Epigenetics

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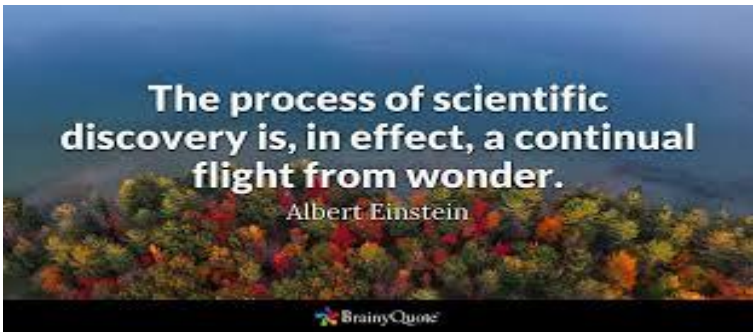


These are exciting times. New science is enabling us to better understand what external and internal factors alter us. Our physical health, our emotional well-being, and our longevity are not only impacted by the hard-wired genetic code we inherit, but our genome is impacted by environmental influences to include as well as the way we live.

Epigenetics literally means "above" or "on top of" genetics. It refers to external modifications to DNA that turn genes "on" or "off." These modifications do not change the DNA sequence, but instead, they affect how cells "read" genes. A very exciting trend in epigenetic research involves investigating the process by which our genetic tendencies are altered or influenced in their expression by outside exposure or stimuli. These epigenetic changes can last through multiple cell divisions for the duration of the cell's life but what is particularly compelling is that these changes may persist for multiple generations within our family line (Kain & Terrell, 2018)

Early trauma, for example, is one of the factors that can cause epigenetic changes and these changes can be passed on to the next generation and beyond. Researchers have come to appreciate that the horrors of the **Holocaust** did not only impact those who suffered the terror of the concentration camps. As one would expect, the survivors of the Holocaust often suffered from PTSD, but this did not stop there. Their children were more likely themselves to develop PTSD and other mood and anxiety disorders, whether or not they were exposed to traumatic events in their own lives (Yehunda et al. 1998).

Another sad example of the impact of trauma on subsequent generations is the **Dutch Famine in World War II**. In September 1944, trains in the Netherlands ground to a halt. Dutch railway workers were hoping that a strike could stop the transport of Nazi troops and help the advancing Allied forces. Sadly, the Allied campaign failed, and the Nazis punished the Netherlands by blocking food supplies, plunging much of the country into famine. By the time the Netherlands was liberated in May 1945, more than 20,000 people died of starvation. Pregnant women, it turns out, were uniquely vulnerable, and the children they gave birth to children where were influenced by the famine throughout their lives. When these children became adults, they ended up a few pounds heavier than average. In middle age, they had higher levels of triglycerides and LDL cholesterol and they experienced higher rates of conditions such as obesity, diabetes, and schizophrenia. By the time they reached old age, those risks had taken an enormous toll, according to the research of L.H. Lumey, an epidemiologist at Columbia University. In 2013, he and his colleagues reviewed death records of hundreds of thousands of Dutch people born in the mid-1940s and found that the people who had been in utero during the famine died at a higher rate by 10% at 68 years of age (New York Times, 2018).

Heijmans and his colleagues found that individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944–45 had, 6 decades later, less DNA methylation of the imprinted *IGF2* gene compared with their unexposed, same-sex siblings. He wrote, “The association was specific for periconceptional exposure, reinforcing that very early mammalian development is a crucial period for establishing and maintaining epigenetic marks. These data are the first to contribute empirical support for the hypothesis that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life” (Heijmans, et al., 2008).

