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Research Article

An overview on Carcinogens and the relationship between cancer progression and mutation of Tumor suppressor genes

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ABSTRACT:

Every year a large number of people die because of different types of cancers. Cancers are a group of diseases with abnormal cell growth and have a potential to spread to different tissues of body. Cancers can be malignant or benign. Several symptoms like bleeding, weight loss, lump and lesion can be seen in different types of cancers. Two views are considered against cancer. The first involves identifying carcinogens and using strategies against them and the second one is to know which strategy should be utilized for which cancer and this can be done by according to identification of the type of cancer, its stage, and the patient's personal profile. During the past years, extensive studies have been done on the relationship between carcinogens and various forms of cancers. There are many different environmental, Physical and chemical reasons for cancer creation. On the other hand, genetic based reasons in cancer occurrence play a key role in cancer occurrence and its progression. Mutation in some functionally important genes like tumor suppressor genes is a good example in this case. Our group has focused on the important relationship between the mutation of tumor suppressor genes and different types of cancers. In this review article we classified different carcinogens with their specific cancers and also several tumor suppressor genes are classified with their genetic locations and their function.

Key words: Carcinogens, Tumor suppressor genes, Cancer progression

INTRODUCTION

Cancers are a group of disease with abnormal cell growth and potential to spread to different tissues of body (1-5). Several symptoms like bleeding, weight loss, lump and lesion can be seen in different types of cancers (6-10). There are many different environmental, Physical and

chemical reasons for cancer creation (11-13). On the other hand it should be considered that there are genetic based reasons in cancer occurrence like hereditary problems or mutation in some functionally important genes like tumor suppressor genes (14-18). There are some routine therapeutic manners for cancer treatment like radiation therapy (19-21), surgery and chemotherapy (22-24); but recently studies have switched on new therapeutic manners like immunotherapy (25, 26), gene therapy (27, 29), entering of nanotechnology by focusing on medical nanotech in proposing new advanced technologies and drugs in cancer treatment (30-32). Abnormal genetic changes can be mentioned as a main reason of cancer occurrence because all chemical and physical triggers change the cell cycle regulation and it's the outcome of changes in the genetic of normal cells (33-35). For a duration of time our group focused on these important genes and changes in their expression in different types of cancers and in this review we gathered our conclusions about these genes together.

Main causes of cancer

Carcinogens are particular substances which are linked to cancers. There are many different causes of cancer like tobacco (36), obesity (37), poor diet (38), lack of physical activity (39), ionizing radiation (40), drinking too much alcohol (41), infections by hepatitis B (42) and hepatitis C (43), HPV(44) and genetic changes.

Table 1 shows the relationship between different 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)
ultraviolet radiation B (82)		non-melanoma skin cancers (82)
Non-fibrous particulate materials (powdered metallic cobalt and nickel and crystalline silica (quartz, cristobalite and tridymite) They must get inside the body (such as through inhalation) and require years of exposure to produce cancer		Lung (83-86)
Rule of hormones in cancers occurrence (87,88)		1. Some hormones can be considered as a cancer occurrence reason. For example insulin-like growth factors and their binding proteins have key role in differentiation and cancer cell proliferation. (89) 2. Some level of some sex-related hormones are different in people who inherited mutated specific muted genes in from their family members. The rule of hormones in some cancers like testis, breast, endometrium, prostate and ovary, thyroid and bone is reported(90) 3. Obese people have higher levels of some hormones associated with cancer and a higher rate of those cancers

	(91). Women who take hormone replacement therapy have a higher risk of developing cancers associated with those hormones (92). On the other hand, people who exercise far more than average have lower levels of these hormones and lower risk of cancer (93).
Hereditary causes of cancer (94)	Despite vast non-hereditary cancers, many cancers are primarily caused by hereditary defects. When these kinds of patients are born, they carry a mutated gene. For example inherited mutated BRC1 gene can increase the risk of breast and ovarian cancers (94).

Tumor suppressor genes:

Tumor suppressor genes are genes which protect cells from being cancerous. These genes affect the regulation of the cell cycle and they can promote apoptosis in damaged cells. These genes can repress the genes that are essential for continuing the cell cycle.DNA repair proteins are usually classified as tumor suppressors as well, as mutations in their genes increase the risk of cancer. Table 2 shows some important tumor suppressor genes and cancers arise if they get mutant (95-100)

Table2: Tumor suppressor genes, their gene location and their function.

