Epigenetic Inheritance: Fact or Fiction?

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There is an age-old adage that nature and nurture combine to control all aspects of an individual's functioning, including risk for disease. Research over the past decade, in a still relatively new field called epigenetics, has provided a sophisticated understanding of how this occurs. A person's "nature" is his or her genetic code, comprised of ~3 billion nucleotides (building block molecules) of DNA packaged within every cell in the body, including nerve cells or neurons. Nurture—representing all of one's life exposures and experiences starting from a fertilized egg in utero through advanced aging—influences a person's genetic potential by regulating the degree to which individual genes are expressed.

This occurs by regulating the interactions between local segments of DNA and a host of proteins in the cell nucleus. The combination of which is called chromatin. DNA is wrapped around octomers of histone proteins (like thread around a spool) to form nucleosomes, the unit of chromatin. The degree to which nucleosomes are spread out versus condensed determines the activity of the genes contained within spans of DNA. Nucleosomes that are relatively spread out allow genes to be expressed (i.e., transcribed into messenger RNA, which in turn is translated into protein), while nucleosomes that are relatively condensed prevent such expression. Such loosening or tightening of nucleosomes is controlled by hundreds of regulatory proteins that chemically modify the histones (e.g., by acetylation or methylation) or the DNA itself (e.g., by several types of methylation). Acetylation reduces the histone binding on the DNA structure allowing for transcription. Methylation usually locks genes in so they "remember" what they are programmed to be (i.e., liver versus nerve cells). Non-coding RNAs (RNA molecules which do not encode proteins) are also important in controlling chromatin structure and gene activity. These mechanisms, a small subset of which is very stable, are referred to as epigenetic (meaning literally on top of the genome).

They were first characterized for their role in controlling the differentiation of cells and tissues during development, for example, forming a liver cell versus a neuron from an undifferentiated stem cell. Equivalent epigenetic mechanisms are now known to operate throughout life in all tissues, including brain, to drive alterations in gene expression that occur in response to environmental challenges.

This includes lasting changes that result from in utero exposures or early life experiences. For example, the impact of a mother's diet on the fetus's life-long feeding behavior, or the effect of a mother's care for her young on the offspring's adult responses to stress, have been shown to be mediated through epigenetic modifications at specific genes within the offspring's brains that last a lifetime. Similarly, our ability to learn and remember is mediated through epigenetic mechanisms. There is increasing evidence that epigenetic changes in neurons are responsible for many of the adult brain's maladaptations to the environment, such as to drugs of abuse to cause addiction or to stress to cause depression and related syndromes.

Recently, there has been increased attention

to the possibility of a very different contribution of epigenetics: namely, that environmentally-induced epigenetic changes, in addition to occurring within the brain, might also occur in germ cells—sperm or egg—which are then passed onto the offspring and modify their responses to those same environmental exposures. This reflects a distinct definition of the term epigenetics, one that would involve the heritable transmission of life's experiences to offspring without a change in DNA sequence.

Such a definition of epigenetics harkens back to Jean-Baptiste Lamarck's theory of inheritance of acquired characteristics in the 19th Century, and closely related ideas promulgated by Trofim Lysenko in the former Soviet Union in the mid-20th Century, views that have long been discredited. As a classic example, an adult's exercising of a muscle, which makes that muscle bigger and stronger, has zero bearing on that muscle's size and strength in the adult's offspring.

Nevertheless, there now are a growing number of provocative demonstrations that behavioral exposures can be passed onto offspring. Isabelle Mansuy and her colleagues at the University of Zurich subjected mouse pups to maternal separation during their first two weeks of life. When the male offspring grew to maturity, they exhibited signs of depression-like behavior. When these males were bred with normal female mice, the resulting offspring showed similar depression-like behaviors as adults, even though they were not subjected to stress during their upbringing. These effects were passed onto the subsequent generation as well. Our group made similar observations. We subjected adult male mice to chronic social stress and, two weeks later, bred them to normal females; the male and female adult offspring of these matings displayed dramatic increases in baseline anxiety-like behavior and greater vulnerability to social stress. Chris Pierce and coworkers at the University of Pennsylvania have reported related data from drug abuse models: male rats that chronically self-administer cocaine, when bred weeks after their last cocaine exposure, sire male offspring that display lowered sensitivity to self-administer cocaine as adults, whereas the female offspring showed no deficits.

