The Legacy of a Life Lived: Trans-Generational Epigenetics and Cancer Development

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Your grandfather smoked everyday, your mother was stressed while pregnant, your father worked in the petrochemical industry, should any of this matter to you? Evidence is emerging that the lives we live affect us far beyond the boundaries of our own body and can reach well into the lives of future generations. These lingering traces of lives lived manifest themselves in changes to the DNA of our cells, commonly referred to as epigenetics. Epigenetics is defined as inheritable changes in gene expression that don’t alter the actual DNA sequence itself, most commonly mediated by DNA methylation and/or histone methylation or acetylation. In this paper, we will discuss some of the epigenetic changes that have been associated with the development of disease with specific focus on the development of cancer. Moreover, we will look at environmental exposures in current generations that may affect cancer development in future generations. We may merely be guardians of our DNA for future generations, and perhaps the impact of the way we treat our bodies should now be examined in this new light.

My parents are children of World War II. They grew up amongst the bombings, death and destruction. Their lives were forever changed by these experiences at a level far deeper than one would expect. Beyond the psychological, emotional or physical impact of those experiences, those moments would forever change their DNA. Such are the findings of Dr. Yehuda, who found that traumatic events can permanently alter the expression of the stress hormone, cortisol.1 Yehuda found that children of mothers who suffered psychological trauma from the events of WWII had children who had lower levels of cortisol production.2 This change in the offspring related to maternal behaviour or experiences has been linked to changes within the DNA of the children. These changes are referred to as epigenetics, which is defined as inheritable changes in gene expression that don’t alter the actual DNA sequence itself.3 In this article, we will explore the relationship between the environment, epigenetics and cancer.

There are two major modalities by which DNA can be altered to change the expression of a particular gene: the methylation of DNA and modification of histones. The methylation of DNA involves the addition of methyl groups to the cytosine bases in the CpG domains.4,5 The modification of histones is the other major epigenetic regulatory mechanism. The more tightly the DNA is wrapped around the histone complex, the lower the expression of the genes coded on that piece of DNA. Histone modification involves the methylation or acetylation of amino acids such as lysine, arginine and serine. Histone acetylation generally results in the loosening of the association between the DNA and the histone, allowing for increased gene expression.6,7 The effects of histone methylation are more variable and can results in the increase or decrease in gene expression depending on which residues are modified and where within the histone protein the modification takes place.6,7

Epigenetic changes have long been associated with cancer. The first major finding was that the DNA of cancerous cells was globally hypomethylated.8 In addition, the degree of hypomethylation of the DNA seemed to correlate with the aggressiveness and prognosis of a particular cancer.4,9 There is some debate as to the
effects of DNA hypomethylation, but several theories have garnered attention. These include the idea that hypomethylated DNA is more unstable and thus leads to deletions and translocations, potentially creating truncated genes or genes that have different promoter elements. Other theories are based on the observation that imprinted DNA, that is selective DNA methylation to inactivate the expression of either a maternal or paternal allele, is disrupted in cancer cells. Therefore, hypomethylated DNA may correspond to the disruption of genomic imprinting. As an example, it is known that the loss of imprinting of the insulin-like growth factor gene is a risk factor for colorectal cancer.

The other major epigenetic mechanism that has been found to be prevalent in cancer cells is the inactivation of tumour-suppressor genes. Tumour-suppressor genes prevent the progression of cancerous cells and some of their functions have been related to the inhibition of cell division, the initiation of apoptosis and the mediation of cell adhesion. Hypermethylation in the promoter regions of tumour-suppressor genes is one of the major steps required for the transformation from benign to malignant. Two well known genes, the retionoblastoma tumour-suppressor gene (Rb) and the breast cancer susceptibility gene 1 (BRCA1) are examples of genes that have hypermethylated promoter regions in cancerous cells. The inactivation of tumour-suppressor genes by hypoacetylation and hypermethylation of histones have been associated with colon cancer, prostate cancer, liver and breast cancer.

The question now concerns why these changes arise and how they result in cancer. We are all familiar with the concepts of nature and nurture intersecting to result in the genetic changes required to initiate the transformation into cancerous cells. For example, lung cancer requires a genetic predisposition on top of an environmental factor, commonly smoking. Research has shown that exposure to cigarette smoke can induce the hypermethylation of BRCA1/BRCA2 and XRCC, all tumour-suppressor genes, as well as the hypomethylation of the pro-metastatic oncogene, SNCG.

