

Oncogenes and tumor suppressor genes as paradigms in oncogenesis

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Summary

Cancer is the result of genetic and epigenetic changes that occur mainly in stem (precursor) cells of various cell types. Two main categories of genes are involved in the process of carcinogenesis. Oncogenes are activated proto-oncogenes and tumor suppressor genes are inactivated by mutation in the global sense, that is point mutation, deletion, rearrangement, and duplication. Both types of genes are required for normal

cell proliferation and differentiation and aberrant expression leads to abnormal cell proliferation. Ras and p53 genes are the paradigms for oncogenes and tumor suppressor genes, respectively, whereas the oncogenes carried by the human papillomaviruses (HPV) comprise the best example of tumor viruses involvement in human cancer.

Key words: human papillomavirus, oncogenes, tumor suppressor genes

Introduction

It is now well established that cancer is caused by a combination of environmental and genetic factors. Cancer rates are influenced by the environment, lifestyle and diet on one hand and heredity and spontaneous mutations on the other [1]. The discovery of cellular oncogenes [2-4] has led to the elucidation of some of the mechanisms which convert a normal cell to a malignant one and provided the information on how to intervene in this process.

Given the fact that the development of cancer is a multi-step or multi-stage process, many genes (oncogenes, tumor-suppressor or others) are involved [5]. The cloning and detailed characterization of oncogenes and tumor-suppressor genes and their protein products has allowed tremendous progress on the diagnosis, prognosis and treatment of human cancer.

Although there are many oncogenes and tumor suppressor genes, it seems that there exist few key players among them in the development of cancer. The ras oncogenes and the p53 tumor suppressor gene seem to be the paradigms in oncogenesis [5]. Papillomaviruses, on the other hand, carrying oncogenes are the main cause of human cervical cancer [6,7]. This is achieved with an

interplay of viral oncogenes with cellular oncogenes and tumor suppressor genes.

The Ras oncogenes

The Ras family is comprised of 3 functional genes [8,9]. The H-ras1 and the K-ras2 genes, which have retroviral homologues, and the N-ras gene, which was discovered by gene transfer (Figure 1). The ras genes encode proteins of molecular weight of 21,000 daltons, called p21, and have been shown to play an essential role in cellular proliferation and differentiation. Quantitative and qualitative changes in the expression of ras genes may be critical in cell transformation. Moreover, ras genes can either block [10] or induce [11,12] differentiation and they can either act as oncogenes [13] or oncosuppressor genes [14,15].

The ras genes are conserved in the coding domains. The introns and flanking regions are poorly conserved apart from a small region in the first intron. Regulatory sequences have been found at the 5' of the gene [16] as well as at the 3'. The variable tandem repeat (VTR) sequences located at the 3' flanking sequences of the human H-ras1 gene have been found to possess an enhancer-like activity [17].

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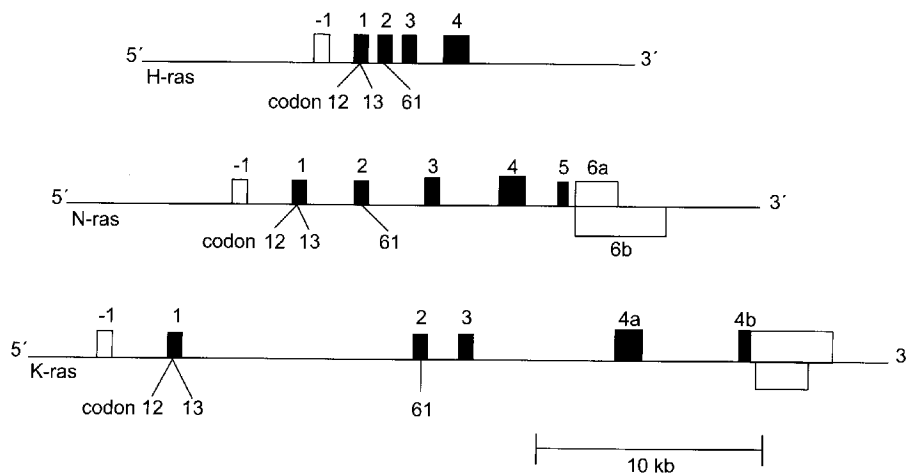


Figure 1. The structure and organization of the H-, K- and N-ras genes. Black boxes indicate the coding and open boxes the non-coding exons.

