EPIGENETICS – LOOKING AT CANCER DEVELOPMENT AND TREATMENT IN A NEW WAY

by Sue Herms, IWMF Trustee

In order to understand epigenetics, we first need to review a quick definition of genetics. If you remember from your high school or college biology class, genetics is the study of the DNA in a cell – the DNA is encoded in genes that are found on your chromosomes and that carry the instructions for building all of the proteins that make each living thing unique. DNA is passed along as each cell divides in your body and is also passed from generation to generation in eggs and sperm.

Derived from the Greek, the word epigenetics literally means "above" genetics. Epigenetics is the study of chemical markers that modify genes but are not part of DNA itself. Like DNA, they can be passed on from cell to cell and from one generation to the next. These modifications are superimposed on top of our genes to tell them whether they should be active or inactive. For example, every cell in your body has the same DNA; however, some cells are specialized for use in the heart, the bones, the brain, the nerves, the stomach, etc. These cells become specialized because different sets of genes are turned on or off at different points in cell development, leading to differences in the types and amounts of proteins produced and determining how the cells look, grow, and act. This is epigenetics in action.

How does the process of epigenetics turn your genes on or off? We currently know of two major methods. The first, called DNA methylation, directly affects your DNA. In this process, chemical tags called methyl groups are attached to or removed from the backbone of your DNA in specific places. A methyl group consists of a carbon atom and three hydrogen atoms and can act as a "red light" by turning certain genes off, or as a "green light" by turning certain genes on. Another way to think of DNA methylation is that it acts like a light switch to turn a gene on or off. This ultimately affects the types and/or amounts of proteins produced by the cell.

The second epigenetic process, called histone modification, indirectly affects the DNA. Histones are spool-like proteins that enable the very long DNA molecule to be tightly coiled into the chromosomes inside the cell nucleus. A variety of chemicals can grab hold of the tails of histones, changing how tightly or loosely they package DNA. If the wrapping is tight, a gene may be hidden from the cell's protein-making machinery and consequently switched off. If the wrapping is looser, a gene that was formerly hidden may now be turned on.

Just as we know that our DNA can change because of mutations, our epigenetics can also change during our lifetime. Lifestyle and environmental factors can expose us to chemicals that change our epigenetic profile. In other words, what we eat and drink, whether we smoke, what medicines we take, what pollutants we encounter, how quickly we age, may affect this process. Look at the case of identical twins. Although they share the same DNA, their bodies may not be exactly identical. One twin may develop arthritis or diabetes, for instance. At least some of these differences are due to changes in our environment that affect our epigenetics.

Research has shown that shortages or excesses of food during a person's childhood can cause epigenetic changes that lead to diabetes, obesity, and early puberty. Genes become epigenetically modified to deal with adverse conditions and then pass on to offspring who may enjoy more comfortable conditions. Changes that made sense during a time of hunger can then transfer to children and grandchildren who live in a time of abundance.

One of the pioneering epigenetic studies was performed by a Swedish preventive-health specialist named Dr. Lars Olov Bygren. He wondered about the long-term effects that feast and famine years in the 19th century might have had on children growing up in a remote area of northern Sweden – and not just on them but their children and grandchildren as well. Using historical records to analyze a sample of 99 individuals, Dr. Bygren determined how much food had been available to parents and grandparents when they were young. Boys who enjoyed rare overabundant winters and who went from normal eating to gluttony in a single season produced sons and grandsons who lived far shorter lives, as much as 32 years shorter. Later studies also confirmed significant drops in lifespan and discovered that they applied to females as well. Simply put, the data suggested that a single winter of overeating as a youngster could initiate a chain of events that would lead one's grandchildren to die decades earlier than their peers did.

A large-scale ongoing study in Great Britain is looking at the association between smokers and health problems in their offspring. Men who as boys had started smoking before age 11 – just as their bodies were preparing to enter puberty – had sons with significantly higher body mass indexes than other boys the same age. It appears that epigenetic changes are occurring on genes in the chromosome of smokers that are being passed on to their sons. This means that the sons of men who smoke in pre-puberty may be at higher risk for obesity and other health problems well into adulthood, and it's likely that these sons will also have shorter life spans.