Do epigenetic mechanisms mediate this trans-generational transmission of behavioral experience? The answer remains far from clear. The Mansuy group has demonstrated very small magnitude changes in the methylation status of several genes in the sperm of the stress-exposed males that correlate with altered methylation of those same genes in the brains of offspring animals and with the abnormal behavior. Likewise, the Pierce group showed altered acetylation of a single gene in sperm, an effect replicated in offspring brains. However, such correlative findings do not provide the degree of proof that is needed to establish epigenetic inheritance. To demonstrate causality, scientists would need: (1) to recreate the change in a gene's methylation or histone acetylation in normal sperm and demonstrate that this was sufficient to impart altered behavioral responses to stress or drug in the offspring; (2) and, conversely, show that correcting that gene's methylation or histone acetylation status in sperm from exposed males ablated any resulting behavioral abnormalities in offspring. Such experiments, while challenging, are now becoming possible and are essential for the field.

Meanwhile, there is evidence that non-epigenetic explanations may also be involved. In our social stress experiment outlined above, when stress-exposed male mice were bred by use of *in vitro* fertilization (IVF), their offspring were mostly normal: only subtle abnormalities resulted in contrast to the dramatic deficits observed after normal sexual reproduction. These observations would suggest that the bulk of the stress-related vulnerabilities are passed on to subsequent generations behaviorally, presumably on the basis of the female detecting that she had procreated with an impaired male.

Indeed, females of numerous species,

from birds to mammals, are known to adjust their reproductive investment depending on the interaction that they had with the male. It is also possible that other constituents of semen, perhaps altered by prior stress, might influence the female's behavior or the sperm and egg cells. Several caveats for the IVF process itself must be considered, for example, the fact that IVF may select sperm that are in different stages of maturation and that may therefore have different degrees of epigenetic programming.

The question of whether true epigenetic inheritance can occur in a mammalian organism remains an open one. It is plausible that certain environmental exposures, like a drug of abuse or stress, would induce epigenetic changes in sperm or egg cells. What's less clear is how such changes would persist during fertilization and early embryonic development when most epigenetic modifications are thought to be erased. Even if a modification persisted during embryogenesis, it would have to persist further during the differentiation of neurons and the generation of billions of them during development, and influence the wiring of the developing and adult brain in such a way as to recreate a specific behavioral vulnerability. Such events are not impossible, but we do not yet know of plausible mechanisms by which they might occur.

Despite this necessary skepticism, other lines of evidence are more suggestive. A small number of genes undergo "imprinting," whereby one copy of a gene (i.e., that derived from either the maternal versus paternal chromosome) and its nearby histones are methylated, leading to a permanent state of inactivation. There is evidence that the imprinting of certain genes is passed onto offspring for several generations, although the precise molecular mechanisms by which such imprinting survives the epigenetic erasure that occurs during early embryonic development is not yet understood. Delineating such mechanisms could help the field understand how behaviorally-induced epigenetic modifications in sperm or egg might similarly be transmitted to subsequent generations.

Moreover, there is compelling evidence from non-vertebrate organisms that some environmental exposures are passed on to progeny. One of the best-established examples is viral immunity in *C. elegans*. Exposure of worms to certain viruses can lead to the induction of microRNAs (a form of non-coding RNA) which help mediate resistance to that virus. Such microRNAs can be passed on to offspring for several generations and promote viral resistance. Understanding how the microRNAs mediate such resistance could provide a template for how similar RNA-based mechanisms might contribute to epigenetic inheritance in mammals.

Much more work is therefore needed before we will know the extent to which epigenetic mechanisms represent a third factor—beyond nature and nurture—in controlling an individual's traits in health and disease.

Further Reading:

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