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Viral genes in human tumors

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The development of malignant human tumors is a complex and slow process that requires the accumulation of multiple genetic alterations. The activation of oncogenes and the inactivation of tumor suppressor genes are necessary and the inhibition of apoptosis seems to be an important step in most tumors, at least in the early stages of malignant transformation. The genetic alterations include mutations, deletions and gene amplifications and, in many cases, a background of genetic instability.

There are many carcinogenic agents, such as chemical compounds, -y-irradiations and viruses. Viruses constitute the second most important etiological factor in human tumors and about 10% of malignant tumors are associated with them. Retroviruses are the most frequent; amongst them are the lymphotropic HTLV, the Moloney retrovirus and so on. Retroviruses may induce insertion mutagenesis and can drive activated oncogenes into the cells. DNA viruses are also numerous and several important groups can be recognized: human papilloma viruses, with over 70 serotypes, which can infect most epithelia and are associated with cervical, skin and upper airway carcinomas; hepatitis B and hepatocarcinomas; Epstein-Barr virus and lymphomas, nasopharyngeal carcinomas, etc.; SV4O virus and some mesotheliomas and brain tumors; herpes type 1 with stromal tumors; herpes type 2 and cervix carcinomas; herpes type 8 with Kaposis sarcoma and body cavity lymphomas.

Viral genes may interact with the main pathways involved in carcinogenesis. In fact, some of their products are capable of inducing cell proliferation, binding tumor suppressor proteins and inhibiting them and activating or inhibiting gene products related with apoptosis. Some viral genes are associated with genetic instability. For example, herpes type 1 may induce microsatellite instability while human papilloma virus and adenoviruses can provoke chromosome instability. Although the association between viruses and cancer is clear in many human tumors, it has to be stressed that, in addition to the viral effects, the accumulation in the cell of other genetic alterations is necessary for the malignant transformation to occur.

On the other hand, viruses play a relevant role in the treatment of human tumors. They are the best vectors to deliver therapeutic genes and most gene therapy protocols are based on viruses. Both retroviruses and adenoviruses are capable of transferring tumor suppressor genes, suicide genes or genes related to apoptosis. There are many clinical approaches in transducing p53, p16, pRb genes or the adenoviral EIA gene. Finally, it is interesting to know that some adenoviruses can replicate more efficiently in malignant cells with selective genetic alterations. These defective adenoviruses proliferate in cells with oncogenic alterations, such as a mutated p53 gene, and kill them; this represents one of the most promising areas in cancer gene therapy.

In this course, we will study the viruses and viral genes most frequently involved in human tumors, analyze the cellular pathways that are activated or inactivated by viral genes and, finally, discuss the perspectives of cancer gene therapy based on viruses.

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