Game-changing research reveals: Epigenetic memories are passed down 14 successive generations

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The past of our ancestors lives on through us: Groundbreaking research illustrates how parental experience is not only epigenetically imprinted onto offspring, but onto an unprecedented number of future generations. Rather than occurring over the elongated time scale of millions of years, genetic change can transpire in real biological time through nanoparticles known as exosomes.

Until recently, it was believed that our genes dictate our destiny. That we are slated for the diseases that will ultimately beset us based upon the pre-wired indecipherable code written in stone in our genetic material. The burgeoning field of epigenetics, however, is overturning these tenets, and ushering in a school of thought where nurture, not nature, is seen to be the predominant influence when it comes to genetic expression and our freedom from or affliction by chronic disease.

Epigenetics: The Demise of Biological Determinism

Epigenetics, or the study of the physiological mechanisms that silence or activate genes, encompasses processes which alter gene function without changing the sequence of nucleotide base pairs in our DNA. Translated literally to mean "in addition to changes in genetic sequence," epigenetics includes processes such as methylation, acetylation, phosphorylation, sumolyation, and ubiquitylation which can be transmitted to daughter cells upon cell division (1). Methylation, for example, is the attachment of simple methyl group tags to DNA molecules, which can repress transcription of a gene when it occurs in the region of a gene promoter. This simple methyl group, or a carbon bound to three hydrogen molecules, effectively turns the gene off.

Post-translational modifications of histone proteins is another epigenetic process. Histones help to package and condense the DNA double helix into the cell nucleus in a complex called

chromatin, which can be modified by enzymes, acetyl groups, and forms of RNA called small interfering RNAs and microRNAs (1). These chemical modifications of chromatin influence its three-dimensional structure, which in turn governs its accessibility for DNA transcription and dictates whether genes are expressed or not.

We inherit one allele, or variant, of each gene from our mother and the other from our father. If the result of epigenetic processes is imprinting, a phenomenon where one of the two alleles of a gene pair is turned off, this can generate a deleterious health outcome if the expressed allele is defective or increases our susceptibility to infections or toxicants (1). Studies link cancers of nearly all types, neurobehavioral and cognitive dysfunction, respiratory illnesses, autoimmune disorders, reproductive anomalies, and cardiovascular disease to epigenetic mechanisms (1). For example, the cardiac antiarrhythmic drug procainamide and the antihypertensive agent hydralazine can cause lupus in some people by causing aberrant patterns of DNA methylation and disrupting signaling pathways (1).

Genes Load the Gun, Environment Pulls the Trigger

Pharmaceuticals, however, are not the only agents that can induce epigenetic disturbances. Whether you were born via vaginal birth or Cesarean section, breastfed or bottle-fed, raised with a pet in the house, or infected with certain childhood illnesses all influence your epigenetic expression. Whether you are sedentary, pray, smoke, mediate, do yoga, have an extensive network of social support or are alienated from your community-all of your lifestyle choices play into your risk for disease operating through mechanisms of epigenetics.

In fact, the Centers for Disease Control (CDC) states that genetics account for only 10% of disease, with the remaining 90% owing to environmental variables (2). An article published in the *Public Library of Science One (PLoS One)* entitled "Genetic factors are not the major causes of chronic diseases" echoes these claims, citing that chronic disease is only 16.4% genetic, and 84.6% environmental (3). These concepts make sense in light of research on the exposome, the cumulative measure of all the environmental insults an individual incurs during their life course that determines susceptibility to disease (4)

In delineating the totality of exposures to which an individual is subjected over their lifetime, the exposome can be subdivided into three overlapping and intertwined domains. One segment of the exposome called the internal environment is comprised of processes innate to the body which impinge on the cellular milieu. This encompasses hormones and other cellular messengers, oxidative stress, inflammation, lipid peroxidation, bodily morphology, the gut microbiota, aging and biochemical stress (5).

Another portion of the exposome, the specific external environment, consists of exposures including pathogens, radiation, chemical contaminants and pollutants, and medical interventions, as well as dietary, lifestyle, and occupational elements (5). At an even broader sociocultural and ecological level is the segment of the exposome called the general external environment, which may circumscribe factors such as psychological stress, socioeconomic status, geopolitical variables, educational attainment, urban or rural residence, and climate (5).

Transgenerational Inheritance of Epigenetic Change: Endocrine Disruptors Trigger Infertility in Future Generations

Scientists formerly speculated that epigenetic changes disappear with each new generation during gametogenesis, the formation of sperm and ovum, and after fertilization. However, this theory was first challenged by research published in the journal *Science* which demonstrated that transient exposure of pregnant rats to the insecticide methoxychlor, an estrogenic compound, or the fungicide vinclozolin, an antiandrogenic compound, resulted in increased incidence of male infertility and decreased sperm production and viability in 90% of the males of four subsequent generations that were tracked (1).

