

Brief notes on cancer

Abstract

In our days, and for many years, cancer occupies the first places in human morbidity and mortality. In this brief communication, we intend to approach the role of genetic and epigenetic alterations and the environmental factors involved in carcinogenesis. The malignant transformation of a cell always depends on the environment, which acts on the epigenome and/or the genome. For the clonal expansion that determines the development of a tumor to take place, it requires the failure of multiple defense mechanisms that involve a significant number of genes and genetic variants, so that cancer is considered a complex disease of multifactorial etiology in all cases. One could think of a special condition of the DNA molecule that facilitated epigenetic modifications to certain conditions of the cellular environment, leading to the multiple failures of protection genes and over-expression of oncogenes, a necessary condition for the development of the disease.

Keywords: cancer, etiology, carcinogenesis

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Introduction

In our days, and for many years, cancer occupies the first places in human morbidity and mortality.¹⁻³ Numerous efforts and resources have been devoted to studying this disease and, even so, it threatens to be the pandemic of this disease century; therefore, despite the advances in the research on its etiology and pathogenesis, no effective treatment has been achieved that can safely solve this health problem. After many years of study, the general opinion is that the disease has not been understood, which has been defined by scholars as complex; but the feeling of many, is to be immersed in an ocean of susceptible genes, proteins and other molecules involved; However, the final solution is not far away. In this brief communication, we intend to make an approach to the genetic and epigenetic alterations involved with carcinogenesis, with the firm idea that the solution of the problem is close; it only about understands what remains hidden before our eyes.

Development

Cancer is the result of the transformation of a cell (or a group of them) that gives it new properties, different from normal cells. Regardless of its etiology, it is a multifactorial genetic disease; For, in order for the malignant transformation of a cell to be triggered, an impressive series of protective systems of the cell must first have failed, involving the genes, the epigenome and the intra- and extracellular environment; therefore, genetic, epigenetic and environmental factors are involved in the etiology of this common disease. Among the genetic factors are genes that are major cancer targets: proto-oncogenes, tumor suppressor genes, DNA repair genes and apoptosis genes.⁴ The frequency with which each of these groups is involved in the disease is not has been able to determine why, in the first place, often in each case there are several of them involved and, secondly, because the path of participation in the disease varies according to environmental factors and genetic and epigenetic individuality of each affected. Proto-oncogenes are genes involved in growth and development; that is, genes that normally regulate the cell cycle

positively,^{5,6} and that can be transformed into oncogenes by different mechanisms: genetic amplification, chromosomal alterations, point mutations, viral insertion and overexpression of the protein product by epigenetic modifications.⁴

The tumor suppressor genes normally regulate the cell cycle in a negative sense; that is, they slow cell growth and proliferation; and the loss or mutation of one allele does not affect the function of the other; therefore, both alleles must be mutated to inactivate the function of the gene.^{5,6} The loss of constitutive heterozygosity is the mechanism most associated with its inactivation and the causes can be: the loss of a complete chromosome containing a normal allele, defective segregation; an unbalanced translocation, resulting in the loss of a chromosomal region containing the normal gene; by loss of a normal gene, when reduplication of the remaining chromosome occurs with an abnormal gene, leaving the cell with two copies of abnormal genes; by loss of normal genes during normal mitotic recombination or as a consequence of a point mutation in the second allele, leading to inactivation of the normal gene; for defective repair of normal gene damage and inadequate methylation of the normal allele.⁴ DNA repair genes normally allow cells, with spontaneous mutations occurring during processes involving DNA such as replication, to repair that damage. Mutations in these genes or their epigenetic silencing can perpetuate damage to the molecule that involves uncontrolled cell proliferation.^{4,7,8} The genes of apoptosis allow the cell to induce its own death in response to certain stimuli. A mutation or epigenetic silencing that slows the function of these genes, implies the perpetuity of a damage in the DNA molecule that causes uncontrolled cell growth.^{4,7,8} On the other hand, epigenetic factors are given by changes in DNA-bound molecules, which cause uncontrolled activation of proto-oncogenes transforming them into oncogenes or silencing of tumor suppressor genes, DNA repair genes or genes of apoptosis. The types of epigenetic changes can be grouped as follows: alterations of the chromatin structure mediated by methylation of the cytosine residues in the CpG dinucleotides; modification of the histone pattern by acetylation or methylation and alterations caused by non-coding RNAs (ncRNA).⁹⁻¹³

