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Review Article

Genetic Disorder and Cancer

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Abstract

The human body is composed of different cell types and tissues and cancers can arise from any of these cells. Cancer, the last stage of tumour growth is driven by genetic and epigenetic alterations that allow cells to proliferate indefinitely and escape mechanisms that normally control their survival and migration and cellular defense barriers. Oncogenes and tumour suppressors are the class of the genes which are responsible for the initiation and progression of tumour. Cancer is of three types of Carcinoma, Sarcoma and Leukemia depending upon the cell of origin and caused by different cancer causing agents known as carcinogen. Cancer is a genetic disease, and a spectrum of DNA variations is responsible or associated with particular type of cancer. Many of these changes map to signalling pathways that control cell proliferation and death leading to distortions of wider signalling networks. These mutations cremoveng cellular proto-oncogenes to oncogenes can cause hyper activation of these signalling, whereas inactivation of tumour suppressor genes removes negative regulators of signalling pathways. These information at molecular level gives insight for the cancer therapy.

Introduction

Cancer is dreadful disease causing a serious burden on human society affecting the health and lifespan. According to *GLOBOCAN project*, in (2012), 8.2 million people die because of cancer [1]. The fundamental abnormality in the development of cancer is the unregulated cell division and proliferation of cells. Fundamentally cancer is a genetic disease mainly caused by mutations in DNA repair genes in somatic cells leading to accumulation of genetic and epigenetic lesions. Many genes are known that are repeatedly altered in human cancer, such genes are termed as cancer-critical genes, meaning genes whose mutation contributes to the causation of cancer. These changes are inherited, spontaneous and external agents such as radiation or chemical induced. Cancer, the last stage of tumour growth results from alterations in critical regulatory genes that control cell proliferation, differentiation, survival and overcoming numerous highly evolved cellular defence barriers.

There are six hallmarks of cancer generally present in all type of cancers and proposed that together these hallmarks constitute an organizing principle that provides a logical framework for understanding the remarkable diversity of neoplastic diseases. Those hallmarks include.

1) independence of external growth signals,
2) insensitive to external anti-growth signals,
3) ability to avoid apoptosis,
4) ability to replicate indefinitely,
5) ability of mass of such cells to trigger angiogenesis and vascularise, and
6) ability to invade tissue and establish secondary tumours [2].

Cell proliferation is carefully balanced by cell division and cell death which gives the definite life span to a cell. This balance was disrupted in malignant transformation of the cell and a single faulty cell may give rise to the clone of identical cells expanding to a considerable size, producing a tumour. A tumour which is incapable of indefinite growth and does not invade the healthy surrounding tis-

sue extensively is known as benign. Tumour with property of continuous growth and progressive invasion is malignant tumour and the term cancer refers specifically to these malignant tumours. In addition to uncontrolled cell division, malignant tumours have the property of metastasis; in this process small clusters of cancerous cells dislodge from a tumour and invade into blood or lymphatic vessels and are carried to other tissues where they continue to proliferate leading to tumour formation. Different types of malignant tumours are classified according to embryonic origin of tissues from which they are originated [3-5] (Figure 1).

