

Light as An Epigenetic Factor for Activating Cancer Genes

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Abstract

Several lifestyle factors have been identified that might modify epigenetic patterns, among them light is one. Disruption of epigenetic processes through biorhythm can also lead to altered gene function and malignant cellular transformation. Normally, menopausal women are more vulnerable to breast cancer, but we found none of the blind menopausal women out of about 2000 suffer with breast cancer. On the contrary, there is high incidence of breast cancer in night shift workers. Such studies indicate changes in the epigenetic landscape due to night light are responsible for incidence of cancer.

Keywords: Cancer Genes

Introduction

Lamarck's theory of inheritance of acquired characters was rejected and replaced by the hereditary genetics [1]. However, in recent years, many scientists have hypothesized and even demonstrated that certain experiences during the life of an individual influence the development of his offspring, even distally (back to Lamarckism). Unlike genetic changes, epigenetic changes are reversible and do not change the DNA sequence, but they can change how the body reads a DNA sequence; for example

1. how the organism itself responds to a changeable environment and/or
2. how his descendants will increase their likelihood of surviving in a specific environment—that is, how information is transmitted to offspring regarding the environment that they will encounter. [2,3].

Many factors such as diet, behaviour, stress, exposure to pollutants, and physical activity have been known to cause epigenetic changes which may be passed down from one generation to the next. A new study shows that stress causes novel DNA modifications in the brain that may lead to neurological problems. [2, 4] Epigenetic changes such as DNA methylation and histone modification help a cell control gene expression by precisely turning genes on or off., It is easy to see the connection between genes and behaviours and environment. Abnormal epigenetic modifications in specific oncogenes and tumour suppressors genes can result in uncontrolled cell growth and division. However, abnormal epigenetic modifications in regions of DNA outside of genes can also lead to cancer. [4-6] Out of so many epigenetic factors here we will deal with only Light, both natural and artificial in relation to cancers.

Artificial and natural Light:

Humans have long created artificial lights by burning or heating materials, and candles as well as other flame operated lamps the advent of electricity brought incandescent lights. Both natural and artificial light disrupt the human body clock and the hormonal system, and this can cause health problems. [7,8].

The ultraviolet and the blue components of light have the greatest potential to cause harm [9,10] Using some types of CFLs for long periods of time at close distances may expose users to levels of UV nearing the limits set to protect workers from skin and eye damage. The wavelength of visible light determines its colour, from violet (shorter wavelength) through to red (longer wavelength). The sun emits radiation over the full range of wavelengths, but the earth's atmosphere blocks a



of UV and infrared radiations [9]. The effect of light on cells depends on the radiation and its wavelength, the type of cell, the chromophore, and the chemical reaction involved [10, 11].

Blind menopausal woman:

In our epidemiological study [12-16] we have drawn conclusion that there is a low prevalence of breast cancer in blind menopausal women. In this study, visually challenged menopausal women has shown the risk of developing breast cancer in lifetime is very much lower 1:169 (n = 2060) since, only two suffered from the disease among our study group. However, Shanthi et al. [17] showed that the risk of developing breast cancer among sighted women in Chennai is 1:78 (Cumulative Risk 35 - 64 age). Since these subjects have high risk of developing cancer but because they do not perceive light, they are less vulnerable to breast cancer compare to same age group of sighted women [14].

Night –Shift workers:

Schrammel et al. [18] confirmed that Women, who reported more than 20 years of rotating night shift work, experienced an elevated relative risk of breast cancer compared with women who did not report any rotating night shift work. Shift work that requires the use of artificial light (in the evening, night, or early morning) leads to suppression of pineal secretion of melatonin, low serum melatonin concentrations have been reported in women with estrogenic-receptor-positive breast cancer. Impaired pineal secretion of melatonin is also associated with 5-lipoxygenase activity in B-lymphocytes, and increased ovarian estrogenic and pituitary gonadotropin production, [19-22] which are associated with increased breast cancer risk. Susceptibility of night shift workers, (for example in hospitals, graveyards and airports) to develop breast cancer has been addressed by many epidemiological studies. This observation has further strengthened by our recent evidence that blind subjects are showing less prevalence of breast cancer. Some researchers speculated that the effect may be due to the changes in levels of melatonin.

Epigenetic modifications:

Another important element of gene-expression control is epigenetic modification. One major class of epigenetic effectors is chemical modification of the proteins, known as histones, that anchor chromosomal DNA and control access to the underlying genes. The researchers showed that they can also alter these epigenetic modifications by fusing TALE proteins with histone modifiers [23]. Epigenetic modifications are thought to play a key role in learning and forming memories, but this has not been very well explored because there are no good ways to disrupt the modifications, short of blocking histone modification of the entire genome(24) The new technique offers a much more precise way to interfere with modifications of individual genes.

