PARTICULAR DISCUSSION OF CELLULAR EVENTS, EPIGENETICS, AND BIOCHEMICAL TARGETS IN CANCER TREATMENT: PLANTS AGAINST CANCER

[1]YEDLA .RAJESHWARI, [2]SUMAN CHINTHALA, [3]HASANTHI LAKSHMI PULAKURHTY, [4]KETHAVATH ANITHA

[1]Professor, [2,3]Assistant Professor, [4]UG Student, [1,2,3,4]Department of Pharmacy, Brilliant Grammer School Educational Society Group of Institutions-Integrated Campus, Hyderabad, India.

Abstract

The word "cancer" refers to a variety of illnesses that can affect any region of the body. The primary characteristic of cancer is the accelerated growth and proliferation of aberrant cells outside of their typical bounds. Normal cells undergo a change into cancerous cells to cause cancer. When cancer cells multiply, they acquire new traits such as altered cellular structure, reduced cell adhesion, and the synthesis of novel enzymes. The cancer cells can expand and infiltrate other tissues as a result of these modifications. Because healthy cells can become cancerous. Changes must be made to the genes that control cell proliferation and differentiation. Cancer mostly impacts the oncogenes and tumour suppressor genes. The DNA damage is caused by tobacco smoke leads to lung cancer. The contribution of field defects and genome instability are the main causes of cancer. The multiple genetic changes the results in cancer take many years to accumulate this time the biological behaviour of pre malignant cells slowly changes from the properties of normal cells to cancer like properties. The most severe cause of dysplasia arereffered to as carcinoma insitu. Cancer cells avoid apoptosis and continue to multiply in an unregulated manner. Proto oncogenes are genes that promote cell growth and mitosis . Several different cell types are critical to tumour growth. The endothelial progenitor cells are very important cell population in tumour blood vessel growth. The activation of proto oncogenes to oncogenes and inactivation of tumour suppressor genes are the cellular events for cancer. Several plants derived compounds are currently success fully employed in cancer treatment. The most significant compound is vincaalkaloid is used in the treatment of hodgokins disease ,leukemia ,lymphomas ,testicular cancer ,breast and lung cancer. Etoposides, teniposide, paclitaxel,Irinotecan ,toptecan, flavopiridol, combretastatin are the another plant compounds.

Keywords: Cancer, Etoposide, Oncogenes,Carcinogenesis, Tumourogenesis

INTRODUCTION

A chain of molecular occurrences that fundamentally change the typical characteristics of cells lead to cancer. The usual regulatory mechanisms that stop cell proliferation and invasion of other tissues are disrupted in cancer cells. These transformed cells do not require unique signals to drive cell growth and division since they divide and develop in the presence of signals that would typically restrict cell growth. These cells alter in shape as they expand, adhesion between cells weakens, and new enzymes are produced, among other traits. These heritable alterations allow the cell and its descendants to divide and develop, even in the presence of normal cells that ordinarily limit the proliferation of surrounding cells. The cancer cells can spread and infiltrate other tissues as a result of these modifications.[1]

The abnormalities in cancer cells usually result from mutations in protein-encoding genes that regulate cell division. Consequently, mutations begin to increase in the cell, causing further abnormalities in that cell and the daughter cells. Some of these mutated cells die, but other alterations may give the abnormal cell a selective advantage that allows it to multiply much more rapidly than the normal cells. This enhanced growth describes most cancer cells, which have gained functions repressed in normal, healthy cells. As long as these cells remain

in their original location, they are considered benign; if they become invasive, they are considered malignant. Cancer cells in malignant tumors can often metastasize, sending cancer cells to distant sites in the body where new tumors may form.[2]

Carcinogenesis or **oncogenesis** or **tumorigenesis** is the creation of cancer. It is a process by which normal cells are transformed into cancer cells. It is characterized by a progression of changes at the cellular, genetic, and epigenetic levels that ultimately reprogram a cell to undergo uncontrolled cell division, thus forming a malignant mass.

Mutations and epimutations in DNA that lead to cancer a series of several mutations to certain classes of genes are usually required before a normal cell will transform into a cancer cell. For a normal cell to transform into a cancer cell, genes that regulate cell growth and differentiation must be altered.[3] Genetic and epigenetic changes can occur at many levels, from gain or loss of entire chromosomes, to a mutation affecting a single DNA nucleotide, or to silencing or activating a microRNA that controls expression of 100 to 500 genes.

There are two broad categories of genes that are affected by these changes.