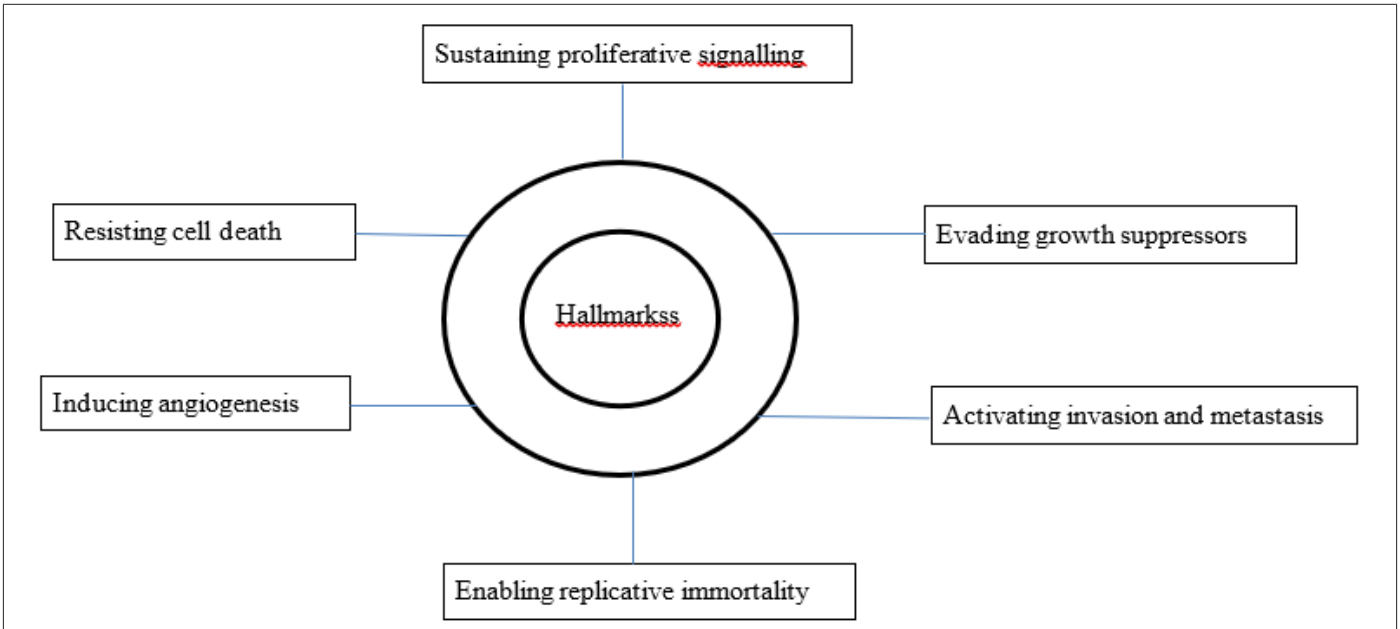

Figure 1: The hallmarks of cancer.

Carcinomas are the tumours derived from endodermal or ectodermal tissues or the epithelial lining of the internal organs. It is the most common (>80%) type of cancer. e.g., Renal cell carcinoma, lung carcinoma, carcinoma of pancreas etc. Leukaemia's and Lymphomas are the malignant tumours of the hematopoietic cells of the bone marrow and accounts almost 9% of the cancer incidence, for example, acute myeloid leukaemia, chronic myleloid leukaemia, Hodgkin's and Non-Hodgkin's lymphoma, etc.

Sarcomas type of cancer arises from mesodermal connective tissue, for example, bone fat cartilage and share only 1% of cancer incidence, for example, soft tissue sarcoma, retinoblastoma, alveolar soft part sarcoma, etc. [3-5].

There are many risk factors causing the cancerous condition and these risk factors include exposure to chemicals or other substances, causing variation in DNA sequence. Environmental factors and genetic disorders play a crucial role in the pathogenesis of human cancers. Studies have shown association between a potential risk factor and an increased risk of cancer. Risk factor association could explain how they could actually cause cancer. Risk factors for developing cancer include the following, which have been most studied or suspected of development of cancer. Advance age, family history, gender, consumption of alcohol, carcinogenic substances, sedentary lifestyle, chronic inflammation, dietary habit, hormones, obesity, suppression of immune system, infecting agents, radiation exposure, sunlight, sustained consumption of tobacco. Limiting exposures to these risk factors may lower occurrence of certain cancers.

Physiology of Cancer Cell

Cellular physiology and metabolic state of a cancer cell is very much different from a normal cell at all aspects of cellular physiology. Uncontrolled cell division is the main feature of all cancer cells suggesting that cell cycle and apoptosis is abnormally regulated. In cancer apoptosis, the cellular programmed cell death is inhibited therefore cells divide but do not die leading to tumour formation. Non-physiological level of oxygen tension owing to the rapid proliferation of cancer cells is known as Hypoxia. Tumour cells rapidly exhausts the oxygen and nutrient supply from the normal vasculature and drives upregulation of the production of angiogenic factors triggering the vascularization of the tumour. Hypoxia induces a number of complex intracellular signalling pathways, for example, Hypoxia-Inducible Factor (HIF) pathway, PI3K/AKT/mTOR, MAPK and the NFκB. These pathways are involved in cell proliferation, apoptosis, metabolism, migration, and inflammation regulating cancer survival. These continually dividing cells need a lot of energy to maintain cell division and feeding this large number of cells. Apart from increasing blood supply by forming new blood vessels, these cancer cells adapt for more energy. Cancer cells alter their metabolism and adapt to promote growth and survival of the tumour. Increase in glucose uptake, fermentation of glucose to lactate

