

The importance of genetic studies of lung cancer

A importância dos estudos genéticos sobre câncer de pulmão

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One of the contributions of the biomedical sciences was the discovery that cancer is a genetic disease. The simplicity of this statement can cause surprise in the view of the pathophysiological complexity of cancers. In fact, cancer initiates as a consequence of multiple alterations in the DNA of a single cell which change its genomic constitution. This cell, in turn, passes these alterations on to its descendents, becoming a group of cells that proliferate uncontrollably. Approximately 10% of cancers are hereditary and occur due to alterations that confer a greater susceptibility to chemical, physical or viral agents. However, most cancers are sporadic and acquired by exposure to those agents. In both cases, the genetic damage occurs in genes that affect the homeostasis of various biological processes such as proliferation, cell growth, apoptosis, angiogenesis, invasion and metastasis.⁽¹⁾ Approximately 384 genes are associated with the development of several cancers, which represents more than 1% of the genes described to date.⁽²⁾ The first cancer for which, in theory, the genetic basis was described was colorectal cancer,⁽³⁾ in which the critical genes of the Wnt signaling pathway, K-ras, transforming growth factor beta and p53 are affected during the progression of the tumor. Currently, the great challenge of the researchers is to elucidate the genetic program responsible for the onset and progression of the tumor in each type of cancer. In this effort, genomics and proteomics have been the best allies of the researchers in identifying biomarkers that can facilitate understanding of the mechanisms involved in the carcinogenesis in various tissues, such as the lung. Worldwide, lung cancer is the tumor with the highest mortality rate.⁽⁴⁾ Lung cancers are categorized as small cell lung cancer, a subtype with a neuroendocrine phenotype, or non-small cell lung cancer, which comprises adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Smoking is the principal risk factor and is associated with 90% of all diagnosed cases.⁽⁵⁾ It is estimated that 15% of smokers will develop lung cancer and that 10% of lung cancers will occur in individuals

who have never smoked. Among nonsmokers, passive smoking and exposure to other carcinogens are risk factors for the development of the tumor. In both cases, the hereditary component is determinant, since it confers a greater genetic predisposition to the individuals. Genes such as p53, p14ARF, p16INK4a, RB, FHIT and RASSF1A are related to lung cancer.⁽⁶⁻¹⁰⁾ In addition to those, another seventy genes have also been associated with the development of lung cancer. Such genes are described on a site that is host to a gene archive (<http://www.bioinformatics.org/LuGenD/index.htm>), which is of fundamental importance for the understanding of the genetic programming involved in the onset and development of lung cancer. Three representatives of this archive—CYP1A1, CYP2A6 and CYP2E1—are P450 cytochrome family members and participate in the metabolism of various drugs, including tobacco-derived substances, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N'-nitrosonornicotine. Genetic variations in this family members increase the risk of developing lung cancer. In this edition of the Brazilian Journal of Pulmonology, Honma et al. describe a study which evaluates the distribution of the CYP1A1*2A allele in 200 patients with lung cancer and 264 negative controls.⁽¹¹⁾ This allele was associated with greater activity of the CYP1A1 enzyme. The initial result revealed no increase in the risk of lung cancer in patients. However, in a second analysis, considering the ethnic composition of the patient and control groups, the CC/TC genotype seemed to increase the risk of lung cancer in African-Brazilian patients, with an odds ratio of 3.19 (95% CI: 1.53-6.65). Additional studies are necessary to confirm such an association. If this association is confirmed, the following question arises: Why is the risk greater among African-Brazilians than among White Brazilians? This question can be answered by taking into account the genetic variation within human populations, which respond differently to endogenous and exogenous stimuli. Specific variations in the human genome are known as polymorphisms.

Conceptually, polymorphisms are variations that occur in more than 1% of the population. These variations can be single-base substitutions, as well as insertions, deletions, variations in the number of repeated sequences, complex rearrangements or structural rearrangements. Single nucleotide polymorphisms (SNPs) are the most commonly observed genetic variation among human beings. It is estimated that, in the human population, there are 10–12 million SNPs, 4% of which occur in encoding areas and can therefore affect protein function. Reflecting a predisposition to genetic-based diseases such as lung cancer, SNPs, such as that of the CYP1A1*2A allele, are distributed among the ethnic groups as a consequence of the evolutionary history of each population. The study of the genetic composition of the individual or population is also an important ally of contemporary medicine in attempts to understand the molecular mechanisms associated with oncogenesis and to develop a cure for cancer.

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