Horizons in Bioscience

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Epigenetics

Looking Beyond Our DNA

While the discovery of the genetic code led researchers to believe that our physical appearance and susceptibility to certain diseases were 'hard-wired" within our DNA, exciting advances in our understanding of the human genome have shown that this is not the entire story. Scientists now know that both biological and environmental factors play an important role in how we develop and age and even in determining our risk of diseases like cancer, cardiovascular disease, and type 2 diabetes. This rapidly emerging area of scientific study is referred to as epigenetics.

Epigenetics (epi — meaning "over" or "on top of") is the study of heritable changes in gene expression due to the DNA being "marked" or modified and not due to changes in the underlying DNA sequence. **Epigenomics** is the study of the global set of epigenetic modifications to a cell's genetic material.

To understand the concept of epigenetics, take the analogy of punctuation in a sentence. The order of words in each of the following sentences is the same, but with an added comma, the meaning is altered:

- Let's eat, Grandma!
- Let's eat Grandma!

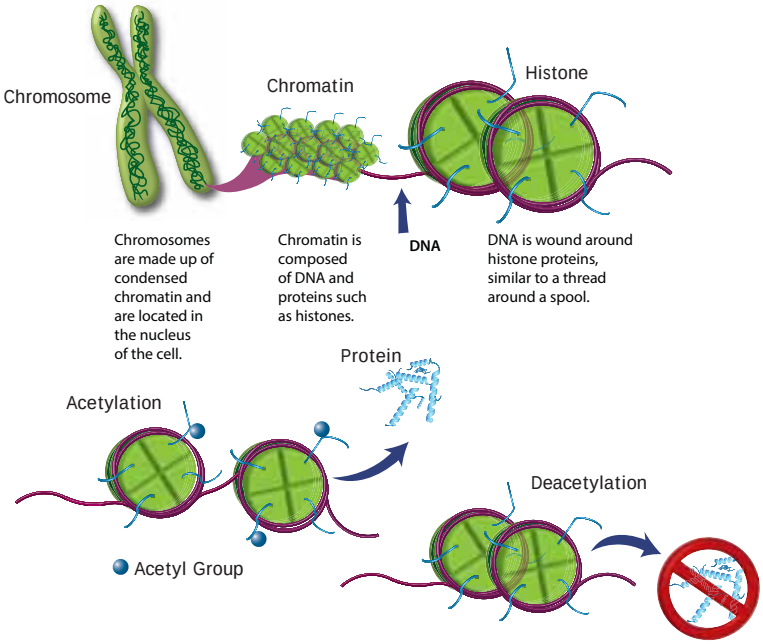
The same concept holds true regarding the genome. All of the cells in the body have the same DNA sequence, but differences in the "punctuation" in certain genes determine when and how they are turned on (gene activation). It is these differences in the activation of genes that result in a broad array of cell types with various functions (i.e., muscle, skin, nerve, bone, etc.), a process known as differentiation.

The most widely recognized and studied epigenetic modifications (punctuation marks) occur through the processes of DNA methylation and histone acetylation (see Figure 1 for further explanation of these mechanisms). Abnormalities in epigenetic modifications are now being identified by researchers as factors in human diseases such as obesity, mental illness, and cancer. Understanding how and why they occur may help researchers to improve upon methods of disease detection, treatment, and prevention.

- DNA methylation is an example of an epigenetic phenomenon.
- It is a biological process where a methyl group (CH_3) is added to a cytosine nucleotide in DNA.
- In general, hypermethylation (over-methylation) is associated with gene silencing.
- In general, hypomethylation (under-methylation) is associated with gene activation.

DNA methylation

Histone acetylation



- Histone acetylation is another example of an epigenetic phenomenon.
- It is a biological process where an acetyl group (C_2H_3O) is added to the tail of a histone molecule.
- The addition of the acetyl group (acetylation) causes the DNA/histone complex to relax allowing the gene to be made into a protein.
- Removal of the acetyl group (deacetylation) causes the DNA/histone complex to constrict thereby preventing the production of protein from the DNA.
- Other histone modifications include methylation, ubiquitylation, formylation, sumoylation, and phosphorylation.

Figure 1: Mechanisms of epigenetics. Figure designed by Anne Deschamps and Corporate Press.

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NURTURE & NATURE

To learn more about the effects of epigenetic changes, scientists often turn to monozygotic (identical) twins because of their matching DNA sequences. Although monozygotic twins share a very similar epigenetic profile at birth, scientists discovered that variations in their epigenome accumulate over their lifetime (Figure 2). In fact, it has been shown that the greatest epigenomic variation occurs in twins who were raised apart.