Oncogenes and Tumor suppressor genes

Oncogenes may be normal genes that are expressed at inappropriately high levels or altered genes that have novel properties. In either case, the expression of these genes promotes the malignant phenotype of cancer

Tumor suppressor genes are genes that inhibit cell division, survival, or other properties of cancer cells. Tumor suppressor genes are often disabled by cancer-promoting genetic changes. [4]

ETIOLOGY:

DNA damage and deficient

DNA repair in carcinogenesis

The central role of DNA damage and epigenetic defects in DNA repair genes in carcinogenesis DNA damage is considered to be the primary cause of cancer. More than 10,000 new naturally occurring DNA damages arise, on average, per human cell, and mainly caused by

- Exogenous Agents
- Endogenous Agents

Exogenous Agents will cause DNA damage,As one example of an exogenous carcinogenic agent, ***tobacco smoke*** causes increased DNA damage, and these DNA damages likely cause the increase of lung cancer due to smoking. ***UV light from solar radiation*** causes DNA damage that is important in melanoma, ***helicobacter pylori*** infection produces high levels of reactive oxygen species that damage DNA and contributes to gastric cancer,and the ***Aspergillus metabolite, aflatoxin***, is a DNA damaging agent that is causative in liver cancer.

Endogenous Agents (naturally occurring) DNA damages can also be caused by.. indicated that macrophages and neutrophils in an inflamed colonic epithelium are the sources of reactive oxygen species causing the DNA damages that initiate colonic tumorigenesis, and bile acids, at high levels in the colons of humans eating a high-fat diet, also cause DNA damage and contribute to colon cancer.

Using molecular biological techniques, it is possible to characterize the mutations, epimutations, or chromosomal aberrations within a tumor, and rapid progress is being made in the field of predicting prognosis based on the spectrum of mutations in some cases. Telomerase mutations remove additional barriers, extending the number of times a cell can divide. Other mutations enable the tumor to grow new blood vessels to provide more nutrients, or to metastasize, spreading to other parts of the body. [5]

Contribution of Field Defects to carcinogenesis

Field defects have been identified in association with cancers and are important in progression to cancer. However, it was pointed out by Rubin that "the vast majority of studies in cancer research has been done on well-defined tumors in vivo, or on discrete neoplastic foci in vitro. Yet there is evidence that more than 80% of the somatic mutations found in mutator phenotype human colorectal tumors occur before the onset of terminal

clonal expansion…Similarly, (Vogelstein et al.) also indicated that more than half of somatic mutations identified in tumors.[6]

Table 1:*Frequency of epigenetic changes in DNA repair genes in sporadic cancers and adjacent field defects*

Cancer	Gene	Frequency in Cancer	Frequency in Field Defect
Colorectal	Mgmt	46%	34%
Colorectal	Mgmt	47%	11%
Colorectal	Mgmt	70%	60%
Head and Neck	Mgmt	54%	38%
Head and Neck	Mlh1	33%	25%
Stomach	Mgmt	88%	78%
Stomach	Mlh1	73%	20%
Esophagus	Mlh1	77%-100%	23%-79%

Genome instability in carcinogenesis

Cancers are known to exhibit genome instability or a mutator phenotype. The protein-coding DNA within the nucleus is about 1.5% of the total genomic DNA. Within this protein-coding DNA (called the exome), an average cancer of the breast or colon can have about 60 to 70 protein-altering mutations, of which about 3 or 4 maybe "driver" mutations, and the remaining ones may be "passenger" mutations. However, the average number of DNA sequence mutations in the entire genome (including non-protein-coding regions) within a breast cancer tissue sample is about 20,000. In an average melanoma tissue sample (where melanomas have a higher exome mutation frequency) the total number of DNA sequence mutations is about 80,000. These high frequencies of mutations in the total nucleotide sequences within cancers suggest that often an early alteration in the field defect giving rise to cancer (e.g. yellow area in the diagram in the preceding section) is a deficiency in DNA repair.

The large field defects surrounding colon cancers (extending to about 10 cm on each side of cancer) were shown by (Fascista et al.) to frequently have epigenetic defects in 2 or 3 DNA repair proteins (ERCC1, XPF and/or PMS2) in the entire area of the field defect. When the expression of DNA repair genes is reduced, DNA damages accumulate in cells at a higher than normal level, and these excess damages cause increased frequencies of mutation and/or epimutation. Mutation rates strongly increase in cells defective in DNA mismatch repair or homologous recombinational repair (HRR).

A deficiency in DNA repair, itself, can allow DNA damages to accumulate, and error-prone translesion synthesis past some of those damages may give rise to mutations. Besides, faulty repair of these accumulated DNA damages may give rise to epimutations. These new mutations and/or epimutations may provide a proliferative advantage, generating a field defect. [7]

Non-mainstream theories

There are several theories of carcinogenesis and cancer treatment that fall outside the mainstream of scientific opinion, These theories may be used to justify various alternative cancer treatments. They should be distinguished from those theories of carcinogenesis that have a logical basis within mainstream cancer biology, and from which conventionally testable hypotheses can be made.

