The influence of the epigenome

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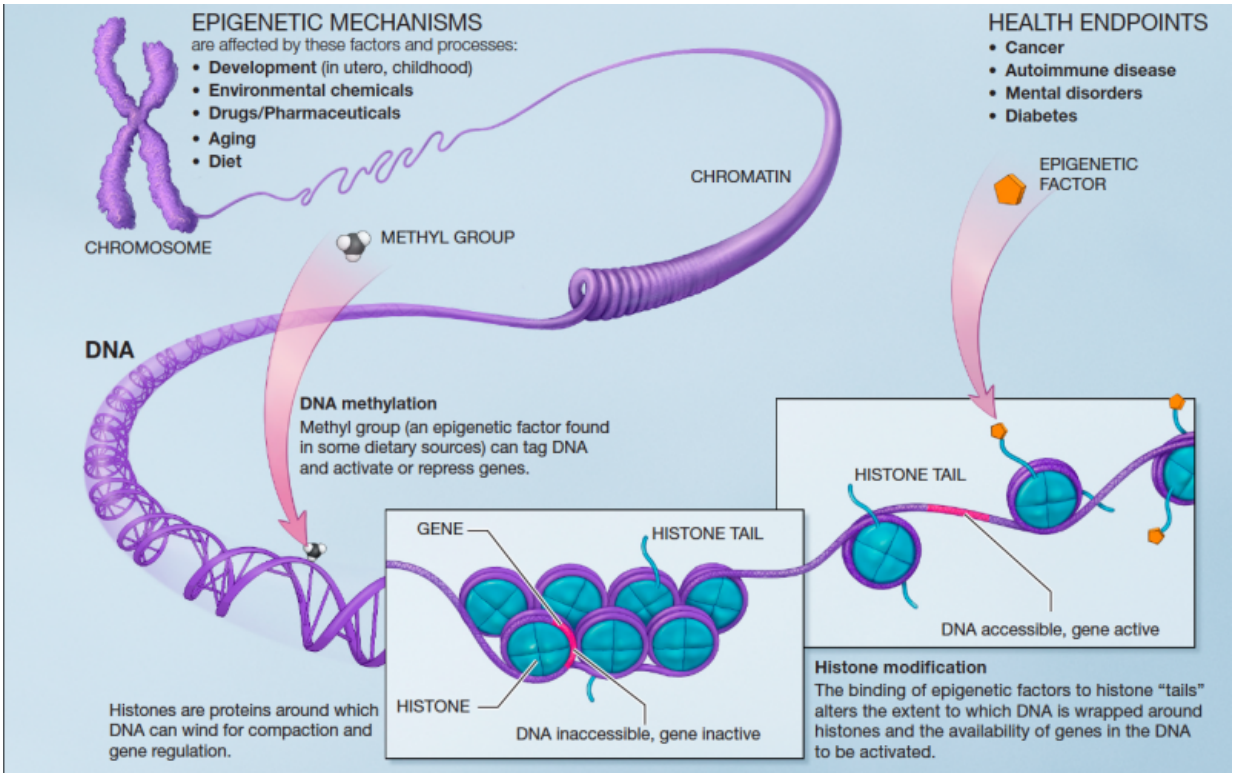

Figure 1. Epigenetic mechanisms, including DNA methylation and histone modification. Credit: National Institutes of Health via Wikimedia.

I first learned about epigenetics in a "fish bowl" meeting room at the University of Pennsylvania in the summer of 2013, when I worked as a research intern in the Ted Abel lab. We were in the middle of a weekly lab meeting, discussing if we need to buy a new sonication machine to do certain experiments. My research mentor, a fifth-year Ph.D. student,

drew a strip of nucleosomes in my notebook and explained that the sonication process uses high-energy sound waves to grind up and remove proteins from DNA, which could be examined in later studies.

Another layer of control: the epigenome

It turns out that our genetic make-up is more dynamic than expected. Since Conrad Waddington first coined the term "epigenetics" in the 1940s, scientists have been discovering how one set of DNA expresses itself in different forms, leading to different organs and tissues in an embryo's development. Something must happen to the DNA that causes it to differentiate.

DNA in our cells is packed up in a condensed string, which wraps itself around proteins called histones (see figure 1). The histones bunch together into complexes called chromatins, placing some genes on the interior and making them inaccessible for transcription. When the genes need to be transcribed, the chromatins unwind, leaving the genes accessible.

There are two forms of regulation that affect DNA and histones. One is histone modification, where specific molecules can bind and change the compaction pattern of histones, exposing DNA string parts that were previously hidden, or wrapping up other string parts tighter. Another is DNA methylation, an enzymatic process that works directly on the DNA by adding or removing "tags" called methyl groups to switch the genes under effect on or off. These two forms of regulation, combined with five families of histones and millions of potential methylation sites, create countless epigenetic possibilities that contribute to the diversity of our world.

Epic epigenetic stories in the animal kingdom

Take the story of the "Agouti Sisters" first. In mice, Agouti is the name of a gene that contributes to their coat color. One version of agouti, agouti viable yellow, or Avy, produces either yellow, brown or mottled fur in its mouse carrier depending on its level of epigenetic methylation. Consider three mouse sisters who are genetically identical and only differ in Avy's methylation level. This piece of epigenetic difference makes the mice phenotypes drastically different. Mouse Sister Yellow has little or no methylation on Avy, lighter colored yellow fur, and is prone to cancer, obesity, and diabetes. Comparatively, Mouse Sister Brown has heavily methylated Avy gene, brown colored fur, and is lean and healthy. The third mouse, Mouse Sister Mottled, has a medium level of methylation, mottled coat mixing brown and yellow, and is less healthy than Sister Brown but healthier than Sister Yellow. Moreover, those phenotypes are actually reversible. In a 1998 study, when researchers fed a brown pregnant agouti mouse diet containing different levels of methylating molecules, they could alter the methylation of Avy, coat color, and health state of her offspring.