Other examples of environmental agents that induce changes to the epigenome resulting in increased incidence of cancer include aniline dyes and bladder cancer, solar UV radiation and skin cancer, and alfatoxins found in the soil and on plants and liver cancer. We are all aware of this direct link between an environmental factor and the development of cancer. But what of the offspring of a person exposed to these environmental agents, are they ultimately at risk as well?

Exposure to environmental toxins has been shown to increase the transgenerational risk of diseases, including cancer. One of the most widely studied toxins is vinclozolin, which is an anti-androgenic compound used as a fungicide in the fruit industry. Transient exposure of gestating rats to vinclozolin leads to a variety of diseases in offspring up to four generations later, including tumour development, prostate disease, kidney disease, immune abnormalities and defects in sperm formation. Bisphenol A is perhaps the most well known endocrine disruptor believed to change the epigenome. Bisphenol A is an organic compound that, until recently, could be found in many baby bottles, baby and children’s toys, and in the epoxy resins that coat almost every food and beverage can. Neonatal exposure to bisphenol A has been shown to alter the methylation status of a variety of genes and result in cellular transformations that promote the development of prostate cancer. Prenatal exposure to bisphenol A has been linked with an increased risk of breast cancer via hypomethylation. While the temporal effects of bisphenol A have been shown in the first generation, further studies are required to determine if changes are transmitted to subsequent generations. Other links have emerged between environmental toxins and cancer including the transgenerational effects of alcohol leading to colon cancer and benzene leading to leukemia. As the research into epigenetics grows, we will undoubtedly continue to see an expansion of the environmental agents that can alter the epigenome.

The relationship between nutrition, epigenetics and the disease processes warrants
further consideration. One of first multi-generational epigenetic studies was done in Sweden, where parish registries and harvest records were used to link disease in generations after feasts or famines. These studies found that if a paternal grandfather experienced a surplus of food before the onset of puberty, the grandchild had a four-fold increased chance of dying from complications of diabetes. Interestingly, the children of mothers who experienced abundance of food before the onset of puberty had children who were protected from diseases related to diabetes. In terms of cancer research, evidence is emerging that links nutrition, epigenome status and cancer development. Excessive maternal weight gain during pregnancy leads to increased risks of breast cancer in the child. In addition, the nutritional content of the diet has been shown to be important in developing and maintaining the epigenome. Specifically, the availability of methyl donors, including folate, choline and methionine seem to be important in preventing disease. In rat models, decreased availability of methyl donors has been shown to induce the development of liver cancer, even in the absence of any known carcinogens. In the agouti mouse models, dietary supplementation in utero with folic acid, vitamin B12, choline, betaine and zinc was associated with a lower risk of cancer, diabetes and obesity and an increased life expectancy. Low protein diets in utero also seem to affect DNA methylation and disease in offspring, leading to increased susceptibility to diabetes, hypertension and cancer.

Since epigenetic changes to the DNA are reversible, it provides the perfect target for cancer therapies. Already, we are seeing the emergence of therapies that are based on altering DNA methylation and histone acetylation. In particular, in vitro evidence using DNA demethylating drugs and the ability to re-express tumour suppressor genes has lead to the development of clinical therapies. Two DNA demethylating drugs, 5-azacytidine (Vidaza) and 5-aza-2’-deoxycytidine (Decitabine), have been approved for the treatment of myelodysplastic syndrome and leukemia. The other major class of drugs developed on the principles of epigenetics is the histone deacetylase (HDAC) inhibitors. These drugs have been found to induce cell-cycle arrest and apoptosis in vitro. Suberoylanilide hydroxamic acid (Vorinostat) is the first HDAC inhibitor approved for the treatment of cancer, specifically cutaneous T-cell lymphoma. While these drugs have been approved, they lack specificity for cell type which may lead to unintended effects, including the expression of previously silenced oncogenes. As with any cancer therapeutic, the eventual goal will be to develop agents that target only cancerous cells, sparing normal tissue and cells.

If the last century belonged to DNA and the genome, this century will surely belong to epigenetics and the epigenome. We are slowly discovering that the epigenome is an important player in the development of disease. What has come as a surprise is the degree to which the epigenome is influenced by the environment, by everything from drugs, toxins to vitamins and caloric intake. Even more astonishing is the emerging data indicating that what we experience in our lives will ultimately influence the lives of our children and perhaps even their children. In effect, we are the guardians of our genes and need to watch over them so that we may pass them on in the best condition we can.

References

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