Several alternative theories of carcinogenesis, however, are based on scientific evidence and are increasingly being acknowledged. Some researchers believe that cancer may be caused by aneuploidy (numerical and structural abnormalities in chromosomes) rather than by mutations or epimutations. Cancer has also been considered as a metabolic disease in which the cellular metabolism of oxygen is diverted from the pathway that generates energy (oxidative phosphorylation) to the pathway that generates reactive oxygen species. All these theories of carcinogenesis may be complementary rather than contradictory.[8]

Another theory as to the origin of cancer was developed by astrobiologists and suggests that cancer is an atavism, an evolutionary throwback to an earlier form of multicellular life The genes responsible for uncontrolled cell growth and cooperation between cancer cells are very similar to those that enabled the first multicellular life forms to group together and flourish. When the newer controlling genes fail for whatever reason, the cell can revert to its more primitive programming and reproduce out of control. The theory is an alternative to the notion that cancers begin with rogue cells that undergo evolution within the body. [9]

CANCER CELL BIOLOGY

Tissue can be organized in a continuous spectrum from normal to cancer.Often, the multiple genetic changes that result in cancer may take many years to accumulate. During this time, the biological behavior of the pre-malignant cells slowly changes from the properties of normal cells to cancer-like properties. Pre-malignant tissue can have a distinctive appearance under the microscope. Dysplasia is an abnormal type of excessive cell proliferation characterized by loss of normal tissue arrangement and cell structure in pre-malignant cells. These early neoplastic changes must be distinguished from hyperplasia, a reversible increase in cell division caused by an external stimulus, such as a hormonal imbalance or chronic irritation.The most severe cases of dysplasia are referred to as "carcinoma in situ." In Latin, the term "in situ" means "in place", so carcinoma in situ refers to an uncontrolled growth of cells that remains in the original location and has not shown invasion into other tissues. Nevertheless, carcinoma in situ may develop into an invasive malignancy and is usually removed surgically, if possible.[10]

Clonal evolution

Just like a population of animals undergoes evolution, an unchecked population of cells also can undergo evolution. This undesirable process is called somatic evolution and is how cancer arises and becomes more malignant.

Most changes in cellular metabolism that allow cells to grow in a disorderly fashion lead to cell death. However, once cancer begins, cancer cells undergo a process of natural selection: the few cells with new genetic changes that enhance their survival or reproduction continue to multiply, and soon come to dominate the growing tumor, as cells with less favorable genetic change are out-competed. This is exactly how pathogens such as MRSA can become antibiotic-resistant (or how HIV can become drug-resistant), and the same reason why crop blights and pests can become pesticide-resistant. [11]

BIOLOGICAL PROPERTIES OF CANCER CELLS

When normal cells are damaged beyond repair, they are eliminated by apoptosis. Cancer cells avoid apoptosis and continue to multiply in an unregulated manner.

The biological properties of malignant tumor cells were summarized as follows

- Acquisition of self-sufficiency in growth signals, leading to unchecked growth.
- Loss of sensitivity to anti-growth signals, also leading to unchecked growth.
- Loss of capacity for apoptosis, to allow growth despite genetic errors and external anti-growth signals.
- Loss of capacity for senescence, leading to limitless replicative potential (immortality)
- Acquisition of sustained angiogenesis, allowing the tumor to grow beyond the limitations of passive nutrient diffusion.
- Acquisition of the ability to invade neighboring tissues, the defining property of invasive carcinoma.
- Acquisition of ability to build metastases at distant sites, the classical property of malignant tumors (carcinomas or others).

The completion of these multiple steps would be a very rare event without :

Loss of capacity to repair genetic errors, leading to an increased mutation rate (genomic instability), thus accelerating all the other changes.

These biological changes are classical in carcinomas; other malignant tumors may not need to achieve them all. For example, tissue invasion and displacement to distant sites are normal properties of leukocytes; these steps are not needed in the development of leukemia. For example, inactivation of a single gene, coding for the p53 protein, will cause genomic instability, evasion of apoptosis, and increased angiogenesis. Not all cancer cells are dividing. [12]

CELLULAR MECHANISMS

Cancer is a genetic disease: For cells to start dividing uncontrollably, genes that regulate cell growth must be damaged. Proto-oncogenes are genes that promote cell growth and mitosis, whereas tumor suppressor genes discourage cell growth, or temporarily halt cell division to carry out DNA repair. But the uncontrolled cell division that characterizes cancer also requires that the dividing cell duplicates all its cellular components to create two daughter cells. The activation of anaerobic glycolysis (the Warburg effect), which is not necessarily induced by mutations in proto-oncogenes and tumor suppressor genes, provides most of the building blocks required to duplicate the cellular components of a dividing cell and, therefore, is also essential for carcinogenesis. [13]

