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Review Article

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ETIOLOGY OF CANCER: A DEADLY OCEAN

S. Akila* and R. Deepti

[1]Shapu Street, Church Cross, Puttur, Chittoor (Dist), Andhra Pradesh, India.
[2]Thanikachellam Nagar, A Block, II Main Road, Ponniamman Medu Post, Chennai – 600 110, Tamil Nadu, India.
[3]Laguvampatty, Murungapatty (P.O), Salem- 636307, Tamil Nadu, India.

***Corresponding Author: S. Akila**

Shapu Street, Church Cross, Puttur, Chittoor (Dist), Andhra Pradesh, India.

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ABSTRACT

Abnormal proliferation of cells that grow beyond its usual boundaries is termed as cancer. Cancer invades adjacent parts of the body and spreads to other organs. World Health Organisation (WHO) has stated that globally near 1 in 6 death is due to cancer. Major cause of this deadly disease are potential risk factors (aging, family history and obesity), environmental agents (chemical, radiation and microorganisms) and mutated genes (tumor suppressor genes, Proto oncogene, DNA repair gene and telomere). Increased secretion of estrogens, leptin and decreased levels of adiponectin can contribute to tumorigenesis. Among all these factors, 22% of cancer death is only due to tobacco. Environmental agents and potential risk factors can cause initiation of cancer by either activating or suppressing the genes.

KEYWORDS: Proto oncogene, adiponectin, tumorigenesis and leptin.

INTRODUCTION

The term cancer applies to a group of disease in which cell grow abnormally. A mass of tissue formed as a result of abnormal excessive, uncoordinated, autonomous, proliferation and migration of cells is called "Malignant neoplasm". In 2018, WHO has stated that cancer is the second leading cause of death globally and was responsible for 8.8 millions death in 2015.[1,2] Approximately 70% death from cancer occur in low and middle income countries.[3]

Around one third of death from cancer are due to the 5 leading behaviours and dietary risks - High body mass index, low fruits and vegetables intake, lack of physical activity, tobacco and alcohol. Tobacco is the most important risk factor for cancer and is responsible for approximately 22% of cancer death. Factors like aging, family history and obesity play a crucial role in initiation of cancer.[4,5] These factors causes DNA instability leads to oncogenesis, hence these factors are called as potential risk factors. Current biological mechanisms of cancer suggest that all cancer are originated from both environment and genetics.[6] All evidence suggest that most cancers are not the result of one single event. Rather around four to seven events are usually required for a normal cell to evolve through a series of premalignant stage into an invasive cancer.[7,8,9]

Causes of cancer

Causes of cancer may be due to inherited mutated genes or environmental agents like chemicals, radiations or potential risk factors like aging, family history and obesity. Many researchers reported that four to six events together is responsible for the cause of the cancer. These events alter the normal properties and functions of cells. cancer cells divide rapidly and develop a new characteristics like changes in cell structure, deceased cell adhesion and production of enzymes in abnormal manner.[10,11] Generally causes of cancer is broadly classified into three groups – potential risk factors, environmental agents and genome.(Fig 1)

A, Potential risk factors

Some factors act more potentially and play a crucial role in the initiation of cancer. Many studies have reported that these factors like aging, family history and obesity highly correlates with tumorigenesis.

I, Aging

Most cancers occur in individuals about 55 years of age. Telomere shortening occurs in human hematopoietic stem cells and progenitor cells during aging. Aging related telomeres shortening can contribute to the genome instability which is highly sufficient to initiate cancer.[12,13]