lead to up-regulation of the pentose phosphate pathway for compensating reduced energy yield in tumours. Tumour cells has ability to break down glucose by glycolysis at a very high rate than in normal tissues, even when oxygen is abundant. This is the Warburg effect and almost all cancer hallmarks could be the consequence of this effect. Warburg effect enables rapidly dividing tumour cells to generate essential biosynthetic building blocks e.g., nucleic acids, amino acids, and lipids from glycolytic intermediates for growth and duplication of cellular components during cell division [6]. Energy metabolism and cell death pathway is regulated by another very important cell organelle known as lysosome. Lysosome is a catabolic cell organelle having the hydrolytic enzymes. Cancer cells have a block in their programmed cell death and could be targeted for therapy through the release of lysosomal enzymes. Importantly, the pathway of lysosomal cell death can be efficiently triggered by many chemotherapeutic regimens [7].

Mechanism of Cancer Pathogenesis

Cancer is a disease with differential phenotypes with the tumour origin and type. Mitogens (growth signals) are essential factors for proper cell growth and proliferation, are transmitted via specific receptors. In cancer these mitogens and receptors are dysregulated leading to uncontrolled cell growth. Cancer, the last stage of tumour formation is a stepwise process:

After genetic or environmental abnormality cells lose their ability to maintain the balance between cell division and cell death, leading to uncontrolled cell growth. This uncontrolled cell division leads to the formation of benign tumour which looks like the tissue with normal cells from which it originated, has a slow growth rate and most importantly they do not invade surrounding tissues and they do not metastasize to other organs. Generally benign tumour needs no treatment if symptoms are not problematic. Major health concern starts when benign tumour transforms into metastatic form of tumour known as Cancer. Epithelial to Mesenchymal Transition (EMT) mediates cellular transformation of benign tumour cell into the cancer cell leads to the activation or upregulation of enzymes which degrades Extra Cellular Matrix (ECM). Degradation of ECM by matrix metalloproteases leads to the invasion of tumour cell into the other organ and metastasized to the new place. This invasion and metastasis are a multistep process.

Immunoglobulins and cadherins class of proteins are involved in the cell-to-cell adhesions while integrins link cells to the ECM. E-cadherin is the most important protein cells to each other and coupling of cells by E-cadherin transmits antigrowth signals known as contact inhibition. N-cadherin helps the cancer cell to slip through blood vessels during migration and its expression increased in migrating cancer cells. Epithelial to mesenchymal transition characterized by the reduced E-cadherin and increased N-cadherin level [8].

After metastasis cells start to grow at the new location and form a tumour known as cancer. These tumours need nutrients to survive; new blood vessels are formed to supply nutrient and energy, this process is known as angiogenesis. Angiogenesis is largely regulated by Vascular Endothelial Growth Factor (VEGF) and stimulates vascular endothelial cell growth, survival, and proliferation. VEGF is a group of 6 structurally related proteins that regulate the formation, growth and differentiation of multiple components of the vascular system, mainly blood and lymph vessels [9].

Carcinogen And Genetic Variations

Cancer is mainly caused by genetic variations caused by toxic chemicals, environmental factors, food etc. All those substances and factors that can lead to cancer are called carcinogens. Carcinogens induce malignancies by generating DNA lesions (i.e., adducts) that can result into the mutations if remain unrepaired. Carcinogens can be divided into three major categories: chemical, physical carcinogens and biological.

Chemical Carcinogens: Exposure to noxious chemicals considered as chemical carcinogens is the single most important contributor to the incidence of human cancer. Exposure of these carcinogens leads to the interaction of the chemical with key biological macromolecules. Interaction with DNA is most dangerous and lead to the variations at the DNA level by the chemical modification of DNA sequences. These changes are cumulative, ultimately leads to a profound change at DNA level causing serious threats to the cell cycle. Example: cigarette smoke and some pesticides, Benzene, Formaldehyde, Mustard Gas [10,11].

