Chapter – 1

Introduction
1.1 CANCER

Cancer is the disease state in which normal growth controlling mechanisms are permanently impaired, permitting the progressive growth of cells without reaching growth equilibrium. These cells show unlimited replication potential, abnormal differentiation and improved survival. About 85% of all the cancers are solid tumors. This abnormal behavior arises out of the activation of certain specialized genes called protooncogenes to Oncogenes in the presence of physical, chemical and viral carcinogens. Once group of such cells are activated, these divide unlimitedly, causing the neighbouring normal cells to strive. There are over 200 different known cancers that afflict humans. Various changes that a cancer cell shows are as described.

1.2 MORPHOLOGICAL CHANGES IN A CANCER CELL

Cytoskeletal changes- The distribution and activity of the microfilaments and microtubules change. These alterations change the ways in which the cell interacts with neighboring cells and alter the appearance of the cells.

Cell adhesion/motility- The reduction of cell-cell and cell:extracellular matrix adhesion allows large masses of cells to form. Cancer cells do not exhibit contact inhibition and are able to continue to grow even when surrounded by other cells. The alterations in cell adhesion also impact on the ability of the cells to move. Cancer cells must be able to move and migrate in order to spread, and cell adhesion plays a major role in regulating cell movement.
Nuclear changes - The shape and organization of the nuclei of cancer cells markedly differ from that of the nuclei of normal cells of the same origin. This change in appearance may be useful in the diagnosis and staging of tumors.

Enzyme production - Cancer cells often secrete enzymes that enable them to invade neighboring tissues. These enzymes digest away the barriers to migration and spread of the tumor cells.

Fig. 1 Morphological changes in a cancer cell
1.3 PATHOGENESIS OF CANCER

Cancer is fundamentally a disease of breakdown of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered.²

The affected genes are divided into two broad categories. **Oncogenes** are genes which promote cell growth and reproduction. **Tumor suppressor genes** are genes which inhibit cell division and survival. Cancer can occur through the arrangement of novel oncogenes, the inappropriate and over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Specifically, changes in multiple genes are required to transform a normal cell into a cancer cell.² Genetic changes occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. More common are mutations, which are changes in
the nucleotide sequence of genomic DNA. These mutations can be large scale or small scale. **Large scale mutations** involve the deletion or gain of a portion of a chromosome. These occur by genomic amplification and translocation. Genomic amplification occurs when a cell gains many copies (often 20 or more) of a small chromosomal locus, usually containing one or more oncogenes and adjacent genetic material. Translocation occurs when two separate chromosomal regions become abnormally fused, often at a characteristic location. **Small-scale mutations** include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus, and resulting in the expression of *viral* oncogenes in the affected cell and its descendants.

Replication of the massive data contained within the DNA of living cells, probabilistically result in some errors (mutations). Complex error correction and prevention is an in-built process, and safeguards the cell against cancer. If significant error occurs, the damaged cell can "self-destruct" through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells.

The errors which cause cancer are **self-amplifying and compounding**, for example:

* A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly.
* A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.

* A further mutation may cause loss of a tumour suppressor gene, disrupting the apoptosis signalling pathway and resulting in the cell becoming immortal.

* A further mutation in signaling machinery of the cell might send error-causing signals to nearby cells.

The transformation of normal cell into cancer is akin to a chain reaction caused by initial errors, which compound into more severe errors, each progressively allowing the cell to escape the controls that limit normal tissue growth. This rebellion-like scenario becomes an undesirable survival of the fittest, where the driving forces of evolution work against the body's design and enforcement of order. Once cancer has begun to develop, this ongoing process, termed clonal evolution, drives progression towards more invasive stages.\(^3\)

1.4 MECHANISM OF METASTASIS

1.4.1 Formation of the primary tumor
Tumor cells invade stroma and communicate with stromal cells. Tumor is avascular.

Both tumor and host cells promote metastasis by activating growth factor pathways, permitting invasion, and endorsing angiogenesis. Host cells inhibit metastasis by putting up tissue barriers, activating immune cells to kill tumor, and inhibiting angiogenesis.
1.4.2 Progressive growth and angiogenesis

Angiogenesis occurs when tumors secrete angiogenic agents such as VEGF and FGF, and by their recruiting lymphocytes and macrophages to secrete these agents as well. The capillary basal membrane degrades locally, creating a vascular deformity and allowing new endothelial modeling. The tumor or macrophages may also secrete anti-angiogenic agents such as angiostatin, endostatin, and thrombospondin.

1.4.3 Invasion

Tumor cells invade host stroma using enzymes, then enter blood stream or lymphatics (which have thinner walls). The host reaction to this invasion is a fibrous extracellular membrane called the “desmoplastic response.”