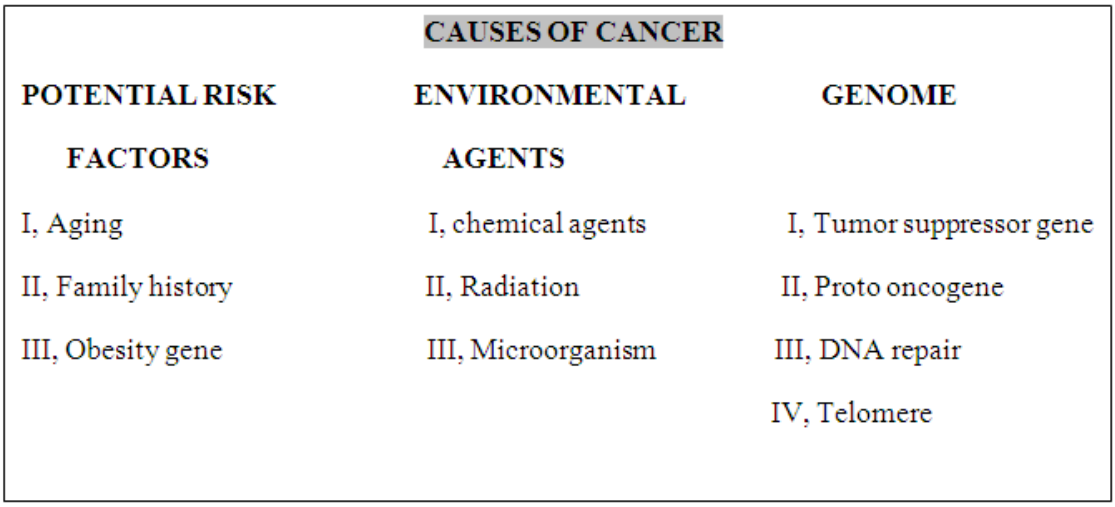

Figure 1: Classification of cancer causes.

II, Family history

7% of all human cancers are due to hereditary mutated genes. Mutation in the germ line genes leads to hereditary cancers. Inherited mutated gene individuals have a high risk of developing cancer but it is not sure individual will develop cancer. Example: individuals with hereditary APC genes mutation lead to familial adenomatous polyposis. Familial adenomatous polyposis is an cancer predisposition

Syndrome and these individuals are more susceptible for hereditary colon cancer.[14]

III, Obesity

Recent researchers have found that obese individuals are at a higher risk of developing cancers like breast, uterus, colon, rectum and prostate cancers. Normally fat tissues produce estrogens, insulin like growth factors, leptin and adiponectin. Increased concentration of estrogens, insulin like growth factors and leptin are responsible to induce cancer.[15,16] Chronic obesity is always related with the insulin resistances and these can cause a dramatic change in turn provides a suitable environment for the tumorigenesis. In the case of obesity, excess of energy is converted to triglycerides and triglycerides are filled up in the adipose tissues which contribute to metabolic dysfunction. Leptin is secreted by the adipose tissue and promotes energy homeostasis. Obese individuals have increased levels of leptin. Adiponectin is also produced by adipose tissue and act as a antagonist of leptin. Decreased adiponectin levels are observed in obesity. Hence increased leptin levels and decreased adiponectin levels are considered as a risk factor for cancer.[17]

Insulin like growth factors are anti apoptotic proteins and promotes cell proliferation and angiogenesis. Estogens can cause cancer in two ways. Estrogens can bind with the receptor and induce cell proliferation through receptor mediated hormonal activity. On the other hand, estrogen metabolism leads to generation of free radicals. Increased levels of free radicals provide a favourable situation for oncogenesis. Increased levels of estrogens is a potential risk factor for breasr cancer.[18.19]

B, Environmental agents

93% of all cancers were initiated by environmental agents. Cancer inducing agents are called carcinogenic agents or carcinogens. Environmental carcinogens cause oxidative stress in cells which affects the DNA structure and functions. Prolonged exposure to carcinogens may lead to development of cancer. Environmental agents join together with genetic factors to cause changes at the cellular and molecular levels. This is responsible for cancer initiation. Individuals having mutated genes can be easily influenced by ssenvironmental agents and more susceptible for cancer. A study concludes that normally 10% population have altered genes and these genes produce excess amount of enzymes. Enzymes reacts with environmental agents and turning them into carcinogens.[20,21,22]

I, Chemical agents

Tobacco products, industrial chemicals like benzene, metal ions like arsenic, cadmium, nickel can also act as chemical carcinogens (Table 1). Chemicals have strong carcinogenic properties but metal ions are weak carcinogens but potentially can act as co carcinogens.[23,24]

Table 1: Environmental potential chemical carcinogens and its associated type of cancer.