Cell types involved in cancer growth

Several different cell types are critical to tumor growth. In particular endothelial progenitor cells are a very important cell population in tumor blood vessel growth. The hypothesis that endothelial progenitor cells are important in tumor growth, angiogenesis, and metastasis has been supported by a recent publication in Cancer Research (August 2010). This finding of endothelial progenitor cells incorporated in tumor vasculature gives evidence for the importance of this cell type in blood vessel development in a tumor setting and metastasis. Furthermore, the ablation of the endothelial progenitor cells in the bone marrow leads to a significant decrease in tumor growth and vasculature development. The continued research into the importance of endothelial progenitor cells may present novel therapeutic targets. [14]

Oncogenes

Oncogenes promote cell growth in a variety of ways. Many can produce hormones, a "chemical messenger" between cells that encourage mitosis, the effect of which depends on the signal transduction of the receiving tissue or cells. Oncogenes often produce mitogens or are involved in transcription of DNA in protein synthesis, which creates the proteins and enzymes responsible for producing the products and biochemicals cells use and interact with.One of the first oncogenes to be defined in cancer research is the ras oncogene. Mutations in the Ras family of proto-oncogenes (comprising H-Ras, N-Ras, and K-Ras) are very common, being found in 20% to 30% of all human tumors. [15]

Proto-oncogenes

Some are responsible for the signal transduction system and signal receptors in cells and tissues themselves, thus controlling the sensitivity to such hormones. They often produce mitogens or are involved in transcription of DNA in protein synthesis, which creates the proteins and enzymes is responsible for producing the products and biochemicals cells use and interact with.

Mutations in proto-oncogenes can modify their expression and function, increasing the amount of activity of the product protein. When this happens, they become oncogenes, and, thus, cells have a higher chance to divide excessively and uncontrollably. The chance of cancer cannot be reduced by removing proto-oncogenes from the genome, as they are critical for growth, repair, and homeostasis of the body. This condition includes also the inactivation of specific tumor suppressor genes. If the condition is not fulfilled, the cell may cease to grow and can proceed to die.[16]

Tumor suppressor genes

Many tumor suppressor genes affect signal transduction pathways that regulate apoptosis, also known as "programmed cell death".

Tumor suppressor genes code for anti-proliferation signals and proteins that suppress mitosis and cell growth. Generally, tumor suppressors are transcription factors that are activated by cellular stress or DNA damage. Often DNA damage will cause the presence of free-floating genetic material as well as other signs and will trigger enzymes and pathways that lead to the activation of tumor suppressor genes. The function of such genes is to arrest the progression of the cell cycle to carry out DNA repair, preventing mutations from being passed on to daughter cells. The p53 protein, one of the most important studied tumor suppressor genes, is a transcription factor activated by many cellular stressors including hypoxia and ultraviolet radiation damage.

Despite nearly half of all cancers possibly involving alterations in p53, its tumor suppressor function is poorly understood. p53 has two functions: one a nuclear role as a transcription factor, and the other a cytoplasmic role in regulating the cell cycle, cell division, and apoptosis.[17]

Multiple mutations

Multiple mutations in cancer cellsIn general, mutations in both types of genes are required for cancer to occur. For example, a mutation limited to one oncogene would be suppressed by normal mitosis control and tumor suppressor genes, first hypothesized by the Knudson hypothesis. A mutation to only one tumor suppressor gene would not cause cancer either, due to the presence of many "backup" genes that duplicate its functions. It is only when enough proto-oncogenes have mutated into oncogenes, and enough tumor suppressor genes deactivated or damaged, that the signals for cell growth overwhelm the signals to regulate it, that cell growth quickly spirals out of control. Often, because these genes regulate the processes that prevent most damage to genes themselves, the rate of mutations increases as one gets older, because DNA damage forms a feedback loop.[18]

non-mutagenic carcinogens

Many mutagens are also carcinogens, but some carcinogens are not mutagens. Examples of carcinogens that are not mutagens include alcohol and estrogen. These are thought to promote cancers through their stimulating effect on the rate of cell mitosis. Faster rates of mitosis increasingly leave fewer opportunities for repair enzymes to repair damaged DNA during DNA replication, increasing the likelihood of a genetic mistake. A mistake made during mitosis can lead to the daughter cells' receiving the wrong number of chromosomes, which leads to aneuploidy and may lead to cancer.

Role of infections

Depending on their location, cells can be damaged through radiation from sunshine, chemicals from cigarette smoke, and inflammation from bacterial infection or other viruses. Each cell has a chance of damage, a step on a path toward cancer. Cells often die if they are damaged, through the failure of a vital process or the immune system; however, sometimes the damage will knock out a single cancer gene. In an old person, there are thousands, tens of thousands, or hundreds of thousands of knocked-out cells. The chance that anyone would form cancer is very low.[19]

Bacterial

*Heliobacterpylori*are known to cause MALT lymphoma. Other types of bacteria have been implicated in other cancers.