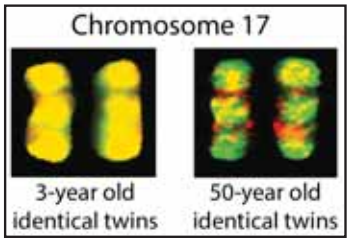

Figure 2: At age three, the epigenetic markers on chromosome 17 of identical twins are quite similar (shown in yellow); however, a comparison between 50-year-old twins shows significant differences in the pattern of epigenetic markers (shown in red and green). Image from Proc Natl Acad Sci U S A. 2005 July 26; 102(30): 10604–10609. Copyright (2005) National Academy of Sciences, U.S.A.

These findings strongly suggest environmental influences on an individual's epigenomic profile and may explain why one twin becomes more susceptible to disease or ages faster than the other. For example, among monozygotic twins, a diagnosis of schizophrenia (SZ) for both twins occurs only 40-50 percent of the time. Researchers found that while discordant twins (i.e., one twin has SZ and the other does not) had similar genomic abnormalities, they had significant differences in the epigenetic pattern of one of the genes linked to SZ. This means that both twins are predisposed to SZ; however, experiencing certain environmental factors, such as psychosocial stressors during early childhood, can increase the risk of developing SZ to the twin exposed to those factors.

In addition to the epigenetic changes that occur throughout a person's lifetime, researchers are also beginning to understand how the fetal environment can alter the epigenome and affect gene expression well into adulthood. To further explore this process, Randy Jirtle, PhD, and his colleagues at Duke University, used viable yellow agouti mice to test how bisphenol A (BPA), the chemical found in some plastics, affects the epigenome and later-in-life development. Normally, the agouti gene is kept in the "off position" through DNA methylation and other epigenetic marks like histone methylation, giving a mouse its brown coat and lean appearance. When the DNA is under-methylated, the agouti gene is "turned on," resulting in a yellow coat color, adult-onset obesity, and a tendency to develop diabetes and cancer.

Dr. Jirtle exposed pregnant female mice to BPA, which resulted in litters with a significant number of yellow and obese offspring. Further research on these offspring demonstrated that the agouti gene was under-methylated, suggesting that BPA alters an organism's epigenome. By introducing compounds that increase DNA methylation (folic acid and vitamin B) along with the BPA into the diets of some of the pregnant mice, the effects of BPA were counteracted, and more offspring were born brown and lean (Figure 3). This was an exciting discovery for the researchers and a potentially important finding in our quest to treat and prevent disease.

MAPPING THE EPIGENOME

The recent availability of enhanced genome sequencing technologies has allowed researchers to study epigenetic variation much more effectively and efficiently. With this technology, research funded by the National Institutes of Health (NIH) has focused on the basic science task of characterizing or "mapping" the occurrence and possible functions of these epigenetic modifications on several types of human cells. Launched in 2008, the NIH Roadmap Epigenomics Program has developed a public database of epigenomes with the goal of identifying specific epigenetic alternations on the genome that could help detect certain diseases at much earlier stages. To date, over 60 epigenomes have been mapped and are helping scientists to better understand how epigenetic abnormalities are linked to genetic diseases.

Figure 3: Despite their differing color and body mass, these one year-old female mice have identical DNA sequences. Maternal dietary supplementation with a methyl donor such as folic acid shifts the coat color of the offspring from yellow to brown and reduces the incidence of obesity, diabetes, and cancer. Image courtesy of Dana Dolinoy, PhD, University of Michigan, and Randy Jirtle, PhD, Duke University.

CONFRONTING THE CANCER EPIGENOME

DNA hypermethylation (silencing) of genes that suppress tumor growth is one of the most common epigenetic alterations observed in cancer. Realizing that some of these alterations are reversible has led researchers to seek therapies that restore the normal behavior of the epigenome and stop tumor growth. Two FDA-approved therapeutics, azacitidine and decitabine, which decrease DNA methylation, have been used to treat blood disorders called myelodysplastic syndromes by "reactivating" the tumor suppressor genes. Another class of FDA-approved epigenetic drugs, called histone deacetylase inhibitors, has been effective in treating a type of lymphoma. Both classes of drugs have shown some encouraging results and continue to be studied in clinical trials. Scientists are also testing whether epigenetic drugs could be used in combination with other conventional treatments, like chemotherapy, to increase therapeutic effects.

There is still much to be discovered about the vast field of epigenetics. However, each new discovery offers the potential to exercise greater control of our health than we ever thought possible.

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