ALS and epigenetics

Nothing illustrates that change is the essence of life quite like the butterfly. How does this cloudless sulphur caterpillar, eating the toxic blooms of a cassia bush, become a butterfly? How did it know the cassia toxin would protect it from predators ensuring a next generation? How did it select the bright colors that warn birds that it has a toxin and they should stay away? And how does it transform into the butterfly for the next phase of its life?

All information for life is carried in genes encoded by DNA. The DNA is a hard code passed from generation to generation from parents to their offspring. If you look closely at two caterpillars you may note differences in size or color. These differences are phenotypic expressions of genes. Phenotype is controlled by modifying molecules that are applied to DNA and can be changed by diet and environment. Amazingly, DNA modifiers can be *inherited from prior generations*. A well-studied transgenerational DNA modifier is the effect of starvation on the genome. Epigenetics is the field of science discovering and understanding DNA modifications and an important branch of this science is an ability to treat disease.

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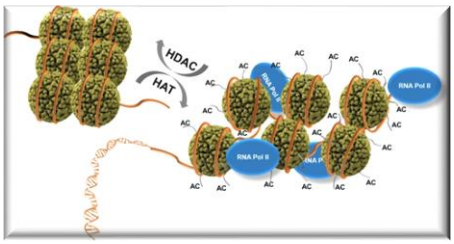
The manipulation of gene expression and silencing can be purposeful and directed. A particularly useful analogy is that DNA is the organisms operating system, OS, while epigenetics refers to apps that can be applied to the OS. The apps give profound plasticity to increasing or decreasing expression of genes. Manipulating gene expression is a natural phenomenon and could be exploited as a step to personized medicine.

An organism's genotype confers the code for everything required to survive. At conception, the stem cell has unlimited potential, the cell receives signals from its local environment and begins a one-way path to its destiny. DNA modifications are tags that are added onto the DNA by the surroundings that up or down regulate, or even silence, genes. Daughter cells from the differentiated cells inherit the DNA modifications. The collective modifications are the resulting phenotype of the organism. Epigenetics is about gene expression or gene silencing, understanding the apps. There are two periods of resetting DNA, at conception, when epigenic tags from the parent are erased and at six to eight weeks of gestation (in humans) when tags are again reset.

The epigenetic clock is a term to describe when on or off signals are expressed. Epigeneticists also realized there is epigenetic memory passed from the mother to the offspring because some tags are not erased. How is the DNA controlled by an epigenetic tag? DNA is packaged in the cell by wrapping around proteins called histones. Mechanisms of histone control are *acetylation* and *methylation*. Acetylation is the modification that relaxes DNA histone binding by an enzyme, histone acetylase. Relaxing the binding of a section of DNA makes the gene available for reading and therefore expressed.



This image shows the DNA helix (orange tube) physically packaged in the cell, wrapped around histone proteins (green balls). The position of acetylation of histone lysine residues by histone acetylase (HAT) are illustrated by the gray strings. You can click this image to read the discussion in Nature and the source of the image. When a gene is expressed, a section of the DNA is unwrapped from its histone, read by enzymes that write/edit/erase the RNA that will code for protein synthesis. The tightness of DNA wrapping on a histone is determined by modifications on the DNA. A *histone deacetylase* (HDAC) will prevent unwrapping and inhibit gene expression because it will remove the acetyl group from histones lysine residues. An enzyme that *inhibits* histone deacetylase results in gene expression, this is a technique that is being employed to create drugs to treat Alzheimer's disease. You can imagine how this system can regulate the amount of a protein that is produced.

Methylation is a modification that make genes inactive. Methylation is inherited to daughter cells. That means gene silencing can be inherited from cell to cell. An adaptation of genes to overcome silencing is a change in location in a chromosome. Methyl donor compounds, and those found in the diet, are also treatment opportunities to overcome disease by silencing genes because increasing DNA methylation is a mechanism that inactivates genes. The drug budesonide, which is DNA methyltransferase activator, results in increased methylation of DNA and ultimately decrease in the size of some tumors that are under the control of tumor suppressor genes. The research suggests that modification of DNA methylation either by hypo- or hypermethylation is effective in different types of tumors.

Genes can gain/lose function. If a gene is moved to a different location in the chromosome or there is a mutation in the genetic code function can change. Some bits of DNA are known to be particularly sensitive to moving location and some areas of DNA code are hyperexcitable and can be particularly prone to mutation. In disease, a tumor suppressor gene can be turned off and result in cancer. It would be possible to impact epigenetic tags to increase the expression of a tumor suppressor gene and stop the tumors growth.

In addition to acetylation and methylation, some RNA molecules are regulatory. Regulatory RNA's can neutralize genes or block messenger RNA. This process isn't all or nothing and gives fine tuning to gene expression.

Transgenerational epigenetic inheritance is recognized and is the transmission of epigenome or epigenetic markers from one generation to the next. This adaptation doesn't affect the structure of DNA but provides a unique survival mechanism allowing organisms to adapt to changing conditions. The effect of starvation has been studied, decreased nutrition was shown to affect subsequent generations through modifications that are inherited from the mother.

The cloudless sulphur larvae becomes a butterfly because the epigenetic tags on the DNA are uniquely choreographed. The larval genes are silenced after sufficient food intake and the next stage genes are turned on, giving wings for flight.

There are many interesting ideas that come to mind, one is the unmet need for biomarkers in amyotrophic lateral sclerosis (ALS). After decades, there are only two licensed medications for ALS, stem cells derived from patients are being tested. What are the considerations for epigenetic memory in these induced cells?

ALS is a disease that involves pathologies from dysregulation of the immune system, oxidative stress, glutamate excitability, apoptosis, abnormal axonal transport, protein misfolding, and mitochondrial toxicity. Different pathologies are present in an individual at different stages of disease and even manifest in different areas of the body. Discovering epigenetic controls of the pathologies in ALS may lead to targeted ALS treatment and hope for the ALS patient.

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