Viral

Viruses that are known to cause cancer such as HPV (cervical cancer), Hepatitis B (liver cancer), and EBV (a type of lymphoma), are all DNA viruses. It is thought that when the virus infects a cell, it inserts a part of its DNA near the cell growth genes, causing cell division. The group of changed cells that are formed from the first cell dividing all have the same viral DNA near the cell growth genes. The group of changed cells is now special because one of the normal controls on growth has been lost.

When the damage occurs in any area of changed cells, something different occurs. Each of the cells has the potential for growth. The changed cells will divide quicker when the area is damaged by physical, chemical, or viral agents. A vicious circle has been set up: Damaging the area will cause the changed cells to divide, causing a greater likelihood that they will suffer knock-outs.[20]

Helminthiasis

Certain parasitic worms are known to be carcinogenic. These include:

- *ClonorchisSinensis* (the organism causing Clonorchiasis) and *Opisthorchisviverrini* (causing Opisthorchiasis) are associated with cholangiocarcinoma
- *Schistosoma species* (the organisms causing Schistosomiasis) is associated with bladder cancer.

EPIGENETICS

Epigenetics is the study of the regulation of gene expression through chemical, non-mutational changes in DNA structure. The theory of epigenetics in cancer pathogenesis is that non-mutational changes to DNA can lead to alterations in gene expression. Normally, oncogenes are silent, for example, because of DNA methylation. Loss of that methylation can induce the aberrant expression of oncogenes, leading to cancer pathogenesis. Known mechanisms of epigenetic change include DNA methylation and methylation or acetylation of histone proteins bound to chromosomal DNA at specific locations. Classes of medications, known as HDAC inhibitors and DNA methyltransferase inhibitors, can re-regulate the epigenetic signaling in the cancer cell.[21]

Cancer stem cells

A new way of looking at carcinogenesis comes from integrating the ideas of developmental biology into oncology. The cancer stem cellhypothesis proposes that the different kinds of cells in a heterogeneous tumor arise from a single cell, termed Cancer Stem Cell. Cancer stem cells may arise from the transformation of adult stem cells or differentiated cells within a body. These cells persist as a subcomponent of the tumor and retain key stem cell properties. They give rise to a variety of cells, are capable of self-renewal and homeostaticcontrol.Cancers are caused by a series of mutations. Each mutation alters the behavior of the cell somewhat.[22]

CELLULAR EVENTS FOR CANCER:

The activation of proto-oncogenes to oncogenes.

Proto-oncogenes are genes that normally control cell division, apoptosis, and differentiation, but which can be converted to oncogenes that induce malignant change by viral or carcinogen action. Mutation at proto-oncogene called ***BCL-2*****,** codes for a protein that blocks cell suicide. When mutated, the *BCL-2* gene produces excessive amounts of the Bcl-2 protein, which prevents the apoptosis program from being activated. Malignant lymphomas that stem from B lymphocytes exhibit this *BCL-2* behavior. The alteration of the *BCL-2* gene is caused by a chromosomal translocation that keeps the gene in a permanent "on" position.[23]

The inactivation of tumor suppressor genes.

Normal cells contain genes that can suppress malignant change-termed *tumor suppressor genes* (antioncogenes).A mutation occurs in a gene that induces apoptosis, such as the tumor-suppressor gene ***TP53***, which encodes a protein called p53, the cell that harbors the gene may fail to respond to death. As a result, the cell may proliferate uncontrollably and form a cancerous tumor.

Apoptosis

Termination of cell propagation is either by two pathways i.e. Apoptosis and Necrosis (Kara Gogers; The Cell). These two pathways, imposed from outside (necrosis) or programmed from within (apoptosis), have different morphological features and involve different intracellular mechanisms. Apoptosis is initiated for various reasons, such as when a cell is no longer needed within the body or when it becomes a threat to the health of the organism. (Seamus et al, 1995) The inhibition of apoptosis contributes to too many disease processes, including cancer. Apoptosis is a normal physiological process that offsets cell proliferation. It is a genetically programmed event that can be set in motion by a variety of internal or external stimuli. A signal activates genes in the cell's

suicide pathway, which encode the proteins that destroy the cell's structural proteins and genetic material (Frederick L. Kiechle and Xinbo Zhang, 2002). Several morphological changes occur in the apoptotic cell-bubble-like formations appear on its surface, and chromatin (chromosomal DNA and protein) in the cell's nucleus condenses. The cell then either is consumed by other cells or breaks up into smaller pieces that are engulfed by scavenger cells. Apoptosis is programmed cell death, and genetic mutations in the antiapoptotic genes are usually prerequisites for cancer; indeed, resistance to apoptosis is a hallmark of the disease. It can be brought about by **inactivation** of proapoptotic factors (*TP53* gene) or by **activation** of antiapoptotic factors (*BCL*gene)-*2* [24]