CARCINOGEN	CANCERS	SOURCES
TOBACCO: Polycyclic aromatic hydrocarbons (PAH) Nitrosamine ketone Nicotine Ethylene oxide Vinyl chloride	Mouth, nose, larynx, trachea, lungs, kidney, ureters, bladder, leukemia, liver breast & skin cancers	Tobacco smoking (active smokers), smoke inhalation (passive smokers) and tobacco chewing
ORGANOCHLORINES Polychlorinated biphenyl Tetrachlorodi benzo dioxin Arylamines	Breast, pancreatic, prostate, lungs, oral, thyroid, gall bladder, lymphoma and fibrosarcomas	Pesticides and solvents
VOLATILE ORGANIC COMPOUNDS Tolulene Formaldehyde Benzene Styrene Asbestos	Lung, leukemia, nasopharyngeal, lymphohemaopoietic, sinonasal cancer, mesothelioma and non Hodgkin lymphoma	Air pollutant, ground water pollutant, industrial solvents, automobile emission and gasoline
METAL IONS Arsenic Cadmium Chromium Nickel	Lung, prostate, pancreas, skin	Paints, batteries, plastics stabilizing agents, chrome plating, welding leather, tanning, refining and electroplating

II, Radiation

Molecules broken up by radiation can become highly reactive free radicals. These free radicals contribute to direct or indirect damage at the chromosomal level. Among the ionizing radiation, radon is the most potent mutagen to induce leukemia, lung, breast, lymphoma and thyroid cancers. Ultraviolet ray comes under non ionizing radiation and prolonged exposure to this ray can cause deadly form of skin cancer like melanoma, basal and squamous cell carcinoma.[25,26]

III, Microorganism

Pathogenic microorganism among viruses, bacteria's, trematodes and fungus can act as powerful mutagenic agents by creating chromosomal instability. This situation facilitates the oncogenesis. VIRUSES: DNA viruses and retroviruses are the best example. Insertion of the virus DNA into proto oncogene or tumor suppressor gene will end up in a mutation. This mutated genes contributes to the cancer formation.[27,28] BACTERIA: Carcinogenic activities of bacteria's are not well understood. Some researchers have reported that bacteria may cause inflammation and results in oxidative stress. Oxidative stress plays a important role in the disturbances of DNA integrity and leading to cancer.[29,30] TREMATODES: Trematodes may cause inflammation by releasing toxins and toxin mechanism can be linked with cancer initiation. FUNGUS: Asperigillus types of carcinogenic fungi secrete a aflotoxin which contributes to p^{53} gene mutation. Due to mutation, p^{53} cannot prevent the cell proliferation also cannot induce the apoptosis process and leading the way to tumorigenesis.[22,31]

Table 2: Viruses, Bacteria, trematodes and fungus inducible type of caner.

MICROORGANISM	FORM OF CANCER
Viruses	
Hepatitis B Liver carcinoma Epstein barr virus (EVB) Burkitt lymphoma, nasopharyngeal carcinoma & Gastric cancer Human T cell leukemia virus (HTLV-1) T cell lymphoma Human herpes virus (HHV-6) Oral squamous cell carcinoma & cervical cancer Human herpes virus (HHV-8) Kaposis sarcoma & B cell lymphomas Hepatitis B virus (HBV) & liver cancer Hepatitis C virus (HCV) Merkel cellpolyomavirus (MCPV) Merkel cell carcinomas Human papillomavirus (HPV) Cervical cancer Simian virus 40 Mesothelioma	
Bacteria	
Borrelia burgdorferi B cell lymphoma Chlamydia pneumonia Lung cancer Helicobacter pylori Gastric cancer Mycoplasma Gastric & colon cancer Salmonella typhi Cholangiocarcinoma Streptococcus bovis Colorectal cancer	
Trematodes	
Clonorchis sinensis Cholangiocarcinoma Opisthorchis vuverrini Cholangiocarcinoma Schistosoma haematobium Bladder cancer	
Fungus	
Asperigillus flavus Asperigillus parasiticus	Hepatocellular cancer

C, Genome

Approximately 35,000 genes in the human genome are associated with cancer, so mutations in these sets of genes can result in cancer. Mutations in the genes can activate the genes responsible for cancer development and suppress the genes which prevent cancer. These leads to the alterations in the signal transduction process and provide a favourable condition for the cells to proliferate without the control of the cell cycle. These genes are broadly classified into three groups Tumor suppressor genes, proto oncogenes and DNA repair genes.[32,33] List of these genes are denoted in the table 3. Telomeres also play an important link between the genes and cancer initiation.