Mutations of ras genes at codons 12, 13 or 61 result in continuous stimulation of cell proliferation. The mutant ras genes have been detected in a significant proportion of all human cancers but their incidence varies. A summary of ras mutation frequencies detected in a variety of human tumors is shown in Table 1. The highest frequency was found in pancreatic cancer (90%).

Ras proteins are small GTP binding proteins localized in the internal part of the cytoplasmic membrane. Wild-type ras protein possesses a weak GTPase activity while its mutant counterparts have several-fold stronger activity. Ras protein is a binary GDP/GTP switch in the inner surface of the cytoplasmic membrane relaying signals from receptors to the cytoplasm. Ras proteins receive farnesyl molecules that anchor them onto the

membrane, and signals to activate the Ras kinase and the MAPK pathway cascade is vital for cell proliferation; enhanced activation of this pathway contributes to the development of the cancer phenotype [18,19].

Although initially ras was identified as an oncogene, its involvement in the regulation of apoptosis, and consequently cell death, is now convincing [15,20]. At first, these ideas seem contradictory, however, they could co-exist taking into account the variety of regulatory elements in the different cell systems.

The p53 tumor suppressor gene

The human p53 tumor suppressor gene is located on chromosome 17p13 and encodes a 563 kDa nuclear phosphoprotein, which plays a central role in many cellular processes, such as DNA repair and apoptosis (Figure 2). Allelic loss of the TP53 locus is observed in more than 50% of human cancers.

p53 exists in two principal polymorphic forms that have either arginine (p53Arg) or proline (p53Pro) at codon 72. It has been proposed that p53Arg protein is more susceptible to inactivation through the E6-ubiquitin pathway than the p53Pro isoform, and that p53Arg/Arg homozygosity is associated with increased risk of developing HPV-associated cervical cancer.

It is demonstrated that the p53Arg homozygous genotype affects the predisposition for laryngeal tumors while the heterozygous status does not [21]. Moreover, individuals harboring the Arg/Arg genotype have an increased risk of developing bladder cancer [22]. In addition, p53 codon 72Arg homozygosity is associated with advanced lung cancer [23] and breast cancer [24].

Table 1. Ras oncogenes in human tumors

Tumor site	Ras gene	Mutation frequency (%)
Pancreas	K	90
Thyroid	H, K, N	60
Colon	K	50
Ovary	K	45
Skin	H, K, N	45
Myelodysplastic syndrome	N, K	40
Liver	N	30
Acute myelogenous leukemia	N	30
Lung adenocarcinoma	K	30
Head and neck	H, K	30
Bladder	H, K	30
Cervix	K, H	30
Brain	N, K	15
Breast	H, K	10
Kidney	H	10

K: Kirsten ras, H: Harvey-ras, N: N-ras

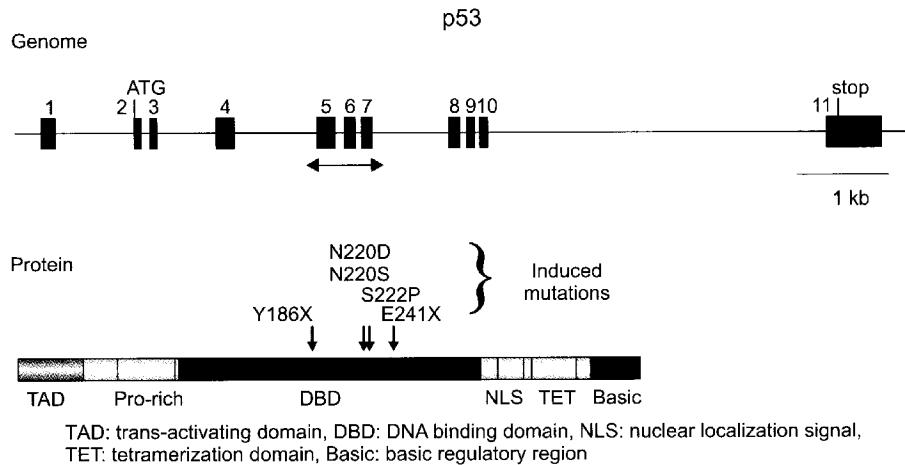


Figure 2. The structure and organization of the human p53 gene and its protein product.

An interplay between the p53 and H-ras 1 gene has also been observed [25].