Telomerase expression

Telomeres are specialized structures that cap the ends of chromosomes-like the small metal tubes on the end of shoelaces-protecting them from degradation, rearrangement, and fusion with other chromosomes. Put simply, DNA polymerase cannot easily duplicate the last few nucleotides at the ends of DNA, and telomeres prevent loss of the 'end' genes. With each round of cell division, a portion of the telomere is eroded, so that eventually it becomes non-functional. The cumulative loss of telomeric DNA sequences acts as a biological clock, eventually limiting the replicative potential of cells when a critical telomere length is reached (Evonne M Rezler, 2002). At this point, DNA replication ceases and the cell becomes senescent.

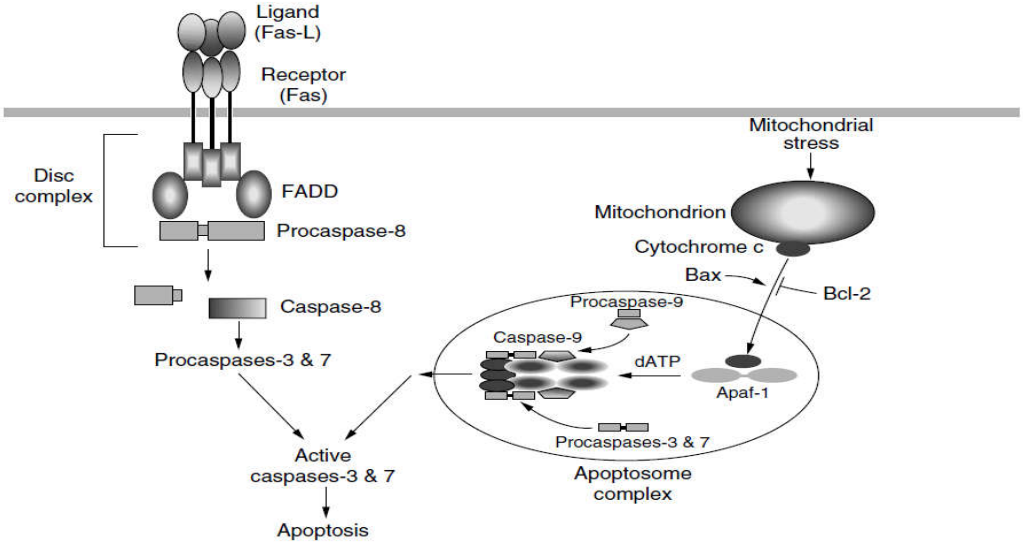

Fig 1: Apoptosis—receptor-mediated and mitochondrial apoptosis cascades. Trimerization ofthe Fas receptor initiates recruitment of the death domain-containing adaptor protein FADD, whichbinds to procaspase-8 promoting trans-catalytic cleavage of prodomain. Caspase-8 initiates thecaspase cascade by acting on downstream effector caspases 3 and 7. In mitochondria-mediatedapoptosis cytochrome c, the release is a key event in apoptosis and is stimulated by Bax and suppressedby Bcl-2. The released cytochrome c binds with Apaf-1 and in conjunction with dATP induces aconformational change in Apaf-1 that permits oligomerization into a _700-kDa complex, which iscalled the apoptosome complex and is capable of recruiting caspases-9, -3, -7.[25]

For a variety of reasons, naturally occurring dietary substances over synthetic agents are preferred by patients to prevent cancer. This approach has largely focused on targeting deregulated intracellular pathways that have been implicated in abnormal cellular function. As a result, there has been an increasing interest in dietary compounds that have an innate ability to modify these pathways thereby delaying the process of carcinogenesis

Targets for cancer prevention strategies canbe either biochemical species produced by theaction of a physical or chemical carcinogen oran enzyme/protein aberrantly expressed as aconsequence of a genetic or environmentalrisk factor (the latter would include exposureto environmental carcinogens).

BIOCHEMICAL TARGETS. [26]

One example ofa biochemical target produced by carcinogensis reactive oxygen species (ROS). Ionizing radiationis a complete carcinogen and producesmuch of its DNA damage through ROS.Several strategies for preventing ROS-inducedcell damage have been developed. Amifostine and its derivatives suppressionizing radiation-induced transformationand carcinogenesis. Antioxidants, includingprotein and **non-protein sulfhydryl** and **certain vitamins**, are effective modulators of ROSproduced by physical and chemical carcinogens.

Antioxidants are effective in inhibitingcarcinogenesis in some experimentalmodels, but their roles in human cancer preventionremain unclear. At least some agentswith antioxidant activity may increase carcinogenesisin some tissues. Both genetic anddietary factors are known to influence intestinalluminal levels of these steroid-like molecules,whose levels are associated with coloncancer risk. components (e.g., calcium, antioxidants)in cancer prevention strategies in humans.