Most notably, these reproductive effects were associated with derangements in DNA methylation patterns in the germ line, suggesting that epigenetic changes are passed on to future generations. The authors concluded, "**The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology**" (6, p. 1466). This may suggest that the endocrine-disrupting, fragrance-laden personal care products and commercial cleaning supplies to which we are all exposed may trigger fertility problems in multiple future generations.

Transgenerational Inheritance of Traumatic Episodes: Parental Experience Shapes Traits of Offspring

In addition, traumatic experiences may be transmitted to future generations via epigenetics as a way to inform progeny about salient information needed for their survival (7). In one study, researchers wafted the cherry-like chemical acetophenone into the chambers of mice while administering electric shocks, conditioning the mice to fear the scent (7). This reaction was passed onto two successive generations, which shuddered significantly more in the presence of acetophenone despite never having encountered it compared to descendants of mice that had not received this conditioning (7).

The study suggests that certain characteristics of the parental sensory environment experienced before conception can remodel the sensory nervous system and neuroanatomy in subsequently conceived generations (7). Alterations in brain structures that process olfactory stimuli were observed, as well as enhanced representation of the receptor that perceives the odor compared to control mice and their progeny (7). These changes were conveyed by epigenetic mechanisms, as illustrated by evidence that the acetophenone-sensing genes in fearful mice were hypomethylated, which may have enhanced expression of odorant-receptor genes during development leading to acetophenone sensitivity (7).

The Human Experience of Famine and Tragedy Spans Generations

The mouse study, which illustrates how germ cells (egg and sperm) exhibit dynamic plasticity and adaptability in response to environmental signals, is mirrored by human studies. For instance, exposures to certain stressors such as starvation during the gestational period are associated with poor health outcomes for offspring. Women who undergo famine before conception of her offspring have been demonstrated to give birth to children with lower self-reported mental health and quality of life, for example (8).

Studies similarly highlight that, "Maternal famine exposure around the time of conception has been related to prevalence of major affective disorders, antisocial personality disorders, schizophrenia, decreased intracranial volume, and congenital abnormalities of the central nervous system" (8). Gestational exposure to the Dutch Famine of the mid-twentieth century is also associated with lower perceived health (9), as well as enhanced incidence of cardiovascular disease, hypertension, and obesity in offspring (8). Maternal undernourishment during pregnancy leads to neonatal adiposity, which is a predictor of future obesity (10), in the grandchildren (11).

The impact of epigenetics is also exemplified by research on the intergenerational effects of trauma, which illuminates that descendants of people who survived the Holocaust exhibit abnormal stress hormone profiles, and low cortisol production in particular (12). Because of their impaired cortisol response and altered stress reactivity, children of Holocaust survivors are often at enhanced risk for post-traumatic stress disorder (PTSD), anxiety, and depression(13).

Intrauterine exposure to maternal stress in the form of intimate partner violence during pregnancy can also lead to changes in the methylation status of the glucocorticoid receptor (GR) of their adolescent offspring (14). These studies suggest that an individual's experience of trauma can predispose their descendants to mental illness, behavioral problems, and psychological abnormalities due to "transgenerational epigenetic programming of genes operating in the hypothalamic-pituitary-adrenal axis," a complex set of interactions among endocrine glands which determine stress response and resilience (14).

Body Cells Pass Genetic Information Directly Into Sperm Cells

Not only that, but studies are illuminating that genetic information can be transferred through the germ line cells of a species in real time. These paradigm-shifting findings overturn conventional logic which postulates that genetic change occurs over the protracted time scale of hundreds of thousands or even millions of years. In a relatively recent study, exosomes were found to be the medium through which information was transferred from somatic cells to gametes.

This experiment entailed xenotransplantation, a process where living cells from one species are grafted into a recipient of another species. Specifically, human melanoma tumor cells genetically engineered to express genes for a fluorescent tracer enzyme called EGFP-encoding plasmid were transplanted into mice. The experimenters found that information-containing molecules containing the EGFP tracer were released into the animals' blood (15). Exosomes, or "specialized membranous nano-sized vesicles derived from endocytic compartments that are released by many cell types" were found among the EGFP trackable molecules (16, p. 447).