Physical Carcinogens: Physical carcinogens include solid physical products operating through pressure or other mechanism, foil, inhaled fibres, asbestos particles, hard and soft synthetic materials, and gels. Some physical carcinogens are naturally occurring, while others are synthetic and highly variable in their chemical structure. X-rays, ultraviolet rays, and heat among the other non-particulate physical agents are responsible for the carcinogenesis. Some physical carcinogens act in concert with other factors such as genetic and other environmental factors to produce cancer. For example, asbestos can cause cancer on its own; however, its carcinogenic potential increased when combined with exposure to cigarette smoke [12].

Biological Carcinogens: 17.8% cancers were caused by viral (12.1%), bacterial (5.6%) and helminthes (0.1%) infection. According to International Agency for Research on Cancer (IARC) infections of all viruses that fulfil the following criteria can be direct carcinogens. First, the viral genome or part of it can usually be detected in each cancer cell. Second, the virus can immortalize after the growth of target cells in vitro. Third, it expresses several oncogenes that interact with cellular proteins and have multifunctional properties leading to disruption of the cell-cycle checkpoints, inhibition of apoptosis and cell immortalization. Four different viruses have been described as direct carcinogens: human papillomavirus family, Human T-cell Lymphotropic Virus type 1 (HTLV-1) and the two herpes viruses: Kaposi sarcoma- associated herpes virus (KSHV) and Epstein-Barr virus (EBV). Infectious agents can be indirect carcinogens by causing chronic inflammation leading to the production of chemokines, cytokines, prostaglandins secreted by

infected cells. It includes two hepatitis viruses HBV and HCV, Helicobacter pylori, Schistosoma haematobium, Opistorchis viverrini, and Clonorchis sinensis [13].

Genetic Basis of Cancer

Cancer is a genetic disease of uncontrolled growth and proliferation developed by a multi-step process that requires the accumulation of many genetic changes over time. Malignant cells have undergone mutations and epigenetic changes and maintain the transformed phenotype even when cultured or injected into immunologically tolerant experimental animals. These nonlethal genetic alterations involve activation of proto-oncogenes to oncogenes, deregulation of tumour suppressor genes and DNA repair genes. These changes are leading to initiation and progression of cancer. Most of the genetic changes in tumours are somatic brought about environmentally or randomly and a small proportion of all cancers are identified as inherited also referred as "genetic".

Tumour suppressor or anti-oncogenes, encodes the proteins that commonly control the fidelity of the cell cycle replication and inhibit cell proliferation and tumour development. Most of these 'classical' tumour suppressor genes have been characterized by the identification of germline mutations associated with the predisposition to human cancers. Tumour suppressor genes are recessive and therefore inactivation of both alleles is required. These genes are lost or inactivated by point mutations or deletion in both alleles of the gene. Loss of function of these genes liberates cells from growth restrictions and contributes to malignant transformation (Table 1).

Table 1: Tumour suppressor genes and the corresponding malignancy.

Tumour suppressor gene	Tumours
Retinoblastoma (Rb)	Retinoblastoma, sarcoma: some carcinomas
P53	Carcinoma of lung and breast: sarcoma
NF1	Neurofibromas, malignant peripheral nerve tumours
APC	Colonic carcinoma
WT1	Wilms' tumour, bladder cancer,
BRCA1&2	Breast cancer

The cumulative effect of genetic changes that inactivate tumour suppressor genes or activate proto-oncogenes is a mechanical failure in the balance between cell proliferation and cell loss because of differentiation or apoptosis leading to the clonal overgrowth of a specific cell lineage. Retinoblastoma susceptibility gene RB is the first recognized tumour suppressor gene which encodes a nuclear phosphoprotein that acts as a "gatekeeper" of the cell cycle. Deletion or point mutation leads to the inactivation of the RB; causing the protein to lose its regulatory capacity. P53 is the second recognized and well-studied tumour suppressor genes, expressed at low levels in normal cells and has regulatory role in the cell cycle, DNA synthesis and repair, transcriptional regulation and programmed cell death [14,15].

