IMPACTO CIENTÍFICO EDITORA

THE TUMOR SUPPRESSOR GENE p53 AND ITS ROLE IN THE ETIOPATHOGENESIS OF NEOPLASMS

O GENE SUPRESSOR DE TUMOR p53 E SEU PAPEL NA ETIOPATOGENIA DE NEOPLASIAS

EL GEN SUPRESOR DE TUMORES p53 Y SU PAPEL EN LA ETIOPATOGÉNESIS DE LAS NEOPLASIAS

https://doi.org/10.56238/edimpacto2025.087-005

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ABSTRACT

The p53 gene is considered the "guardian of the genome", a protein located in the position 1.3 of the short arm of chromosome 17, whose main function maintaining genome stability under normal conditions and also its integrity. The p53 by having the function of preserving genome integrity, assigns a significant role in carcinogenesis, their relationship has been established due to the high rate of mutations found in malignant tumors from different tissues. Its performance in almost all human tumors, directly or indirectly, has been observed in the pathogenesis. When stabilized, p53 is converted into a functional protein due to its translational modifications in response to cellular stress derived from DNA damage, which follows the start of the realization of some functions due to genetic damage, such as particularly in genes that regulate the cell cycle, DNA stability and programmed cell death (apoptosis).

Keywords: p53 Gene. Neoplasms. Pathology.

RESUMO

O gene p53 é considerado o “guardião do genoma”, uma proteína, localizada na posição 1.3 do braço curto do cromossomo 17, que tem como principal função manter a estabilidade do genoma em condições normais e a sua integridade. Por possuir como função a preservação da integridade do genoma, o gene p53 atribui um papel significativo na carcinogênese e sua relação tem sido estabelecida devido ao alto índice de mutações encontradas em tumores malignos de diferentes tecidos. A sua atuação em uma quantidade expressiva de neoplasias humanas, de forma direta ou indireta, tem sido observada na etiopatogenia. Quando estabilizada, a p53 é convertida em uma proteína funcional devido as suas modificações transducionais em resposta ao estresse celular derivado do dano ao DNA, o que decorre ao início da realização de algumas funções devido ao dano genético, tais como: particularmente

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nos genes que regulam o ciclo celular, a estabilidade do DNA e a morte programada da célula (apoptose).

Palavras-chave: Genes p53. Neoplasias. Patologia.

RESUMEN
El gen p53 se considera el "guardián del genoma", una proteína ubicada en la posición 1.3 del brazo corto del cromosoma 17. Su función principal es mantener la estabilidad e integridad del genoma en condiciones normales. Debido a su función de preservar la integridad del genoma, el gen p53 desempeña un papel significativo en la carcinogénesis, y su relación se ha establecido debido a la alta tasa de mutaciones encontradas en tumores malignos de diversos tejidos. Su papel en un número significativo de neoplasias humanas, directa o indirectamente, se ha observado en la etiopatogenia. Al estabilizarse, el p53 se convierte en una proteína funcional debido a sus modificaciones transduccionales en respuesta al estrés celular resultante del daño del DNA. Esto conduce al inicio de ciertas funciones debidas al daño genético, como las de los genes que regulan el ciclo celular, la estabilidad del DNA y la muerte celular programada (apoptosis).

Palabras clave: Genes p53. Neoplasias. Patologia.

1 INTRODUCTION

The Industrial Revolution, in the eighteenth century, was a great advance that triggered change in the daily life of society. This encouraged rural men to migrate to the cities in search of a better quality of life. This transition triggered a change in the quality of life in the family economy, the loss of autonomy to produce their own food, the beginning of the consumption of industrialized products, vegetables with pesticides. And it was unknown to them that this change would be accompanied by an increase in their exposure to a high array of chemical, physical and biological agents with mutagenic and carcinogenic potential, which implies the growing incidence of cancer in Brazil and worldwide.[1]

In Brazil, today, one of the main causes of mortality and morbidity is malignant neoplasms. It represents the second single cause of mortality. Neoplasms, both benign and malignant, are diseases of uncontrolled gene expression, which is why they are called genetic diseases.[2]