i, Tumor suppressor gene

Tumor suppressor genes encode the proteins that inhibit the cell proliferation by interfering the cell cycle and prevent tumor formation. Tumor suppressor genes control the regulation process of the cells through transcription factors and signal transduction pathway. Mutation in these genes contributes to uncontrolled cell division and cell growth. Mutation in the single allele of tumor suppressor gene can even inhibit the tumor formation. But mutation in the both the allele of tumor suppressor genes will make these genes inactive or non functional genes.[34,35,36]

ii, Proto oncogenes

Proto oncogenes produce proteins that normally enhance the cell division and inhibit programmed cell death. In normal cells, these proteins send signal to the nucleus to stimulate cell division. These signalling proteins acts in a series of steps called signal transduction cascade. Mutated forms of proto oncogenes are termed as oncogenes and oncogenes are responsible for the uncontrolled cell proliferation. Mutation in one allele of proto oncogene is highly sufficient to convert it to oncogene which promotes tumorigenesis.[26,37]

iii, DNA repair gene

DNA repair genes are involved in DNA repair and maintenance of chromosome integrity. Carcinogenic agents cause damages to the genes and may result in mutations. DNA repair genes removes the mutations and prevents the normal cell turning into cancerous cell.[10,38]

Table 3: Functions of tumor suppressor genes, Proto oncogenes and DNA repair genes. Mutation of these genes is susceptible of inducing cancer.

GENES	FUNCTIONS	TYPE OF CANCER
TUMOR RB_1	**SUPPRESSOR GENES:** Rb protein plays a key role in cell cycle regulation. Rb prevents the cells entry into S phase of the cell cycle from G_1 phase. Rb binds with E2F transcription factor which is involved in cell cycle & inactivates the factor. Loss or mutation of Rb_1 gene promotes tumorigenesis by rapid cell proliferations.	Retinoblastoma
P^{53}	P^{53} transcriptional factor inhibits tumor formation by two processes. P^{53} activates the P^{21}Cdk inhibitor gene in response to DNA damage and blocks cell proliferation. P^{53} induces the apoptosis process. Mutation in this gene contributes to oncogenesis.	Li Fraumeni syndrome – cancer predisposition syndrome. Sarcomas, breast cancer, brain tumor & leukemia.
APC	Beta catenin is responsible for the up regulation of cell proliferation. APC protein causes degradation of beta catenin & inhibits the proliferation. Increased cell proliferation occurs in the case of non functional APC gene.	Familial adenomatous polyposis of the colon
NF_1	NF_1 encodes protein neurofibromin which facilitates conversion of active RAS to inactive RAS. Loss of this gene , makes the RAS to remain in the active mode itself & RAS promotes cell proliferation.	Neurofibrosarcomas
PROTO HER 2 / Neu	**ONCOGENES:** This gene code for receptor tyrosine kinase &receptor signals through RAS-MAPK pathway which drives cell proliferation. Over expression of this gene which in turn leads to increased receptors & signals and rapid cell proliferations.	Breast cancer
RAS	RAS gene codes for Ras & Rho proteins. Ras protein activates the MAP kinase pathway & contributes to cell proliferation. Mutation in gene prevents the conversion of active Ras to inactive Ras, hence rapid proliferation occurs. Rho protein controls the cell cycle. Mutated RAS gene contributes to tumorigenesis by stimulating proliferation & angiogenesis	Pancreatic cancer
MYC	Myc protein acts as signal molecule for cell proliferation through cascade mechanism. Chromosomal rearrangement leads to increased production of myc protein which in turn results in aberrant cell division.	Burkitt's lymphoma
Cyclin D	Cyclin D inactives the Rb by phosphorylating it. Chromosomal inversion up regulates cyclin D gene & contributes to cell proliferation rapidly.	Parathyroid adenomas
Bcl-2	Bcl-2 gene codes for Bcl-2 protein. Over expression of this protein makes the cells escape programmed cell dealth.	Follicular cell lymphomas
DNA BRCA-1 & BRCA-2	**REPAIR GENES** These genes codes for nuclear proteins and nuclear proteins read the site of DNA damage and plays vital role in DNA repair. Mutation in these genes leads to accumulation of DNA damage which is potential cause for oncogenesis.	Ovarian cancer & hereditary breast cancer
MLH-1	This gene contributes to the mismatch DNA repair. Inactivation of MLH-1 leads to the microsatellite instability or replication errors.	Colorectal cancer
XP	XP gene expresses XPA proteins which are involved in the nucleotide excision repair. Due to the mutation in this gene, nucleotide excision repair mechanism Cannot take place.	Xeroderma pigmentosum - cancer predisposition syndrome. Skin cancer