Food rations that were dropped into the Netherlands in 1945.Credit...Dutch National Archive

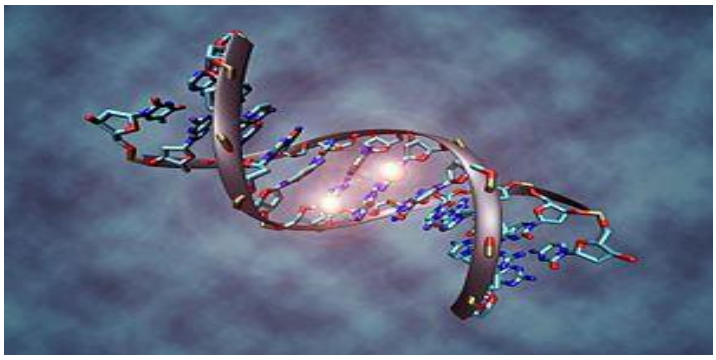
For the science nerds among us: There are three primary mechanisms through which epigenetic changes in gene expression occur which I will describe in a minute. But first a biology refresher: DNA from humans is made up of approximately 3 billion nucleotide bases. There are four fundamental types of these bases that comprise DNA: Adenine, Cytosine, Guanine, and Thymine, commonly abbreviated as A, C, G, and T, respectively. The sequence, or the order, of the bases is what determines our life instructions. Interestingly, our DNA sequence is mostly similar to the DNA of a chimpanzee and only a fraction of distinctively different sequences makes us human. There are about 20,000 genes in total. Genes are specific sequences of bases (parts of DNA) that provide unique and tailored instructions on how to make important proteins (What is Epigenetics, 2019). Proteins are large and very complex molecules that play many critical roles in the body and do most of the work in cells. Proteins are required for the structure, function, and regulation of the body's tissues and organs and are made up of hundreds and thousands of smaller units called amino acids, which are attached to one another in long chains. There are 20 different types of amino acids which combine to make various proteins. The sequence of amino acids is what determines each protein's unique 3-dimensional structure and its specific function. Proteins can be described according to their very large range of functions in the body to include: antibody, enzyme, messenger, and structural component (NIH, 2020).

With that brief biology refresher out of the way, we can explore the three most well-known and best understood of several mechanisms through which epigenetic changes in gene expression occur. As noted earlier, although a person's complement of genes—in other words, his or her genome—remains essentially the same from birth onward, except for the occurrence of mutations that can change the function of genes, different environmental exposures during development, diet, stress, emotional problems, etc., throughout a person's life chemically modify DNA and the proteins bound to it. In addition, individual's histones, or the proteins around which DNA winds when it is compacted into chromosomes, carry different chemical tags which are also influenced by environmental events. These tags are thought to alter the extent to which DNA is wrapped around the histones, thereby affecting the availability of genes for activation. (Suitable my Nature, 2014; Fraga et al., 2005).

Three basic epigenetic processes:

DNA methylation:

The first type of epigenetic modification occurs on the DNA strand itself. This reaction, called DNA methylation, is a biological process by which methyl groups are added to the DNA molecule and thereby changes the activity of a DNA segment without changing the sequence. When located in a gene promoter, DNA methylation typically acts to repress or block gene transcription, effectively turning that gene off (University of Leicester, 2020):



Representation of a DNA molecule that is methylated. The two white spheres represent methyl groups. They are bound to two cytosine nucleotide molecules that make up the DNA sequence (Wikipedia, 2020b)