Cyclooxygenase-2 and Cancer.

Cyclooxygenase (COX) enzymes catalyze prostaglandinsfrom arachidonic acid. There are two COXisoforms, COX-1 and COX-2. Several studies have implicated COX-2 incarcinogenesis. COX-2 protein levels, andtherefore, prostaglandin production, isupregulatedin many tumor types, including pancreatic,gastric, breast, skin, and colon cancers.Several lines of evidence suggest thatoverexpression of COX-2 plays an importantrole in colonic polyp formation and cancer progression.COX-2 modulates metastatic potentialby inducing MMPs, which can be directlyinhibited by COX-2. NSAIDs that inhibitboth COX-1 and COX-2 have been associatedwith reduced cancer risk in severallarge epidemiology studies.Both oncogenes and tumor suppressorgenes have been shown to modulate COX-2 incell model systems.

Other Targets.

Technologies such asDNA microarrays are identifying genes thatare aberrantly upregulated in human intraepithelialneoplasia (EIN). ODC, the first enzyme in polyamine synthesis,is up-regulated in a variety of IEN as aconsequence of specific genetic alterations. Difluoromethylornithine(DFMO), an enzymeactivated irreversible inhibitor of ODC, is apotent suppressor of several experimentalmodels of epithelial carcinogenesis and is beingevaluated in human cancer prevention trials. Pathways signaling cell behaviors are also activated in specific cancers. Several agents, including NSAIDs and componentsof green and black teas, have beenshown to inhibit certain signaling pathways incell-type and tissue-specific manners.

Importance of Studying Gene Expression.

Cancer, among other diseases, is causedby the deregulation of gene expression. Somegenes are overexpressed, producing abundantsupplies of their gene products, whereas othercrucial genes are suppressed or even deleted.The expression levels of genes associated withcancer influence processes such as cell proliferation,apoptosis, and invasion. Genes involved in growth, for example, are often overexpressedin tumor tissues compared withnormal adjacent tissue from the same organ.It is imperative to elucidate which genes areoverexpressed or down-regulated in tumorsbecause these genes represent critical therapeutictargets.Theability to analyze global profiles of gene expressionin normal tissue compared withtumor tissue can help reveal how gene expressionaffects the overall process of carcinogenesis.

MMP Inhibitors.

Several MMP inhibitorsare currently being developed for cancertreatment. If MMPs do play an integral role inmalignant progression, then pharmacologicalinhibition of MMPs could inhibit tumor invasiveness. MMP inhibitors fall into three categories:(*1*) collagen peptidomimetics and non- peptidomimetics, (*2*) tetracycline derivatives,and (*3*)bisphosphonates. The peptidomimeticMMP inhibitors have a structure that mimicsthat of collagen at the site where the MMPbinds to it. Batimastat, a peptidomimeticinhibitor,was the firstMMPinhibitor to be evaluatedin cancer patients and is not orally available.

Anticoagulants.

One theory surroundingthe invasion process is that bloodclottingcomponents may play a role in metastasisby either trapping the tumor cells incapillaries or by facilitating their adherence tocapillary walls. Large numbers of tumor cellsare released into the bloodstream duringthe metastatic process, and they must be ableto survive the wide range of host defensemechanisms. Tumor cells have been shown tointeract with platelets, lymphocytes, andleukocytesand this may serve to promote metastasis.Studies have been done that inhibit tumorcell-platelet interactions, and these haveresulted in a decreased probability of metastasisformation. It has also been shown that fibrinis always located in and around cancerouslesions, which may indicate that the cells usethe fibrin structure as a support on which toattach themselves and grow. It may also serveas protection against host inflammatory cellsso that the tumor is not destroyed.So far, the experimental evidence indicatesthat anticoagulants or inhibitors of plateletaggregation are useful in the prevention ofmetastases.

Inhibitors of Angiogenesis.

The growthand expansion of tumors and their metastasesare dependent on angiogenesis, or new bloodvessel formation. Angiogenesis is regulated bya complex of stimulators and inhibitors. The balance between the positive andnegative regulators of angiogenesis inside atumor environment is important for the homeostasisofmicrovessels. Tumor cells can secreteproangiogenic paracrine factors, whichstimulate endothelial cells to form new bloodvessels. The use of angiogenesis inhibitorsmay be a potential mode of therapy and is stillin early clinical trials. This type of therapywouldbe a way of controlling the diseaserather than eliminating it.

PLANTS AS ANTICANCER AGENTS

Nature is an attractive source of new therapeutic candidate compounds as a tremendous chemical diversity is found in millions of species of plants, animals, marine organisms, and microorganisms. One of the approaches used in drug discovery is the ethnomedical data approach, in which the selection of a plant is based on the prior information on the folk medicine use of the plant. It is generally known that ethnomedical data provides a substantially increased chance of finding active plants relative to the random approach.