P53, because its function is to preserve the integrity of the genome, attributes a significant role in carcinogenesis, its relationship has been established due to the high rate of mutations found in malignant tumors of different tissues. Therefore, it is considered the "guardian of the genome", a protein, located at position 1.3 of the short arm of chromosome 17, whose main function is to maintain the stability of the genome under normal conditions and also its integrity.[3,4,5,6]

When stabilized, p53 is converted into a functional protein – capable of binding to the response elements of its genes to regulate transcription – due to its transductional modifications in response to cellular stress derived from DNA damage, which results from the beginning of the performance of some functions due to genetic damage, such as: particularly in the genes that regulate the cell cycle, DNA stability and programmed cell death (apoptosis).[5] The tumor suppressor gene, p53, is an important transcription factor, plays a central role in the mechanisms of cell cycle regulation and inactivation, and is considered an important event in carcinogenesis.[7, 8, 9]

Thus, this article is justified by seeking to disseminate more and more knowledge about the "guardian of the genome" and about its genetic, clinical and even social implications.

2 METHODOLOGY

This is a descriptive study with a qualitative approach, carried out through a bibliographic survey related to the theme "Tumor suppressor gene p53" published from January 2000 to January 2016 in four databases, *NCBI, Medline, Lilacs* and *Scielo*. In the

NCBI, "tumor suppressor p53" were used as descriptors, while in *Medline, Lilacs and Scielo* "tumor suppressor gene p53", "gene p53", "protein p53". As inclusion criteria, articles were chosen that presented the keywords as well as involved the p53 gene as a central theme. As exclusion criteria, articles outside the years of analysis were excluded.

3 THEORETICAL FRAMEWORK

3.1 THE GENE AND THE P53 PROTEIN

The p53 gene is considered the "guardian of the genome", located at position 1.3 of the short arm of chromosome 17, it covers 20kb of DNA with 11 exons, whose transcription results in 3.0 kb of mRNA. In translation, this mRNA produces a 53kDa protein, hence the name p53.[10, 11]

p53 is responsible for regulating an extensive system that controls the integrity of the genome in the face of cellular damage, such as metabolite depletion, hypoxia, heat shock, chromosomal alterations, viral oncoproteins, and activation of cellular oncogenes.[12, 13,14]

There is activation of the gene through cell damage, and its transcription factor interrelates with at least six other genes. An example is the binding to the promoter of the p21 gene, whose product is a cyclin-dependent kinase inhibitor that acts to block the inactivation of pRb by CDK4. This action leads to the arrest of the cell cycle in the G1 phase, with no duplication of the DNA, phase S, thus allowing the restoration of the damaged DNA.[15]

An alternative route of action of p53 to unrepaired damage is the induction of apoptosis, which is programmed cell death. Thus, when p53 has a mutation, cells with impaired DNA flee from the restoration of this damage or its extermination and, thus, give rise to a malignant clone.[15.16]

3.2 THE ACTIVATION OF P53

The inactive p53 protein is located in the cytoplasm in low concentration and has an average life of about twenty to thirty minutes, being relatively short. Under these conditions, the p53 protein needs to receive signals or undergo modifications and convert it into a functional protein. The signals or events that lead to the activation of p53 are mainly linked to situations of cellular stress, such as DNA damage by ionizing or ultraviolet radiation; the reduction of nucleotide content, as occurs in the use of many chemotherapy drugs; hypoxia; the activation of oncogenes; or the modifications in molecules in the cell.[17]

These stimuli cause a rapid increase in p53 levels in the cell, by increasing the stability of the protein as well as by its biochemical activation, allowing the protein to act as a transcription factor, to bind DNA to regions determined by specific base sequences located

in promoter regions, and to regulate the expression of its genes. The duration and kinetics of the increase in protein levels differ according to the activating factor of p53 and the genes that have been transcriptionally regulated by the protein.[17.18]

3.3 LOSS OF P53 PROTEIN FUNCTION

The p53 protein can lose its function due to several situations, including: genetic alterations; interaction of viral proteins with p53 and interaction of proteins that regulate the cell cycle with p53.[18, 19]