iv, Telomeres

Telomeres are complexes of non coding DNA and proteins located at the ends of linear chromosomes. Telomeres maintain the structural integrity of the chromosome, preventing attack from nuclease and allow DNA repair systems to distinguish a true end from a break in double stranded DNA. In normal human somatic cells, telomeres shorten with each successive cell division. Once telomeres are shortened beyond some critical length, the cell is no longer able to divide and is said to be senescent cell. These senescent cells enter apoptosis. In germ cells or stem cells or cancer cells, telomeres do not shorten and the cells do not senesce. This is due to the presence of telomerase which maintains telomeric length in these cells.[39]

Cancer cells have to depend on telomere maintenance mechanisms in order to have immortal proliferation capacity. Most of the human tumor utilizes the enzyme telomerase which is normally responsible for synthesizing telomeres through de novo pathway. 10% to 20% of human tumors may also activate the alternative mechanism of telomere lengthening(ALT). In normal cells, ALT is responsible for maintaining the tissue growth. Activation of homology directed repair(HDR) of DNA can mediate telomerase independent lengthening of telomeres by ALT. This causes genome instability and cancer initiation. Through this, cells gain a capacity of immortal cell growth.[40]

Most prominent features of telomeres and its association with telomere binding proteins are involved in both repair and replication of telomeres (Figure 2). In humans, most somatic cells lack telomerase activity but stem and progenitor cells have detectable levels of telomerase. Stem and progenitor cells are responsible for cancer formation. Aging related telomere shortening can also contribute to the genome instability and tumor cells reply on genome instability. Recent researches reported that human stem cells have an age dependent increase in mutations and cancer formation.[41,42]

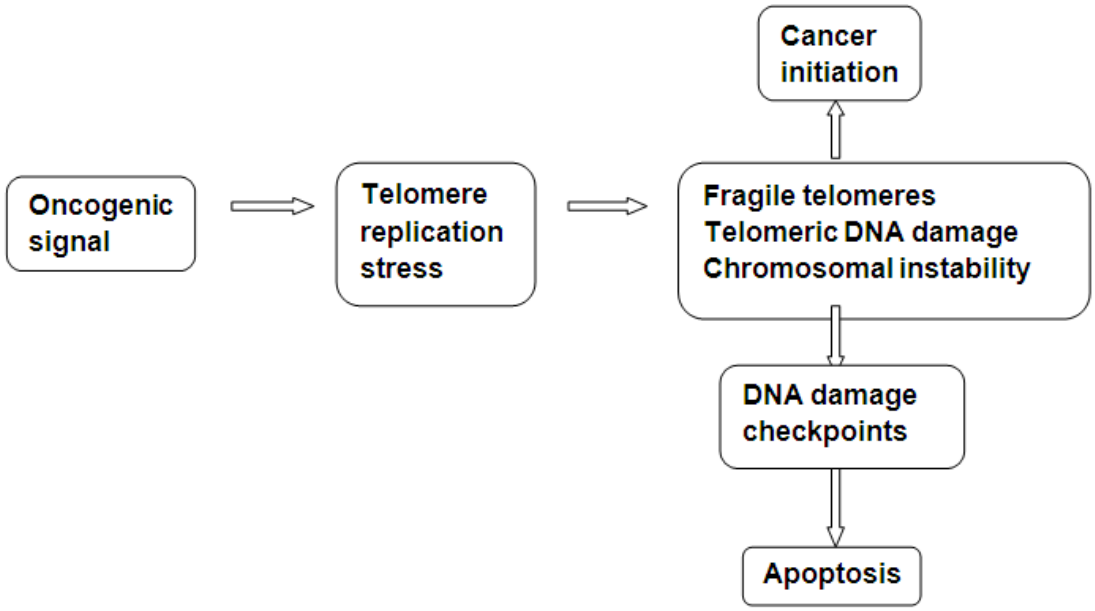

Figure 2: Telomeres serve as sensors for oncogene activation signal.

CONCLUSION

This review article highlights the environmental agents which can trigger or cause mutation in a set of genes and finally step on the tumorigenesis. “Prevention is better than cure”

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