Human papillomaviruses and cancer

It is well established that persistent infection of the uterine cervical epithelium with oncogenic HPV types is a necessary but insufficient causal factor in the carcinogenesis of cervical cancer. For 13 HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66) there is sufficient evidence that they can cause cervical cancer whereas for another 5 types (HPV 26, 53, 68, 73 and 82) studies indicate possible involvement [26-28]. Oncogenic papillomaviruses carry two oncogenes, the E6 and E7 from which are derived the corresponding early viral oncogenic proteins (Figure 3). The capsid of papillomaviruses is composed of two viral proteins: the major capsid protein, ORL1 and the minor capsid protein, ORL2. Prophylactic vaccination is aimed at making antibodies to the late viral protein thus blocking infection. Therapeutic vaccination is aiming at stimulating T-cell responses against the early viral oncogenic proteins, E6 and E7.

Conclusions

The genetic basis of cancer has been well established by the discovery of oncogenes [1-5]. The study of ras oncogenes and the p53 tumor suppressor gene as paradigms to elucidate the mechanisms of carcinogenesis have been very fruitful. Moreover, the study of HPV and its oncogenes as a model system has been decisive in the understanding of cervical cancer. The progress made in the above directions has helped in the diagnosis,

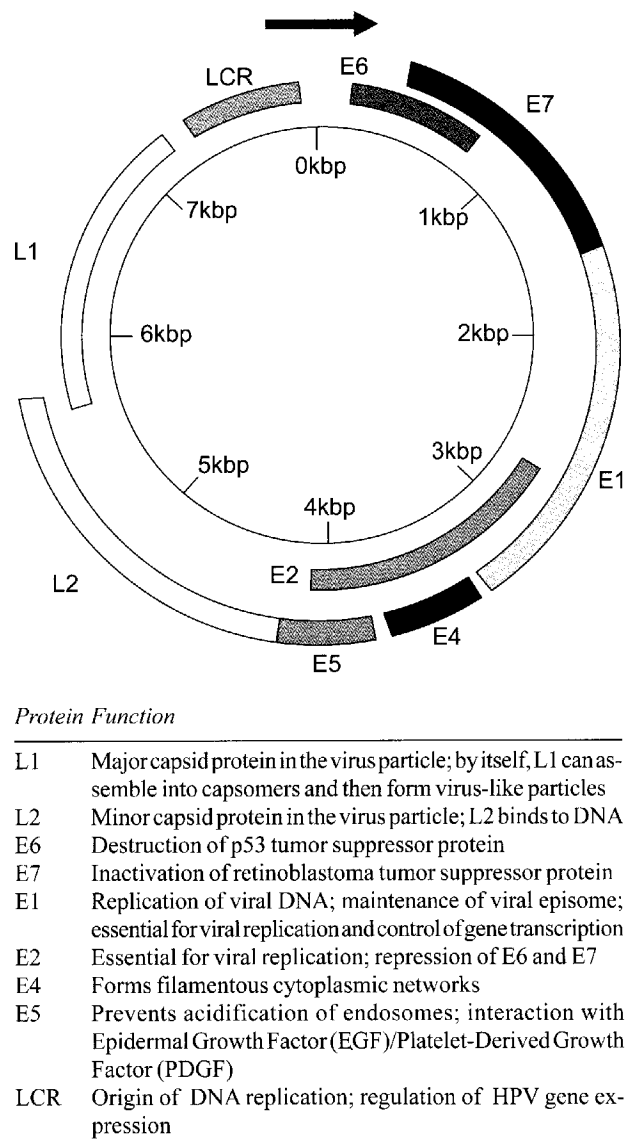


Figure 3. The structure and organization of the human papillomavirus.

prognosis and treatment of human cancer. However, despite the tremendous progress made in the area of genetic contribution to the development of cancer we should not forget the involvement of epigenetic events and their role in carcinogenesis.

An example of epigenetic mechanisms that may occur in parallel to genetic events is the demonstration of aberrant methylation and deacetylation of the DLC-1 (detected in liver cancer) gene in prostate cancer [29]. Thus, apart from the activation of an oncogene (growth factor) [30] or an inactivation of a tumor suppressor gene (DLC-1), epigenetic events (methylation or deacetylation) may contribute to the multi-stage process of prostate carcinogenesis.

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