3.3.1 Genetic alterations

There may be a point mutation, also called *missense*; a gene deletion, called *nonsense,* of one or more alleles of the p53 gene; and insertion, in the DNA sequence, of nucleotides.[19, 20]

Missense consists of the exchange of a nucleotide, which is the most common form of mutation of the p53 gene found in neoplasms. The *nonsense mutation*, in turn, can lead to the transcription of a truncated and also non-functional protein.[19]

Missense or *nonsense*, a mutation in the p53 gene significantly alters the p53 protein, leading to an incompetence to promote cell cycle arrest or lead to apoptosis. The mutated forms of the protein also have the ability to interact with the wild protein, preventing tumor suppression, and this phenomenon is known as the "negative dominant effect", since the mutation of one of the alleles of the p53 gene produces what appears to be a dominant effect on the remaining normal allele.[19]

3.3.2 Interaction of viral proteins with p53

The interaction of the p53 protein with viral proteins is possibly linked to the triggering of neoplasms. Two common models of this process are inactivation or stabilization, which occur for example when EBNA5 of the Epstein Barr virus (EBV) interacts with the p53 protein, and degradation of p53, which commonly occurs during the interaction of the E6 antigen of the HPV virus with the protein.[21]

3.3.3 Interaction of proteins that regulate the cell cycle with p53

An example of this interaction is the contact of the p53 protein with that of MDM2, which leads to the overexpression of the MDM2 protein in RKO cells. In addition, there is also impairment of transactivation and checkpoint in G1 mediated by p53.[22]

3.4 P53 AND NEOPLASMS

Cancer, a pathology with a multifactorial cause, results from genetic alterations, environmental factors and lifestyle. There are proto-oncogenes, which are genes in charge of the positive regulation of cell proliferation, and tumor suppressor genes, which have the function of inhibiting cell multiplication. When a neoplasm develops, there is the activation of proto-oncogenes and, at the same time, the inactivation of tumor suppressor genes. When mutation occurs, there are unrestricted cell divisions, in the case of oncogenes, and, in the case of tumor suppressor genes, there is the production of defective proteins.[19,18,23]

The main alteration found in human neoplasms is the mutation of the tumor suppressor gene p53, which occurs in more than 50% of tumors. The p53 gene is not active in cells with damaged DNA. If there are problems in the DNA, the gene interrupts the cell cycle until the damage is repaired. When there is a mutation in p53, the cell cycle progresses unbridled and damaged DNA is reproduced, promoting an uncontrolled proliferation of cancer cells. When the DNA of the mother cell is damaged, so is that of the daughter cells, and their cycle is likewise unrestrained.[13.19]

3.3.4 P53 in Lung Cancer

Lung carcinomas have 50 to 70% of cases mutations in a p53 allele, often associated with loss of the wild allele. Most mutations correspond to G:C to T:A/A:T transversions, which occur predominantly in 7 codons. Studies conducted to date have shown that p53 alterations in lung cancer are associated with a worse prognosis, in addition to being relatively more resistant to chemotherapy and radiation.²4

3.3.5 P53 in Breast Cancer

Breast cancer has a variation in mutation rates in p53, in 50% of cases are inflammatory and in 20% to 30% of cases are defined as non-inflammatory.[25]

3.3.6 P53 in Ovarian Cancer

The tumor suppressor p53 is linked to ovarian cancer by being modified by O-GlcNAc. Most solid tumors have a p53 mutation, leading to their loss of function. Ovarian neoplasms have a high frequency of p53 mutation.[26]

4 PERSPECTIVES

Despite being the most researched tumor suppressor gene, p53 still has many unknown issues. It is known that patients who have the mutation have a negative prognosis. However, with several studies being developed, there is hope for success in the results, providing greater knowledge on the subject and favoring numerous patients.[19]

5 CONCLUSION

This article illustrates the change in human behavior throughout history and its relationship with genetic alterations, such as the p53 gene, responsible for preserving the integrity of the genome, which has drastic consequences for the life of the human being, after all, the main alteration found in human neoplasms is the mutation of the tumor suppressor gene p53, which occurs in more than 50% of tumors.

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