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A COMPREHENSION STUDY ON CARCINOGENS AND THE RELATIONSHIP BETWEEN CANCER PROGRESSION AND TUMOR SUPPRESSOR GENES

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Abstract:

Tumor suppressor genes commonly contribute to the fidelity of the cell cycle replication process. They may act as negative regulators of oncogenes, cell cycle check points, or gene products that supply the appropriate nutrients or components to complete a faithful cell cycle division in the absence of stress. The basic aim of the study is to find carcinogens and the relationship between cancer progression and tumor suppressor genes. Evidence that viruses could cause cancer first came from a series of studies by Peyton Rous beginning in 1911. He excised fibrosarcomas (connective tissue tumors) from chickens, ground them up, and removed cells and debris by centrifugation. After passing the supernatant through filters with very small pores, which retained even the smallest bacteria, Rous injected the filtrate into chicks. Carcinogens are particular substances which are linked to cancers. There are many different causes of cancer like tobacco, obesity, poor diet, lack of physical activity, ionizing radiation, drinking too much alcohol, infections by hepatitis B and hepatitis C, HPV and genetic changes. It is concluded that the best way to prevent cancer is increasing the knowledge about risk factors and changing the lifestyle in order to be less exposed to carcinogens.

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INTRODUCTION:

Tumor suppressor genes commonly contribute to the fidelity of the cell cycle replication process. They may act as negative regulators of oncogenes, cell cycle check points, or gene products that supply the appropriate nutrients or components to complete a faithful cell cycle division in the absence of stress. Mutations in tumor suppressor genes are loss-of-function mutations and so occur in both alleles of a gene (the mutations act in a recessive fashion). Deletions, nonsense mutations, frame-shift mutations, insertions, or missense mutations that inactivate functional activity of a protein are all observed in tumor suppressor genes [1]. Some tumor suppressor genes have a haplo insufficient phenotype. In animals or humans with one mutant allele and one wild-type allele of a tumor suppressor gene, a suboptimal level of the gene product results in a lower level of function and a loss of fidelity. The *p53* tumor suppressor gene in the heterozygous condition has a lower level of apoptosis in lymphocytes exposed to stress in both mice and humans (Li-Fraumeni syndrome) when compared to two wild-type copies of that gene [2].

The majority of 'classical' tumor suppressor genes have been characterized through the identification of germline mutations associated with predisposition to human cancer. Most of these genes have been first isolated using linkage analysis in rare, large families with highly penetrant autosomal dominant genetic predisposition to cancer. *Rb* is the first example of a tumor suppressor gene identified by this approach [3]. These inherited cancer syndromes account for less than 5% of the global cancer burden. A different strategy will be required to identify high-prevalence, low-penetrance predisposition genes, mostly using association studies and linkage disequilibrium. The proportion of cancers attributable to these genes is probably much higher than 5% [4].

Tumor suppressor genes are recessive at the cellular level and therefore inactivation of both alleles is required. This is more often accomplished by mutation of one allele and deletion of the second allele. The second allele in some cases is targeted by deletion (homozygous deletions), methylation with consequent loss of expression, or mutation [5]. Finally some mutations act as dominant negative, and effectively a single event inactivates both alleles. *p53* was the first human tumor suppressor gene identified by mutational analysis of sporadic tumors, and since then several others have been described. Classic tumor suppressor genes are defined by mutation in both familial and sporadic forms of cancer. An increasing number of candidate tumor suppressor genes are identified by somatic mutations and have not been associated with genetic predisposition [6].

Objectives of the study

The basic aim of the study is to find carcinogens and the relationship between cancer progression and tumor suppressor genes.

Tumor Suppressor Genes

Tumor suppressor genes, or anti-oncogenes, encode proteins that transduce negative cell growth regulation signals such as those involved in cell cycle arrest and apoptosis.[29] In contrast to oncogenes, which are activated by mutation of only one of the two gene copies, tumor suppressor genes are inactivated by point mutations or deletion in both alleles of the gene in a "two-hit" fashion [7]. Once tumor suppressor genes are inactivated, the cell escapes stringent cell cycle control and is predisposed to uncontrolled growth and division. "Loss of function" of multiple tumor suppressor genes is thought to be the major event leading to the development of malignancy.

