Radiation carcinogenesis is an extremely complex phenomenon that progresses over time in a staged and successive manner. The progressive nature of human cancer is now well established. Atypical proliferation, in situ carcinoma, invasive cancer and metastatic dissemination are the main stages of its development. From a molecular standpoint, the basic mechanism of carcinogenesis includes the activation of oncogenes, the inactivation of suppressor genes and, very probably, the involvement of genes related to apoptosis. In radiation carcinogenesis, the Moolgavkar-Knudson (M-K) two-stage clonal expansion model proposes that radiation can act not only as an initiator but also as a promoter of neoplastic transformation, and the Mendelsohn-Pierce (M-P) model postulates that the induction of solid cancer result from the random, and successive, accumulation of mutations at specific loci of the cell genome. According to the latter hypothesis, radiation acts as a general mutagenic agent capable of producing any of these mutations, with a dose-dependent probability proportional to that of their spontaneous occurrence. In contrast to previous assumptions, the M-P model predicts that the age at the time of exposure and the time elapsed since radiation exposure exert little influence on the subsequent development of cancer. According to the best estimates, the risk of cancer from exposure to low radiation doses is $5 \times 10^{-5}$ per millisievert of equivalent absorbed dose. Considered overall, the carcinogenic potential of radiation can be regarded as weak.

Key words: carcinogenesis, radiation, clonal expansion, mutation, dose.


Mecanismos, modelos y riesgos de la carcinogénesis por radiación

La carcinogénesis por radiación es un fenómeno extremadamente complejo que progrese en el tiempo por fases sucesivas. La naturaleza progresiva del cáncer humano está ahora bien establecida. Proliferación atípica, cáncer in situ, cáncer invasivo y diseminación metastásica son los principales estadios de su desarrollo. Desde un punto de vista molecular, el mecanismo básico de la carcinogénesis incluye la activación de oncogenes, la inactivación de genes supresores y, muy probablemente, la participación de genes relacionados con la apoptosis. En la carcinogénesis por radiación, el modelo de expansión clonal en dos fases de Moolgavkar-Knudson (M-K) propone que la radiación puede actuar no sólo como iniciador, sino como promotor de la transformación neoplásica, y el modelo de Mendelsohn-Pierce (M-P) postula que la inducción de cánceres sólidos resulta de una acumulación aleatoria y sucesiva de mutaciones en loci específicos del genoma celular. De acuerdo con la última hipótesis, la radiación actúa como un agente mutagénico general capaz de producir cualquier una de estas mutaciones, con una probabilidad dependiente de la dosis proporcional a la de su ocurrencia espontánea. En contraste con previas hipótesis, el modelo M-P predice que la edad en el momento de exposición y el tiempo transcurrido desde la exposición a la radiación ejercen poca influencia en el desarrollo subsiguiente de cáncer. De acuerdo con las mejores estimaciones, el riesgo de cáncer por la exposición a dosis bajas de radiación es de $5 \times 10^{-5}$ por milisievert de la dosis equivalente absorbida. Considerado globalmente, el potencial carcinogénico de la radiación puede estimarse como bajo.

Palabras clave: carcinogénesis, radiación, expansión clonal, mutación, dosis.
INTRODUCTION

Tumor development

Carcinogenesis is an extremely complex process that evolves over time in a progressive and multi-step manner. From a mechanistic standpoint, its development is characterized by three stages: tumor initiation, promotion, and progression. Initiation is the basic triggering element of neoplastic transformation. It can be defined as the alteration produced by carcinogens in a given tissue from which areas of cell proliferation develop, some of which serve as starting points for the subsequent malignant process. Available scientific evidence indicates that tumor initiation results from the induction of molecular lesions in the cellular genome. The most important of these are point mutation and clastogenic damage, which includes different changes such as deletion, rupture, translocation and chromosomal recombination.

Tumor promotion is the process by which initially transformed cells proliferate under the action of different stimuli (hormones, growth factors) giving rise to the formation of differentiated cell populations of benign character. Protein-kinase C plays a major role in this process. Protein-kinase C plays a major role in its function as receptor of a wide group of promoter agents. This protein is a second messenger that participates in the transmission of exterior stimuli to the interior of the cells, suggesting the existence of a common molecular mechanism for various classes of tumor promoters.

Once the cell proliferation process of the promotion stage is definitively established, tumor progression starts when the cells at one or some of these foci undergo additional genetic alterations that lead to the expression of the malignant phenotype. During this phase, the cells show a marked genomic instability and acquire two of the essential characteristics of malignization: the capacity for invasion of adjacent tissues and metastasizing power.

Progressive nature of human cancers

The multi-stage and progressive nature of carcinogenesis has been demonstrated by in vitro experiments and in vivo studies. Despite the intrinsic difficulties of the latter type of study, the progressive nature of human cancer is now well documented. Thus, a) it is known that most malignant tumors in humans are preceded by a series of pre-neoplastic lesions ranging from atypical hyperplasia and epithelial dysplasia to in situ carcinoma (in breast cancer patients, recent comparative molecular analyses support this hypothesis and confirm that most invasive tumors arise through clonal evolution from pre-existing in situ disease); b) analyses of genetic predisposition conducted in families with a high incidence of cancer indicate that, besides an inherited genetic error (germline mutation), a second change (acquired somatic mutation) is required in such cases for the expression of the tumor phenotype, and c) studies of radio-induced carcinogenesis and mathematical models analyzing the influence of age on the development of cancer suggest that the development of neoplastic transformation is unlikely without the accumulation of a certain number of mutations.

At present, it can be assumed that malignant tumors progress through defined clinical and pathological stages, starting with initially benign then atypical hyperproliferation, progressing to in situ then invasive carcinomas, and culminating in metastatic disease. On the other hand, many invasive human tumors are biologically heterogeneous, probably because different tumors originate from different stem cells and follow different tumor progression pathways. Besides improving our understanding of carcinogenesis, this event has important clinical implications, suggesting that different tumor types should be treated differently. In addition to comparing different stages of tumor progression, one of the major promises of genomic technology is the ability to predict the clinical behavior of tumors and to use this information for defining prognostic and therapeutic subgroups of patients.

MOLECULAR MECHANISMS OF CARCINOGENESIS

Nowadays, it is generally accepted that the basic mechanism of carcinogenesis involves the activation of oncogenes and the inactivation of tumor suppressor genes. One or other process derives from the transformation of normal genes (that regulate critical functions such as cell proliferation, differentiation and/or senescence) into oncogenic genes, which results in the acquisition by the transformed cells of the properties that characterize a malignant tumor (unlimited clonal expansion/invasive capacity).

Oncogenes

Oncogenes are found in a mutated or abnormally expressed form in many human cancers. They can be activated by point mutation (solid tumors), by chromosomal rearrangement (leukemias/lymphomas), or by gene amplification. Because oncogenes arise from gain-of-function mutations, only one of the two copies of the gene needs to be activated for their effects to be expressed. Hence, oncogenes act in a dominant rather than a recessive fashion. The oncogenes most frequently associated with the development of sporadic human cancers and with radio- or chemo-induced malignant tumors belong to...