Name of tumor suppressor gene	Gene location	Function
Retinoblastoma protein	Chr 13: 48.3 – 48.48 Mb (Human) Chr 14: 73.18 – 73.33 Mb (Mouse)	1.Restricts cell's DNA replication ability in which the progress from G1 to S phase of the cell division cycle is prevented (101,102) 2. E2F transcription factor family is inhibited by this gene. (103,104)
P53	Chr 17: 7.66 – 7.69 Mb (Human) Chr 11: 69.58 – 69.59 Mb (Mouse)	1.Activates DNA repair proteins(105). 2.It is able to halt growth by keeping the cell cycle at G1/S regulation point in the process of DNA damage recognition (106). 3.Apoptosis initiation (107). 4.Senescence response to short telomeres (108). 5.A lot of genes' expression such as microRNA miR-34a and WAF1/CIP1 are activated by active p53 binding to DNA(109,110).
ST14 and ST7	Chr 11: 130.16 – 130.21 Mb (Human) Chr 9: 31.09 – 31.13 Mb (Mouse)	A complex is formed with Kunitz-type serine protease inhibitor (HAI-1). Sphingosine-1-phosphate is the activator of this process (111,112, 115). Activates and cleaves hepatocyte growth factor and scatter factor. Urokinase plasminogen activator(113,114, 116).
YPEL3	Chr 16: 30.09 – 30.1 Mb (Human) Chr 7: 126.78 – 126.78 Mb (Mouse)	Is a p53-inducible gene (117). Being a part of p53 pathway response as well as an anti-proliferation role, Cellular senescence has attracted a lot of attention due to its relationship with tumor suppressor genes. (117,118)
ST5	Chr 11: 8.69 – 8.91 Mb (Mouse) Chr 7: 109.52 – 109.7 Mb (Human)	Nude mice tumorigenicity hella cells are suppressed by this gene (119). Preferential binding of this protein to SH3 domain of c-Abl kinase results in MAPK1/ERK2 kinase regulation and reduces cell's tumorigenic phenotype (120).
APC	Chr 5: 112.71 – 112.85 Mb (Human) Chr 18: 34.22 – 34.32 Mb (Mouse)	A destruction complex is normally built by APC protein and glycogen synthase kinase 3-alpha or beta (GSK-3α/β) and axin by interactions with 20 AA and SAMP repeats (121-123). The aforementioned complex is able to bind β-catenins. GSK-3β can phosphorylate β-catenin for the second time with the help of casein kinase 1 (CK1). As a result, β-catenin is targeted for ubiquitination and degradation which is done by cellular proteasomes. Therefore the translocation into nucleus and acting as a transcription factor for proliferation genes is prevented.It is also believed that APC targets microtubules via PDZ binding domain and stabilizes them.The binding ability of APC to β-catenin is considered to be a part of the protein's

		mechanistic function in the destruction complex. (124-126) The binding ability of APC to β-catenin is considered to be a part of the protein's mechanistic function in the destruction complex.
BRCA1	Chr 17: 43.04 – 43.17 Mb (Human) Chr 11: 101.49 – 101.55 Mb (Mouse)	Double-strand breaks in DNA are repaired by a complex. BRCA1 is a part of the complex.(127,128)
BRCA2	Chr 13: 32.32 – 32.4 Mb (Human) Chr 5: 150.52 – 150.57 Mb (Mouse)	BRCA2 protein, that functions similar to BRCA1, interacts with RAD51 protein as well. These three proteins play a role in maintaining the stability of human genome as they influence DNA damage repair. Additionally, BRCA1 is involved in mismatch repair in which an interaction with MSH2 mismatch repair protein happens (129-131).
HER2	Chr 17: 39.69 – 39.73 Mb (Human) Chr 11: 98.41 – 98.44 Mb (Mouse)	AS a member of human epidermal growth factor receptor, HER2 overexpression or amplification is shown to have a major role in the development and progression of certain aggressive types of breast cancer. (132,133).In 15-30% of breast cancers and over-expression of the *ERBB2* gene occurs (134). Over-expression also occurs in other form of cancer such as adenocarcinoma of the lung, stomach and aggressive forms of uterine cancer (135,136).In approximately 7-34% of patients who suffer from gastric cancer and in 30% of salivary duct carcinomas, HER-2 is over-expressed(137).
HER3	Chr 12: 56.08 – 56.1 Mb (Human) Chr 10: 128.57 – 128.59 Mb (Mouse)	ERBB3 gene encodes HER3 (human epidermal growth factor receptor 3) which is a membrane bound protein In humans. (138,139). Kinase-impaired ErbB3 forms active heterodimers with other ErbB family members such as the ligand binding-impaired ErbB2.
P21	Chr 6: 36.68 – 36.69 Mb (Human) Chr 17: 29.09 – 29.1 Mb (Mouse)	Cyclin-CDK2, -CDK1, and -CDK4/6 complexes activity are inhibited when p21 (CIP1/WAF1) protein binds to them. Therefore, p21 functions as a cell cycle progression regulator at G_1 and S phase. (140-144)

CONCLUSION:

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. For example there are newly worked gene editing techniques which can be utilized for modifying the mutated genes.

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