Experiments have also shown how foods can cause epigenetic changes in the womb. In 2003 Duke University researchers conducted an experiment on pregnant mice that carry a particular gene for yellow coats and an associated likelihood for obesity and diabetes. The researchers fed one group of these pregnant mice a diet rich in B vitamins (folic acid and vitamin B12). Another group of genetically identical pregnant mice did not receive this prenatal nutrition. The B vitamins acted as methyl group donors – they caused methyl groups to attach more frequently to this gene in the fetal mice, thereby altering its expression. The mothers treated with B vitamins produced healthy brown mice that were of normal weight and not prone to diabetes.

Why is the study of epigenetics important to someone who has WM? For many years, it was thought that cancers are caused only by mutations in the DNA itself. That is one reason why there was such a push in the 1990s to complete the Human Genome Project, when medical researchers created a detailed map of all the genes in the human body. We now know that cancer can be caused by epigenetic changes as well. For example, adding or removing methyl groups (DNA methylation, as discussed above) can switch genes involved in cell growth off or on. If these changes occur at the wrong time or in the wrong cell, they can convert normal cells into cancer cells that grow out of control. If a gene is inappropriately switched on or off during cancer development, a treatment to reverse this process could stop or even reverse the growth of the cancer.

Also, if we can determine risk factors from our diet or environmental exposures that cause epigenetic changes, we may be able to predict those who are more likely to develop cancer and use measures to try to prevent its occurrence.

In 2004 the FDA approved the first epigenetic drug, azacitidine (trade name Vidaza), to treat myelodysplastic syndrome, often referred to as a type of pre-leukemia. Azacitidine blocks DNA methylation in the abnormal (myelodysplastic) cells, thereby activating tumor suppressor genes that had been turned off when they were methylated as a result of the epigenetic process. When these tumor suppressor genes are now activated, they can begin to suppress the disease again. The Dana-Farber Cancer Institute has evaluated the effects of azacitidine in WM cell lines and reported that it induced apoptosis (programmed cell death).

Vorinostat, also called Zolinza, is another epigenetic drug used in the treatment of cancer. Specifically, it is one of a class of drugs called histone deacetylase (HDAC) inhibitors that interact with histones, in the manner described above, by causing them to be more tightly coiled and "hiding" or silencing gene expression. The HDAC inhibitors are one of the fastest growing classes of new drugs now becoming available for the treatment of many forms of cancer, including lymphoma and multiple myeloma. At least 80 clinical trials are testing more than eleven different HDAC inhibitory agents for both hematological and solid malignancies. Vorinostat is currently approved for cutaneous T-cell lymphoma. In the laboratory it has induced apoptosis in WM cell lines and is at present being tested on B-cell lymphomas in combination with other cancer therapies in Phase I/II clinical trials.

Yet another HDAC inhibitor of interest in WM is called LBH589 or panobinostat, manufactured by Novartis. Panobinostat is currently in a Phase II clinical trial for relapsed/refractory WM at Dana-Farber. The drug is oral and is administered once a day on Monday, Wednesday, and Friday of each week for four weeks; trial participants may continue to receive the drug for as long as they are benefiting. Panobinostat is also being combined with everolimus (RAD001) in Phase I/II clinical trials at Mayo Clinic for multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's lymphoma.

Now that we are beginning to understand the importance of epigenetics in causing disease, several projects are attempting to determine, on a large scale, just where and how epigenetic changes can impact specific disease development. In Europe, a consortium of public and private institutions began collaborating on the Human Epigenome Project in 2000, with the idea of mapping DNA methylation sites in seven different human tissues. The project has now been expanded to map DNA methylation sites in all 30,000 human genes in approximately 200 tissue samples. In 2008, the National Institutes of Health in the U.S. started a comparable project called the Roadmap Epigenomics Program, which is a five-year, $190 million push to accelerate research into the epigenetic modifications that alter gene behavior. Making an epigenetic map will not be easy. Not only does one's epigenetic pattern change over time, it also differs in every major cell type. Researchers say this will be time-consuming but possible. As our knowledge of epigenetics expands, it is anticipated that our efforts to diagnose, treat, and prevent cancer and other diseases will improve.

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