, mercapturic acid metabolites, indoles, and polyphenols.[9] Different types of food intake may impact HDAC, and hence epigenetids, in different ways.

Allergens and other immune triggers

Impact of allergens on epigenetics may be mediated by their pro-inflammatory impact, since inflammation has marked epigenetic consequences.[10] Certain substances such as gluten may amplify vulnerability to allergens and other immune triggers by contributing to compromise of the integrity of the intestinal gut-blood barrier, thereby increasing quantity and persistence of exposure to potentially allergenic, pro-inflammatory and incompletely digested exogenous peptides.[11] Such exposures can also promote mast cell activation which can also compromise the blood-brain barrier.[12] This cascade of proinflammatory changes and tissue compromise has great potential for contributing to maladaptive epigenetic change.

Noxious exposures

Toxicants, electromagnetic fields and radiofrequency radiation (EMF/RFR) may alter epigenetics (as well as exert frank genotoxic damage to coding and non-coding DNA[13]). A particularly epigenetically relevant pathway of influence is through inhibition of methylation pathways and inhibition of the synthesis of glutathione.[14,15]

Inadequate or aberrant microbiome

Emerging research is showing both inadequate levels of normal components of the intestinal microbiome and aberrant organisms in ASDs.[16,17] The microbiome is shaped by perinatal exposure to either vaginal or delivery room flora as well as to antibiotics should this transpire. It is also heavily nutritionally conditioned from early infancy.[18] It plays important roles both in production of epigenetically active intermediary metabolites and in immune modulation.[18] The impact of its products on the function of the brain is increasingly being elucidated[19] and these mechanisms may

turn out to include epigenetic components.

Sleep

Sleep is a reparative, restorative process, but it is often compromised in ASDs. Disordered sleep can be both cause and consequence of inflammation, which as mentioned can impact epigenetics. Melatonin, a substance importance to sleep, is commonly compromised in ASDs.[20] Melatonin has epigenetic impacts,[21,22] and it is also important in mitigating mitochondrial dysfunction,[23] which is common in autism spectrum disorders.[24] Mitochondrial bioenergenetics provides an important interface between the environment and the epigenome, with an increasing number of epigenetic diseases being associated with mitochondrial dysfunction. [25]

Stress and Nurture

Some studies have associated stress during pregnancy with increased risk for autism spectrum disorders,[26,27] though others have not. [28] Among the many mechanisms that could mediate this are impacts on steroid metabolism[29] and impacts on oxidative stress. Stress and the quality of co-regulation of infant and care-giver are also shown to have epigenetic impacts.[30,31] A sick, colicy child may elicit less effective nurturance from its mother or caregiver due to its chronic, exhausting intractable discomfort that is not responsive to normal measures available to the mother. This could potentially have negative impacts on both the ability of the mother to nurture and ability of the child to experience being nurtured, with consequent impacts on epigenetics.

Exercise and activity

Many children with ASDs spend their days in cubbies getting behavioral therapy, which may involve frequent use of low-nutrient density high glycemic index food reinforcers in combination with very little exercise. This, in further combination with atypical antipsychotics often associated with marked weight gain and hormonal dysregulation, may produce a situation of obesity, pre-diabetes and inflammation, which is most likely associated with epigenetic changes that increase risk of chronic illness and suboptimal brain function. Institution of a regular exercise regimen may reverse many of the adverse epigenetic impacts of this situation and reduce risk of metabolic dysregulation. Physical exercise is well-known to have positive epigenetic impacts both in the brain, through improved hippocampal function and increased BDNF, and systemically, through damping down of inflammatory pathways. BDNF, in turn, is very important for neuronal development and plasticity.[32]

WHAT'S ON THE HORIZON FOR TARGETED EPIGENETIC INTERVENTIONS?

Drugs intervening in epigenetic processes could theoretically involve pre-emption of molecular or cellular abnormalities before they arise, or reversal of emerging or established abnormalities.[33] However while at present there are a range of pharmaceutical agents that target epigenetically relevant targets, these substances impact a wide range of pathways, and we have hardly begun to evaluate the safety and efficacy. Moreover, such evaluation will be complicated and protracted due to intrinsic concerns with slow to emerge long-term consequences, particularly if the treatments are used early in development. Thus at this point in time we do not have drugs that allow us to target specific epigenetic processes safely and effectively. It may become possible to do this pharmaceutically in the future, but the model of targeting specific epigenetic processes for therapeutic processes remains fraught with risks of unintended additional effects that may cause adverse effects that could be profound.

Meanwhile environmental modulation through presently available lifestyle modification involves evolutionarily tried and true approaches that can significantly shift the baseline for large numbers of people, and remove obstacles that interfere unnecessarily with treatment and progress for affected individuals. Promoting more constructive cellular processes through lifestyle modification such as improving diet, getting plenty of exercise and sleep and avoiding toxins may be a safer approach to impacting epigenetics than molecular targeting.

Moreover given the underlying nutritional, metabolic, microbiome and immune imbalances that are more and more abundantly being documented in the ASDs, we need to be concerned that as people with ASD grow older they may face a markedly increased risk of chronic diseases such as cancer, obesity, diabetes, chronic immune conditions and neurodegenerative diseases. It is no coincidence that the same basic lifestyle modifications discussed above in relation to ASDs are being shown to have preventive power in relation to these other chronic illnesses.

A deeper issue that deserves mention is that the very idea that treatments aimed at specific targets are superior to treatments that have broader impact may be challenged by the power of everyday epigenetics. For example, the transplantation into Rett Syndrome mice of wild-type microglial cells without the MECP2 mutation restored health and neurological function to these mice without targeting specific synaptic deficits.[34,35]

PUBLIC HEALTH AND LIFESTYLE EPIGENETICS CAN BE IMPLEMENTED NOW

At present we already know enough to improve the everyday epigenetics of vast numbers of people. The problem here is not scientific but economic and political. While targeted epigenetic treatments may emerge in the future, and while some of them may turn out to be benign, we do not have to sit on our hands doing nothing while we wait for these clinical trials to proceed (and often fail). For myriad reasons a concerted attempt to improve the baseline everyday epigenetics of the general population, and particularly the at risk populations, is a path that we need to take as soon as possible to reduce the comorbidity patterns and suffering we are facing in autism spectrum disorder as well as many other severe health conditions such as diabetes and obesity where very similar considerations apply. The political and economic programs are spelled out provocatively in a New England Journal of Medicine guest editorial in the fall of 2012 entitled "What's Preventing Us from Preventing Type II Diabetes?"[36] where it is shown that we know how to

prevent a large proportion of the illness on which we are spending $750 billion per year in the US - it would basically require lifestyle coaching in diet and exercise - and yet we do not do it.

It may well take a grass roots epigenetics/lifestyle medicine revolution to shake off the worsening health trends we are facing in the setting of a progressively sicker and more endangered planet. In order to improve our diet, reduce toxins, allergens and infection, reduce stress and increase exercise and sleep and better nurture each other, we not only need to make healthy personal choices but aggregate these together to make healthier social and planetary choices. Let everyday epigenetics inform science of what is possible so that we can respond on an appropriate scale to the magnitude of the crisis we are facing.

CONFLICT OF INTEREST

None.

BIO

Dr. Martha Herbert is author of The Autism Revolution: Whole Body Strategies for Making Life All It Can Be (Harvard Health Publications/Random House, 2012), a neurologist and neuroscientist at the Massachusetts General Hospital/Harvard Medical School, and author of many publications and blogs available at www.marthaherbert.org, www.AutismRevolution.org, www.autismWHYandHOW.org and www.transcendresearch.org.

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