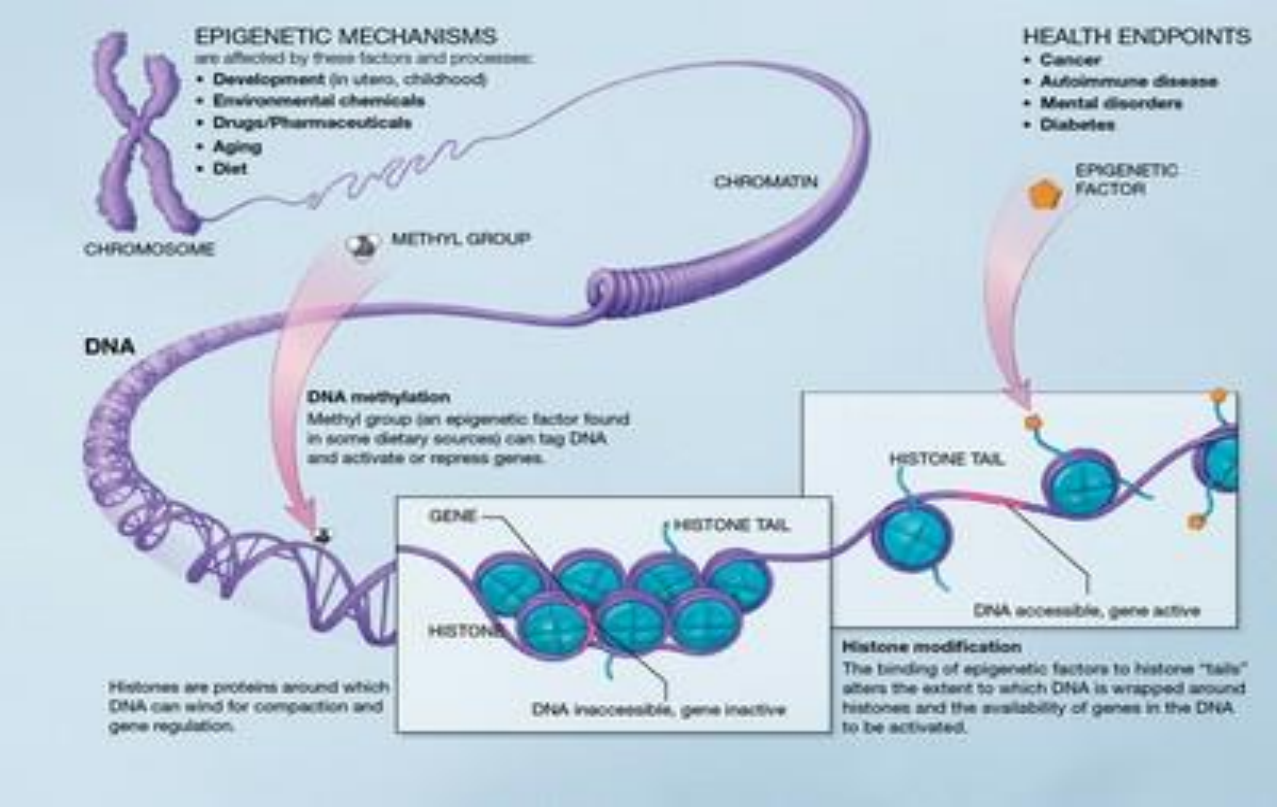
Histone modifications:

Histones are the proteins that hold chromosome together. In histone modification, genes are actually wrapped up tightly so the genes cannot be accessed (essentially turned off), or unwrapped so they can be accessed or activated (essentially turned on). There are multiple types of histone modifications which are catalyzed by a number of enzyme families; the most well characterized modifications include acetylation and methylation:

Histone Acetylation is performed by *histone acetyltransferases (HATs)* which add an acetyl group to lysine amino acids (which are positively charged) in the histone tail which acts to mask the positive charge. This causes loosening of chromatin to promote gene activation (Strahl and Allis, 2000).

This is reversed by *histone deacetylases (HDACs)* which remove the acetyl group to unmask the positive charge, causing chromatin condensation or tightening and gene inactivation.

Histone Methylation can occur on lysine or arginine amine acids and can occur in mono-, di- or tri-methylation events by *histone methyltransferases*. This mark does not substantially alter the charge of amino acids and can be associated with both gene activation and inactivation (Laura,2008).



Takeaway: Knowing about epigenetics is both scary and amazing at the same time. Terrifying in that we know that if we live poorly, paying little attention to how we live, i.e., the impact of poor diet, lack of exercise, living in stress, exposing ourselves to environmental toxins, overreliance on

medications, etc., our genome will be altered, resulting in poor physical and/or emotional health and that this effect can be passed on to our progeny for generations to come. On the other hand, good choices bless us and our future generations.

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