Cancer causing Retroviruses

Evidence that viruses could cause cancer first came from a series of studies by Peyton Rous beginning in 1911. He excised fibrosarcomas (connective tissue tumors) from chickens, ground them up, and removed cells and debris by centrifugation. After passing the supernatant through filters with very small pores, which retained even the smallest bacteria, Rous injected the filtrate into chicks. Most of the injected chicks developed sarcomas. The transforming agent in the filtrate eventually was shown to be a virus, called *Rous sarcoma virus (RSV).* Some 50 years later, in 1966, Rous was awarded the Nobel prize for his pioneering work. The long delay in recognizing the importance of his discovery was due to the absence of any obvious molecular mechanism by which a virus could cause cancer, either in birds or in humans [5].

The next breakthrough came in 1977 when Michael Bishop and Harold Varmus showed that normal cells from chickens and other species contain a gene that is closely related to the RSV v-*src* gene. This normal cellular gene, aproto-oncogene, commonly is distinguished from the viral gene by the prefix "c" (c-*src*). The landmark discovery of the close relationship between a viral oncogene and cellular proto-oncogene fundamentally reoriented thinking in cancer research because it showed that cancer may be induced by the action of normal, or nearly normal,

genes. RSV and other oncogenic viruses are thought to have arisen by incorporating, or *transducing*, a normal cellular proto oncogene into their genome. Subsequent mutation in the transduced gene then converted it into an oncogene [7,8].

Relationship between different carcinogens and their related cancers

Carcinogens are particular substances which are linked to cancers. There are many different causes of cancer like tobacco, obesity, poor diet, lack of physical activity, ionizing radiation, drinking too much alcohol, infections by hepatitis B and hepatitis C, HPV and genetic changes [9].

Table 01: Shows the relationship between carcinogens and their related cancers

Carcinogens		Cancers
Tobacco smoking (36)		a.Larynx (45), b.Head (46), c.Neck (47), d.Stomach (48), e.Bladder (49), f.Kidney (50), g.Esophagus (51), h.Pancreas (52)
Alcohol exposure (41)		a.Liver, b.Digestive tract
Benzene(53)		Leukemia (53)
Asbestos fibers(54,55) Naturally occurring and synthetic asbestos-like fibers, such as wollastonite, attapulgite, glass wool and rock wool, are believed to have similar effects		a.Lung cancer (56) b.Mesothelioma (57)
high-salt diet (58,59)		Gastric cancer (58,59)
Aflatoxin B1 (60,61)		Liver cancer (60,61)
Betel nut chewing (62,63)		Oral cancer (62,63)
Oncoviruses	human papillomavirus (64,65)	Cervical cancer (64,65)
	Epstein–Barr virus (66,67)	B-cell lymphoproliferative disease and nasopharyngeal carcinoma (66,67)
	Kaposi's sarcoma herpesvirus (68,69)	Kaposi's sarcoma and primary effusion lymphomas (68,69)
	hepatitis B and hepatitis C viruses (70)	hepatocellular carcinoma (71) T-cell leukemias (72)
	human T-cell leukemia virus-1 (73,74)	Lymphoma and Leukemia (73,74)
Helicobacter pylori(75)		Gastric carcinoma (75)
Parasitic infections associated with cancer (76)	*Schistosomahaematobium* (77)	Squamous cell carcinoma of the bladder and the liver flukes (79,80)
	Opisthorchisviverrini and *Clonorchissinensis (78)*	Cholangiocarcinoma (81)

CONCLUSION:

It is concluded that the best way to prevent cancer is increasing the knowledge about risk factors and changing the lifestyle in order to be less exposed to carcinogens. Different chemical, physical, environmental carcinogens can cause different types of cancer which were mentioned above. Knowing these carcinogens and their effect on body can help people to prevent cancers and live longer. As it was shown in our previous researches, the rule of tumor suppressor genes can be considered as a key point in cancer occurrence. As it's proofed before, these genes affect the regulation of the cell cycle and they promote apoptosis in damaged cells. Knowing their specific genetic location of these genes is really important in genetic engineering researches.

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