Exosomes, which are synthesized by all plant and animal cells, contain distinct protein repertoires and are created when inward budding occurs from the membrane of multivesicular bodies (MVBs), a type of organelle that serves as a membrane-bound sorting compartment within eukaryotic cells (16). Exosomes contain microRNA (miRNA) and small RNA, types of non-coding RNA involved in regulating gene expression (16). In this study, exosomes delivered RNAs to mature sperm cells (spermatozoa) and remained stored there (15).

The researchers highlight that this kind of RNA can behave as a "transgenerational determinant of inheritable epigenetic variations and that spermatozoal RNA can carry and deliver information that cause phenotypic variations in the progeny" (15). In other words, the RNA carried to sperm cells by exosomes can preside over gene expression in a way that changes the observable traits and disease risk of the offspring as well as its morphology, development, and physiology.

This study was the first to elucidate RNA-mediated transfer of information from somatic to germ cells, which fundamentally overturns what is known as the Weisman barrier, a principle which states that the movement of hereditary information from genes to body cells is unidirectional, and that the information transmitted by egg and sperm to future generations remains independent of somatic cells and parental experience (15).

Further, this may bear implications for cancer risk, as exosomes contain vast amounts of genetic information which can be source of lateral gene transfer (17) and are abundantly liberated from tumor cells (18). This can be reconciled with the fact that exosome-resembling vesicles have been observed in various mammals (15), including humans, in close proximity to sperm in anatomical structures such as the epididymis as well as in seminal fluid (19). These exosomes may thereafter be propagated to future generations with fertilization and augment cancer risk in the offspring (20).

The researchers concluded that sperm cells can act as the final repositories of somatic cell-derived information, which suggests that epigenetic insults to our body cells can be relayed to future generations. This notion is confirmatory of the evolutionary theory of "soft inheritance" proposed by French naturalist Jean-Baptiste Lamarck, whereby characteristics acquired over the life of an organism are transmitted to offspring, a concept which modern genetics previously rejected before the epigenetics arrived on the scene. In this way, the sperm are able to spontaneously assimilate exogenous DNA and RNA molecules, behaving both as vector of their native genome and of extrachromosomal foreign genetic material which is "then delivered to oocytes at fertilization with the ensuing generation of phenotypically modified animals" (15).

Epigenetic Changes Endure Longer Than Ever Predicted

In a recent study, nematode worms were manipulated to harbor a transgene for a fluorescent protein, which made the worms glow under ultraviolet light when the gene was activated (21). When the worms were incubated under the ambient temperature of 20° Celsius (68° Fahrenheit), negligible glowing was observed, indicating low activity of the transgene (21). However, transferring the worms to a warmer climate of 25°C (77° F) stimulated expression of the gene, as the worms glowed brightly (21).

In addition, this temperature-induced alteration in gene expression was found to persist for at least 14 generations, representing the preservation of epigenetic memories of environmental change across an unprecedented number of generations (21). **In other words, the worms transmitted memories of past environmental conditions to their descendants, through the vehicle of epigenetic change, as a way to prepare their offspring for prevailing environmental conditions and ensure their survivability.**

Future Directions: Where Do We Go From Here?

Taken cumulatively, the aforementioned research challenges traditional Mendelian laws of genetics, which postulate that genetic inheritance occurs exclusively through sexual reproduction and that traits are passed to offspring through the chromosomes contained in germ line cells, and never through somatic (bodily) cells. Effectively, this proves the existence of non-Mendelian transgenerational inheritance, where traits separate from chromosomal genes are transmitted to progeny, resulting in persistent phenotypes that endure across generations (22).

This research imparts new meaning to the principle of seven generation stewardship taught by Native Americans, which mandates that we consider the welfare of seven generations to come in each of our decisions. Not only should we embody this approach in practices of environmental sustainability, but we would be wise to consider how the conditions to which we subject our bodies-the pollution and toxicants which permeate the landscape and pervade our bodies, the nutrient-devoid soil that engenders micronutrient-poor food, the disruptions to our circadian rhythm due to the ubiquity of electronic devices, our divorce from nature and the demise of our tribal affiliations-may translate into ill health effects and diminished quality of life for a previously unfathomed number of subsequent generations.

Hazards of modern agriculture, the industrial revolution, and contemporary living are the "known or suspected drivers behind epigenetic processes...including heavy metals, pesticides, diesel exhaust, tobacco smoke, polycyclic aromatic hydrocarbons, hormones, radioactivity, viruses, bacteria, and basic nutrients" (1, p. A160). Serendipitously, however, many inputs such as exercise, mindfulness, and bioactive components in fruits and vegetables such as sulforaphane in cruciferous vegetables, resveratrol from red grapes, genistein from soy, diallyl sulphide from garlic, curcumin from turmeric, betaine from beets, and green teacatechin can favorably modify epigenetic phenomena "either by directly inhibiting enzymes that catalyze DNA methylation or histone modifications, or by altering the availability of substrates necessary for those enzymatic reactions" (23, p. 8).