The environmental factors related to carcinogenesis are numerous and widely discussed in the literature on the subject. They are subdivided into three groups: physical, chemical and biological. Among the physical factors are solar radiation and ionizing radiation. The chemical factors that are commonly related to the malignant transformation of the cell can directly affect the DNA or the epigenome; among the first are: pit and tar, soot, sulfur mustard, smoke and tobacco derivatives, nickel and its derivatives, etc. The chemical agents that affect the epigenome are diverse: oral contraceptives, steroid estrogens, cyclosporin A and azathioprine. There is a group of identified chemical carcinogens in which the specific target has not been specified, these are: alcoholic beverages, arsenic and its derivatives, benzene, untreated mineral oils, etc. As biological agents that cause cancer, chronic parasitism and viruses are mentioned; among the latter are DNA viruses such as papilloma (HPV), Epstein Barr (EBV) and hepatitis B (HBV); and human retroviruses such as human T-cell lymphotropic viruses (HTLV) and herpes virus associated with Kaposi's sarcoma (KSAHV).¹⁴⁻¹⁷ Although the aforementioned environmental agents turn out to be those traditionally related to cancer, since 1981 Doll and Peto, begin to refer to dietary factors as a factor of great importance. In 2012, an EPIC study demonstrated the effects of dietary intake on cancer; for example, various nutrients have been implicated in the risk of colorectal cancer, such as folate, vitamin D, fiber, butyrate and red meat; also several studies have reported that diets rich in fats are a risk factor associated with breast cancer.¹⁸⁻²⁰

On the other hand, this complex disease has been related to the action of the enzyme methylenetetrahydrofolate reductase (MTHFR), which is an important protein in methylation reactions. The polymorphism C667T (alanine to valine) in the MTHFR gene, produces a reduction in enzymatic activity and is inversely associated with the presence of colorectal cancer and acute lymphocytic leukemia. A low intake of folate, vitamin B12, vitamin B6 or methionine is also associated with an increased risk of cancer among those with the MTHFR TT.²¹ genotype.²² Despite the foregoing, it has been internationally accepted that, depending on the genetic component, cancer may be: sporadic (80%), familial (15%) and hereditary (5%).^{17,22} Hereditary cancer is one in which a mutated gene with high penetrance has been inherited, which predisposes the individual to cancer. The genes of high penetrance are those that confer a high relative risk of suffering cancer in the carriers. However, the fact of having inherited a gene of high penetrance does not mean that inexorably suffer from the disease; it will depend on the activity or not of other genes or genetic variants (polymorphisms) and the participation of environmental factors. In general, the inherited mutated gene is a tumor suppressor, which is recessive and requires the loss of constitutive heterozygosity to initiate malignant transformation. But still, this condition is not enough, because the inactivation or epigenetic silencing of other genes is needed for the tumor to develop. Susceptibility manifests itself in different individuals of a family group through the generations, with a pattern of Mendelian segregation. Hereditary cancer usually appears at younger ages and the risk of developing it is related to the degree of kinship. In the predisposed individuals it is frequent the presence of multifocal tumors, the bilateral development of the disease and the association of multiple neoplasms. Neoplasms that affect family members are usually of the same type, but other tumors or even a grouping of different neoplasms can also be found in the same family.^{17,22}

Familial cancer refers to the inheritance of several genes of low penetrance, each with a small additive effect and genetic variants of moderate penetrance. Each of these variants would confer a moderate increase in the relative risk of suffering from the disease. Moderate penetrance gene variants include low frequency single nucleotide polymorphisms, subpolymorphic variants, and mutations.²² The role of adverse environmental factors in this group is greater, and a certain threshold must be exceeded for the disease to appear. Sporadic cancer depends on the transformations that environmental factors can develop in the epigenome, that make the genome susceptible to mutation or that there is silencing of some genes or overexpression of others; it will also depend on inherited rare genetic variants that can make the individual more susceptible to certain environmental factors.

Commentary

In this way, as can be seen, the malignant transformation of a cell always depends on the environment, which acts on the epigenome and/or the genome. On the other hand, for the clonal expansion that determines the development of a tumor to occur, the failure of multiple defense mechanisms that involve a large number of genes and genetic variants is required, so that cancer is considered a complex disease, of multifactorial etiology in all cases. One could think of a special condition in the energy dynamics and stability of the DNA molecule that facilitates epigenetic modifications to certain conditions of the cellular environment, leading to the multiple failure of protection genes and on-expression of oncogenes, a necessary condition for the development of the illness.

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Conflict of interest

The author declares there is no conflict of interest.

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