1.4.4 Transport of cancer cells

Single cells or aggregates detach. Blood stream is very intimidating to cancer cells, so aggregates survive better, and become trapped in microvasculature downstream. These aggregates adhere to endothelial cells or even the basal membrane and invade distant tissue. Interestingly, presence of cancer cells in circulating blood and bone marrow is not associated with worse clinical outcome. Cancer cells deposit based on circulation mechanics and chemokines in target tissue. GI cancers go to liver, breast cancers to lungs. Cancer then has to set up new microenvironment – this is an inefficient step. Growth factors supporting new cancer include TGF-β and IGF1. Tumor cells express chemokine receptors complementary to target organ chemokines. Therefore, chemokines influence patterns of spread between organs.
1.4.5 Dormancy

One model for relapse is that dormancy has persistent tiny pre-angiogenic metastases, in which tumor cell growth is balanced by apoptosis.

1.5 CANCER INCIDENCE WORLDWIDE

Cancer is the leading cause of death worldwide, as per WHO worldwide statistics 7.8 million died of cancer in 2008. A total of 1,638,910 new cancer cases and 577,190 deaths from cancer are projected to occur in the United States this year i.e. 2012. Based on the projections, cancer deaths will continue to rise with an estimated 9.0 million people dying from cancer in year 2015 and Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030.
### Fig. 3 Cancer Incidence Worldwide

As we can see from the statistics (figure 3) above that major deaths per year are occurring due to cancer and unfortunately we still have limited number treatments available. Treatments available also have great deal of patient incompliance. This draws the great attention of researchers to develop treatments for this deadly disease. Conventional methods available for the treatment include surgical removal of the tumor followed by radiotherapy and chemotherapy to kill the residual cells and prevent the relapse. The effectiveness of cancer therapy in solid tumors depends on adequate delivery of the therapeutic agent to tumor cells. Inadequate delivery would result in residual tumor cells, which in turn would lead to re-growth of tumors and possibly development of resistant cells.

1.6 IMPACT OF CANCER IN INDIA

The myth that cancer affects people mostly in the developed countries is being broken by the fact that, of the 10 million new cancer cases seen each year worldwide, nearly 5.5 million are in the less developed countries. Cancer is the second most common cause of death in the developed world and a similar trend has emerged in the developing countries too.

Cancer frequency in India is projected to be around 2.5 million, with over 8,00,000 new cases and 5,50,000 deaths occurring each year due to this disease. More than 70% of the cases report for diagnostic and treatment services in the advanced stages of the disease, which has lead to a poor survival and high mortality rate. The impact of cancer is far greater than mere numbers. Its diagnosis causes immense emotional trauma and its treatment, a major economical burden, especially in a developing country like India. The initial diagnosis of cancer is perceived by many patients as a grave event, with more than
one-third of them suffering from anxiety and depression. Cancer is equally distressing for
the family as well. It could greatly affect both the family's daily functioning and
economic situation. The economic shock often includes both the loss of income and the
increase of expenses because of the treatment and health care. This disease is associated
with a lot of fear and despair in the country.

1.6.1 Distribution of Various types Cancers across the Subcontinent

Among men, lung, esophagus, stomach, oral and pharyngeal cancers are more prevalent,
while in women, cancers of cervix and breast are most common, followed by those of
stomach and esophagus.

1.6.2 Different cancers occur in different states of our country.12-14

- Esophageal cancers: Southern states of India like Karnataka and Tamil Nadu and
  also in Maharashtra and Gujarat.
- Stomach cancers: Southern India with the highest incidence in Chennai.
- Oral cancers: Kerala (South India)
- Pharyngeal cancers: Mumbai (Western India)
- Thyroid cancers among women: Kerala
- Gall bladder cancer: Northern India, particularly in Delhi and West Bengal.

1.6.3 Trends in Incidence of Cancer in India

A trend analysis of the data on cancer incidence for the period 1964–96 has demonstrated
that the overall occurrence of cancer is increasing with among females. The greatest
increase among females was for cancer of the breast and among males for cancer of the
prostate. There was an increasing trend for lymphoma, urinary bladder, gall bladder and brain tumors in both sexes. Cancer of the colon was increasing in females and that of the kidney in males. Esophageal and stomach cancers were decreasing in both sexes. Cervical cancer showed a decreasing trend.  

1.7 THERAPEUTIC STRATEGIES FOR THE TREATMENT OF CANCER

Cancer control strategies include early detection, treatment and palliative care. Present cancer therapy should be based on the philosophy, "even a single cancer cell should not remain untreated in the body and nothing less than complete elimination of tumor from an individual can be accepted".

Some approaches for the cancer therapy include:

2. Antiangiogenesis therapy: Inhibit the formation of the blood vessels that supply the tumor.
3. Hormonal therapy: Inhibit the growth of hormones, thereby preventing proliferation of prostatic and breast cancer.
4. Antimetastatic therapy: Inhibit or prevent the invasive growth and metastatic spread.
5. Immunostimulant therapy: Reinforce the functions of the immune system.