This quintessentially underscores that the air we breathe, the food we eat, the thoughts we allow, the toxins to which we are exposed, and the experiences we undergo may persevere in our descendants and remain in our progeny long after we are gone. We must be cognizant of the effects of our actions, as they elicit a ripple effect through the proverbial sands of time.

References

1. Weinhold, B. (2006). Epigenetics: The Science of Change. Environmental Health Perspectives, 114(3), A160-A167.

2. Centers for Disease Control and Prevention. (2014). Exposome and Exposomics. Retrieved from here

3. Rappaport, S.M. (2016). Genetic factors are not the major causes of chronic diseases. PLoS One, 11(4), e0154387.

4. Vrijheid, M. (2014). The exposome: a new paradigm to study the impact of environment on

health. Thorax, 69(9), 876-878. doi: 10.1136/thoraxjnl-2013-204949.

5. Wild, C.P. (2012). The exposome: from concept to utility. International Journal of Epidemiology, 41, 24-32. doi:10.1093/ije/dyr236

6. Anway, M.D. et al. (2005). Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science, 308(5727), 1466-1469.

7. Dias, B.G., & Ressler, K.J. (2014). Parental olfactory experience influences behavior and neural structure in subsequent generations. Nature Neuroscience, 17(1), 89-98.

8. Stein, A.D. et al. (2009). Maternal exposure to the Dutch Famine before conception and during pregnancy: quality of life and depressive symptoms in adult offspring. Epidemiology, 20(6), doi: 10.1097/EDE.0b013e3181b5f227.

9. Roseboom, T.J. et al. (2003). Perceived health of adults after prenatal exposure to the Dutch famine. Paediatrics Perinatal Epidemiology, 17, 391-397.

10. Badon, S.E. et al. (2014). Gestational Weight Gain and Neonatal Adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Study-North American Region. Obesity (Silver Spring), 22(7), 1731-1738.

11. Veenendaal, M.V. et al. (2013). Transgenerational effects of prenatal exposure to the 1944-45 Dutch famine. BJOG, 120(5), 548-53. doi: 10.1111/1471-0528.

12. Yehuda, R., & Bierer, L.M. (2008). Transgenerational transmission of cortisol and PTSD risk. Progress in Brain Research, 167, 121-135.

13. Aviad-Wilcheck, Y. et al. (2013). The effects of the survival characteristics of parent Holocaust survivors on offsprings' anxiety and depression symptoms. The Israel Journal of Psychiatry and Related Sciences, 50(3), 210-216.

14. Radke, K.M. et al. (2011). Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. Translational Psychiatry, 1, e21. doi: 10.1038/tp.2011.21.

15. Cossetti, C. et al. (2014). Soma-to-Germline Transmission of RNA in Mice Xenografted with Human Tumour Cells: Possible Transport by Exosomes. PLoS One, https://doi.org/10.1371/journal.pone.0101629.

16. Zomer, A. et al. (2010). Exosomes: Fit to deliver small RNA. Communicative and Integrative Biology, 3(5), 447-450.

17. Balaj, L. et al. (2011) Tumour microvesicles contain retrotransposon elements and amplified oncogene sequences. Natural Communications, 2, 180.

18. Azmi, A.S., Bao, B., & Sarkar, F.H. (2013). Exosomes in cancer development, metastasis, and drug resistance: a comprehensive review. Cancer Metastasis Review, 32, 623-643

19. Poliakov, A. et al. (2009). Structural heterogeneity and protein composition of exosomes-like vesicles (prostasomes) in human semen. Prostate, 69, 159-167.

20. Cheng, R.Y. et al. (2004) Epigenetic and gene expression changes related to transgenerational carcinogenesis. Molecular Carcinogenesis, 40, 1-11.

21. Klosin, A. et al. (2017). Transgenerational transmission of environmental information in C. elegans. Science, 356(6335).

22. Lim, J.P., & Brunet, A. (2013). Bridging the transgenerational gap with epigenetic memory. Trends in Genetics, 29(3), 176-186. doi: 10.1016/j.tig.2012.12.008

23. Choi, S.-W., & Friso, S. (2010). Epigenetics: A New Bridge between Nutrition and Health Advances in Nutrition: An International Review Journal, 1(1), 8-16. doi:10.3945/an.110.1004.

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