Another fascinating facet of epigenetics is how quickly the change can take effect: rather than years, it can take only days. In a 2010 PLOS Biology paper researchers discovered that honey bee queens and workers derived from the same genome have different brain DNA methylation patterns. The paper also noted that a distinct difference in patterns also exists in bee workers acting as "nurses," who take care of the larvae, versus "foragers," who find food for the community. In a 2012 Nature Neuroscience paper, researchers found that when they deliberately coaxed the "nurses" to take on the "foragers"' role or vice versa, the DNA methylation patterns associated with these roles switched as well: "the first evidence in any organism of reversible epigenetic changes associated with behavior" (Herb et al., 2012, p.1371). In the honey bees' world, at least, the seemingly unchangeable genome of an individual could be modified by its behaviors in the epigenome level within 12-14 days.

Maternal care during an animal's childhood can impact epigenetics as well. In a 2012 study led by Dr. Stephen Suomi, scientists found a genome-wide difference of methylation patterns in the T cells of baby monkeys reared by a real mother monkey versus those of babies reared by a surrogate mother. When discussing this research at the AAAS 2016 annual meeting that I attended (see figure 2), Dr. Moshe Szyf, who also contributed to the study said, "the immune system [of the baby monkeys] already knows, by day fourteen, I have a mother versus I don't have a mother."

Epigenetics in human beings

Suomi's study using monkey models investigated how maternal care can impact epigenetics. Epigeneticists have also verified the power of maternal care on epigenetics in human beings. One of the genes affected encodes the glucocorticoid receptor, which detects stress hormone cortisol in the hippocampus and then shuts down the stress circuit. When compared to controls, suicide victims who had suffered from child abuse had more methylation in the promoter region of this gene. These findings offer one biological explanation for these victims' stress responses.

Environmental chemicals like air pollution could also leave their marks in the human epigenome and impact overall health. When assessing the air pollution in a steel plant, a 2009 study found that one of the fine particles particulate matter PM10 is associated with a decrease in global DNA methylation in post-exposure blood samples from male steel workers. Another study on children who lived in urban environments with high air pollution exposure found up- or down-regulation of gene activities in children's brain samples that normally protect against neuroinflammation and oxidative stress. These abnormal changes in gene expression could be due to pollution-induced epigenetic mechanisms, which ultimately led to the appearance of amyloid beta deposits in

children's brains, pathologies associated with Alzheimer's disease.

Other chemicals, whose negative impacts are demonstrated in animal studies, also pose a potential biological danger to humans. Maternal exposure to bisphenol a (BPA) used in the manufacturing of polycarbonate plastics could decrease the methylation level of Avy, the agouti gene controlling the coat color of mouse offspring. Developmental exposure to methylmercury, a chemical that might be present at high levels in seafood, is shown to induce epigenetic suppression of BDNF (Brain Derived Neurotrophic Factor) gene activity and predispose mice to depression-like behaviors. Cautious as we already are to BPA and methylmercury, learning more about what happens on the epigenetic level from animal studies will help us develop targeted treatment to diseases induced by these chemicals.

A case of epigenetic therapy

Recalling the basics of DNA methylation and histone modification, it is an enzymatic process that adds or removes molecular "tags." With pharmaceutical and behavioral approaches, those processes could be manipulated in our favor as epigenetic therapy.

Scientists have demonstrated the proof-of-concept of epigenetic therapy in addiction studies using rats as a model. Once they trained the animals to self-administer cocaine – or associate lever pressing with drug infusion – the researchers stopped giving the animals access to cocaine, creating a withdrawal stage, which could be equivalent to sending the rats into a rehab facility. When comparing DNA methylation patterns before drug administration, after drug administration, and after withdrawal, the researchers found that DNA methylation pattern changes following both drug administration and withdrawal. These findings show that epigenetic mechanisms are at play in altering the addictive behaviors of rats.

The researchers then investigated whether anything can be done to reverse those methylation patterns. When treated with a methylation inhibitor just once after the rehab, the addictive rats' behavior returned to normal. Moreover, such an effect persisted when the researchers examined the same animals again after a month. The results of this experiment suggest the promise of epigenetic therapy, which has also been tested in other areas, such as clinical trials for cancer treatment.

What else can be done?

While epigenetic "tags" are continually changing, this dynamic process is not random. It responds to signals coming from our social world as well as the physical and chemical environment.

At the symposium at AAAS 2016 Annual Meeting, From Toxins to Culture: How Environment Shapes the Infant Brain, Dr. Bruce McEwen from Rockefeller University commented on the dynamic of epigenetics. "There is plasticity. It might require more and more work [as one grows from childhood into adulthood], but it's possible," Dr. McEwen said optimistically in response to my question after the symposium. "I think we are beginning to develop tools that everybody can use. It is not just somebody taking a magic pill. Life-style interventions could work as well, like [being careful about] what we eat and doing regular exercises. It is very important for the government as well as private sectors to educate the public to do the right thing."

Stepping outside the conference room, I thought about how epigenetics has been mentioned more and more frequently in the science-related fields since I first heard the term in 2013. There must be a lot more amazing research to do and applications to explore. As for the general public, one take-home message would be: thanks to epigenetics, we are not just our DNA.

More information: Frank Lyko et al. The Honey Bee Epigenomes: Differential Methylation of Brain DNA in Queens and Workers, *PLoS Biology* (2010). DOI: 10.1371/journal.pbio.1000506