Except for a few cancer types (e.g. breast cancer), for which hormonal therapy or immunotherapy is used, cytotoxic drugs remain the major form of chemotherapy for cancer. Cytotoxic drugs are a diverse class of compounds that treat cancer primarily by being toxic to cells that are rapidly growing and dividing. Despite the long history of their use, and the development of numerous new multiple drug regimens for improved clinical success, treatment failure is still frequently encountered.
1.7.1 Conventional drug delivery methods and their limitations

In chemotherapy, pharmacologically active cancer drugs reach the tumor tissue with poor specificity and dose limiting toxicity. Conventional drug delivery methods include oral and i.v. routes. There are several disadvantages to these methods; for example, oral administration of tablets or capsules could result in disorderly pharmacokinetics due to the exposure of these agents to the metabolic pathways of the body. This can result in larger than necessary doses being administered, which can further cause increased toxicity. Another route includes i.v. route. Following a systemic administration, drug delivery to cells in solid tumors involves three processes, i.e., transport within a vessel (e.g., blood circulation), transport across vasculature walls into surrounding tissues, and finally to tumor cells. The traditional i.v. routes are often even more problematic. The specificity of some conventional i.v. drugs is low, resulting in harmful effects to healthy tissues. Thus, to deliver therapeutic agents to tumor cells in vivo, one must overcome the following problems:

- Drug resistance at the tumor level due to physiological barriers (non cellular based mechanisms),
- Drug resistance at the cellular level (cellular mechanisms),
- Distribution, biotransformation and clearance of anticancer drugs in the body.

Transport of an anticancer drug in interstitium will be governed by physiological (i.e. pressure) and physiochemical (i.e. composition, structure and charge) properties of the interstitium and by the physicochemical properties of molecules (size, configuration,
charge and hydrophobicity) itself. Therefore the designing of the delivery system should be in a manner to eventually overcome the aforementioned problems.

a. Systemic toxicity

Chemotherapy clutches a towering risk, and number of times it has been noticed that more the drug is effective; more is the risk of toxicity it carries. This is mainly due to relatively narrow therapeutic window where the maximum tolerated dose is limited by dose dependent toxicity. Depending on the choice of drugs, different organs or tissues can be affected by the non-specific action of the cytotoxic agents. Some of the important side effects includes: Cardiotoxicity, Hepatotoxicity, Nephrotoxicity, Ototoxicity, Pain, Anemia, Depression of the immune system, Hemorrhage, Secondary neoplasms, Erythema, Nausea, Diarrhea or constipation, Malnutrition, Hair loss, Memory loss, Dehydration, Vertigo, Hematoma, Dry mouth/ xerostomia, Weight loss or gain, Water retention and Sexual impotence.

b. Lack of target specificity

Conventionally administered cytotoxic agents often extensively and indiscriminately bind tissues and serum protein in a highly unpredictable manner. Many current therapies are administered into the bloodstream and rely on the leaky vasculature of tumor tissue to accumulate the drug within the cancer. Only a small fraction of the drugs reach the tumor site, which in turn leads to reduced therapeutic efficacy and increased systemic drug toxicity.

c. Drug Resistance

Drug resistance is the foremost cause of the treatment failure in cancer. This is the core problem being faced by the broad class of the hydrophobic cytotoxic drugs. Mechanisms
behind it mainly involves family of energy dependent transporters that causes increased efflux of these hydrophobic moieties. These energy dependent transporters are known as ATP-binding cassettes or shortly ABC transporters. Proteins falling under this family includes p-glyco proteins also known as ABCB1 or MDR 1. There is intensive research going on for improvement in the treatment of cancer to that includes new chemical entity development and the development of novel ways to deliver existing drugs leading to improved therapeutic index and reduced side effect. Improved delivery is made possible by encapsulating the drug in novel drug delivery systems such as, liposomes, nanoparticles, micelles, microspheres and micro emulsions.

d. Poor Drug Solubility
Most anticancer drugs, especially those with excellent anticancer effects such as taxanes (paclitaxel and docetaxel), camptothecins (topotecan and 9-aminocamptothecin), topoisomerase II inhibitors (etoposide and teniposide) the anthracylines (doxorubicin, epirubicin and daunorubicin), all Vinca alkaloids (vincristine, vinblastine, vinorelbine), ifosfamide and mitoxantrone have low bioavailability due to limited aqueous solubility. Adjuvants such as emulsifiers like cremophore EL for paclitaxel have to be used for the clinical administration of these drugs, which themselves are associated with serious side effects, some of which are life threatening.

Keeping in mind these shortcomings of the available therapeutic strategies, aims and objectives of the contemporary research were set and achieved, that would be discussed in the chapters impending in line.
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