DNA Methylation in Cancer:

Cancer cells often have a different epigenome, or epigenetic profile, than normal cells. DNA with less than normal amounts of

DNA methylation are said to be hypomethylated. DNA with more methylation is said to be hypermethylated. A cancer cell's epigenetic profile is typically characterized by decreased methylation across much of the genome (global DNA hypomethylation [25]. The decreased methylation affects the activity of large numbers of genes. Because methylation is associated with decreased gene activity, the overall effect of hypomethylation is to increase the activity of the affected genes. If genes involved in cell growth have decreased methylation, the increased activity, and resulting cell division can lead to the development of cancer. As noted, DNA methylation changes do not have to be within protein-encoding genes to be important. Changes to DNA sequences that function as gene regulators can also cause problems.

Although the DNA of cancer cells is most commonly hypomethylated, the opposite can also be true. [26] DNA hypermethylation in cancer cells tends to be limited to very specific regions ('hot spots'). This site affected vary by cancer type. The effect of increased DNA methylation is the opposite of hypomethylation. Hypermethylated genes tend to show decreased activity. DNA hypermethylation in cancer cells is frequently found at tumour suppressor genes; genes that function to repair DNA and control cell division. When tumour suppressor genes are silenced by increased methylation, the decrease in their activity can result in cancer development.

How do these small changes affect cancer growth? Cells with hypermethylated tumour suppressor genes are likely to grow faster than cells with normally methylated tumour suppressor genes. However, this doesn't explain why specific sequences are found to be hypermethylated in some cancer cells but not others. The exact reason and mechanisms behind this are still unclear but, it may have something to do with how cell populations evolve over time. It is likely that the hypermethylation occurs to many genes in different cells. SOME of those changes will give those cells an advantage. Those cells will reproduce more rapidly, and take over the population [27] A good example is BRCA1, a gene linked to breast cancer, which is often found hypermethylated in breast and ovarian tumours but unmethylated in other types of tumours.[28]

Histone Modifications Seen in Cancer:

Changes to the epigenetic modifications of histones also play an important role in the development of cancer. As previously mentioned, modifications of these proteins alter the interactions between the histones and the DNA. This changes the shape of the DNA-histone complexes (nucleosomes) and alters the way that other proteins can interact with the DNA.

The epigenome of cancer cells is typically marked by a loss of histone acetyl markers, due to increased histone deacetylation. The process of histone deacetylation is catalysed by enzymes known as histone deacetylases or HDACs. As expected, increased activity of HDACs has been found in different types of cancer cells, making HDACs an important target of epigenetic cancer treatments.[29].

Histone methylation is also found to be affected in cancer cells. Histone methyltransferases (HMTs) are enzymes that carry out the addition of methyl groups to histones, while histone demethylases (HDMs) have the opposite function. In cancer cells,



HMTs may be altered so that they are placing methyl groups at the wrong spot, often silencing tumour suppressor genes. HDMs can also be similarly affected, leading to increased activity of oncogenes. As previously mentioned, histone methylation is very complex. The effect of methylation on gene activity can differ depending on the specific amino acid affected. As such, methyl marks on histones are categorized as either activating or repressing, depending on their effect on gene activity. An additional complication is that some HDMs have been found to be able to remove both activating and repressing marks. This poses a challenge for people developing epigenetic therapies to target HDMs - their functions must be fully understood in order to know how the drugs will affect the cancer cells.

Management of cancer by regulation of light:

Cancer is usually curable, if it is detected in early stages. Causative factors for breast cancer are genetic, environmental (including light conditions) and food [30,31] The effect of each individual risk factor in developing the disease may not be very significant but the cumulative effect of individual factors may increase the rate up to 99 percentages.[32]. However, blind woman model indicated that exposure of light is a single factor that regulates the breast cancer incidence, may be because, longer exposure of fluorescent light the following disturbances in hormonal milieu sets up

- Diminished functions of the pineal gland lower its melatonin production.
- Lesser melatonin production allows for ovarian growth and greater hormonal production.
- Greater hormonal production leads to earlier sexual maturation, early puberty and greater breast cancer development.

Melatonin is involved significantly in the metabolic activities and also a new member of an expanding group of regulatory factors that control cell proliferation and apoptosis and is the only known chronobiotic hormonal regulator of neoplastic cell growth. At physiological as well as pharmacological concentrations, melatonin suppresses cell growth, multiplication and inhibits cancer cell proliferation in vitro, through specific cell cycle effects. At these levels' melatonin acts as a differentiating agent in some cancer cells and lowers their invasive and metastatic status by altering the concentration of adhesion molecules, maintaining gap junction and intercellular communication. In other cancer cell types, melatonin, alone or with other agents, induces programmed cell death [33].

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