As historically, plants and their products form the basis of medicines and also in present days. However, the medicinal value of plants depends on the nature of the plant constituents present in it, which is known as the active principle or active constituent (Secondary metabolites). These are used as medicine, food, flavors, colors, dyes, poisons, perfumes,*etc.*

At present about 25- 30% of the anticancer drugs in development are compounds of plant origin. These compounds have a wide variety of novel structures and mechanisms of actions.[27]

- Several plant-derived compounds are currently successfully employed in cancer treatment One of the most significant examples is the **vinca alkaloid** family isolated from the periwinkle *Catharanthusroseus*. They were the first agents to advance into clinical use for the treatment of cancer. The introduction of the vinca alkaloid vincristine was responsible for an increase in the cure rates for Hodgkin's disease, leukemia, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma. Vincristine inhibits microtubule assembly, inducing tubulin self-association into coiled spiral aggregates. [28]
- Epipodophyllotoxin is an isomer of podophyllotoxin (which was isolated as the active anti-tumor agent from the roots of *Podophyllum*species, *Podophyllumpeltatum*Linnaeus, and *Podophyllumemodi*Wallich (Berberidaceae). **Etoposide** and **Teniposide** are two semi-synthetic derivatives of Epipodophyllotoxin. They are usedfor their high cure rates in testicular cancer, lymphomas, and bronchial cancer. Etoposide is a topoisomerase II inhibitor, stabilizing enzyme–DNA cleavable complexes leading to DNA breaks[29]
- **Paclitaxel** was originally isolated from the bark of the yew tree *Taxusbrevifolia showed* antitumor activity was observed in various types of cancer, including ovarian and breast adenocarcinoma. Paclitaxel stabilizes microtubules, leading to mitotic arrest.

- Camptothecin derivatives I**rinotecan** and **Topotecan** obtained from the bark and wood of Nyssacea*Camptothecaacuminate*and act by inhibiting topoisomerase I have shown significant antitumor activity against colorectal and ovarian cancer. [30]
- **Homoharringtonine** is an alkaloid isolated from the Chinese tree *Cephalotaxusharringtonia*(Cephalotaxacea). Is has been used for the treatment of acute myelogenous leukemia and chronic myelogenous leukemia. The principal mechanism of action of homoharringtonine is the inhibition of protein synthesis, blocking cell-cycle progression.
- **Ipomeanol** is a pneumotoxic furan derivative isolated from the sweet potato *Ipomoea batatas*(Convolvulaceae) is a lung-cancer- specific antineoplastic agent. This compound is converted into DNA-binding metabolites upon metabolic activation by cytochrome P450 enzymes that are present in cells of the lung. [31]
- **Flavopiridol** is a synthetic flavone derived from the plant alkaloid rohitukine, which was isolated from the leaves and stems of *Amoorarohituka*and later from *Dysoxylumbinectariferum*(Meliaceae) is first cyclin-dependent kinase inhibitor to enter the clinic. It acts by interfering with the phosphorylation of cyclin-dependent kinases, hampering their activation and blocking cell-cycle progression at growth phase 1 (G1) or G2. [32]
- **Elliptinium**, a derivative of ellipticine, isolated from a Fijian medicinal plant *Bleekeriavitensis*A.C. Sm., is marketed in France for the treatment of breast cancer [33]
- Synthetic agent **Roscovitine** which is derived from natural product olomucine, originally isolated from *Raphanussativus*L. (Brassicaceae), is in Phase II clinical trials in Europe.
- **Combretastatin** was isolated from the bark of the South African tree *Combretumcaffrum*(Eckl. &Zeyh.) Kuntze (Combretaceae) (Pettit et al., 1987). Combretastatin A-4 is active against colon, lung, and leukemia cancers. [34]
- **Betulinic acid**, a pentacyclictriterpene, is a common secondary metabolite of plants, primarily from *Betula*species (Betulaceae). It displayed selective cytotoxicity against human melanoma cell lines [35]
- **Pervilleine A** was selectively cytotoxic against a multidrug-resistant (MDR) oral epidermoid cancer cell line (KB-V1) in the presence of the anticancer agent vinblastine. Pervilleine A is currently in preclinical development.
- **Silvestrol** was first isolated from the fruits of *AglailaSylvestre*(M. Roemer) Merrill (Meliaceae). Silvestrol exhibited cytotoxicity against lung and breast cancer cell lines [35]
- Two novel alkaloids, **Schischkinnin,** and **Montamine** have been isolated from the seeds of *Centaureaschischkinii*and*CentaureaMontana.* Both of the alkaloids exhibited significant cytotoxicity against human colon cancer cell lines. [36]

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