Oncogenes

Oncogenes were first discovered in cancer-causing viruses; however, they are present in all normal cells. More than 40 different highly oncogenic retroviruses have been isolated from a variety of animals. All of these viruses, like RSV, contain at least one oncogene that is not required for virus replication but is responsible for cell transformation (Cooper GM, book chapter). Example of retroviral oncogenes: abl(Mouse), ets(Chicken), fos(Mouse), jun(Chicken), rasH(Rat), rasK(Rat), src(Chicken) etc.. The unmutated wild-type allele of an oncogene is known as the proto-oncogene, and these proto-oncogenes converted to oncogenes by amplification, translocation, and point mutation of DNA.

Mutations in proto-oncogenes are typically dominant in nature and act through either overexpression or activating mutations. Oncogenes encode proteins that control cell proliferation, apoptosis which possess the ability to cause cellular transformation. The proteins encoded by oncogenes can be classified into six broad groups: transcription factors, chromatin remodelers, growth factors and its receptors, signal transducers, and apoptosis regulators [16]. Chromosomal translocations activate transcription-factor genes in lymphoid cancers, solid tumours, and certain sarcomas. Chromosome inversions and translocations are common cytogenetic increase or deregulate transcription of the oncogene. Most of the hematopoietic tumours and soft tissue sarcomas are initiated by the activation of an oncogene, followed by alterations in tumour suppressor genes and other oncogenes. In contrast, most carcinomas are initiated by the loss of function of a tumour-suppressor gene, followed by alterations in oncogenes and additional tumour suppressor genes [16]. Duration and aggressiveness of the tumour can be changed by introducing activated oncogenes or inactivated tumour-suppressor genes in mouse model of cancer.

Genetic Instability and Cancer

As mentioned earlier cancer is a genetic disease and different types of cancer has associated landscape of genomic variation. Some of the most common cancer is discussed below:

Breast Cancer

Breast cancer is among the most commonly diagnosed cancer and ranks second among causes for cancer related death in women. Breast cancer is most strongly associated with highly penetrant germline pathogenic variants in *BRCA1* and *BRCA2*. BRCA1 (Breast Cancer susceptibility gene 1) and BRCA2 are tumour suppressor genes transcriptional regulated in response to DNA damage and contribute to DNA repair. 5-9% of all breast cancers are Hereditary in nature and estimated that the *BRCA1* and *BRCA2* gene mutations are responsible for ≈80% of the families with hereditary breast cancer. Apart from *BRCA1* and *BRCA2* there are many other genes which are associated with breast cancer, for example, TP53, ATM, PTEN, LKB1, HRAS1, NAT1, NAT2, GSTM1, CYP1A1, etc [17-19].

Cervical Cancer

Cervical cancer is one of the leading causes of death of women in developing countries. Epidemiological and laboratory studies have identified that infection of one of 15 high-risk Human Papillo-ma Virus (HPV) types as a necessary but not sufficient for the cervical cancer. Most HPV infection is transient and harmless and cleared by immune response but persistent infection with high-risk human papillomavirus can cause cancer. Genetic variations in the host genes involved in immune response pathways may be related to clearance of HPV, and HPV E6/E7 oncoproteins interacting or downstream genes may contribute to the outcome of HPV infection and cervical cancer. The most important among the known risk factors is the HLA class II DRB1-DQB1 haplotype, such as DRB1*1501-DQB1*0602 and DRB1*1301-DQB1*0603 associated with increased and decreased risk of cervical cancer, respectively [20-22].

Gastric Cancer

Gastric cancer is associated with poor survival rates leading to high proportion of global cancer mortality. Approximately 90% of gastric cancers are adennocarcinoma and it is well known that the development of gastric cancer is associated with underlying gastric diseases, *Helicobacter pylori (H. pylori)* infection and genetic susceptibility factors. Almost 10% of gastric cancer cases display familial clustering whereas only 1-3% of gastric carcinomas arise due to inherited gastric cancer predisposition syndromes. Co-segregation of germline *E-cadherin (CDH1)* mutations with early onset diffuse gastric cancer in families with an autosomal dominant pattern of inheritance (HDGC) show that gastric cancer is hereditary in nature. APC, a tumour-suppressor gene and is associated with colorectal cancer [23-25].

Oral Cancer

According to International Classification of Diseases, oral cancer is the cancer of the oral cavity and pharynx, including cancer of the lip, salivary glands, tongue, gum, floor and other areas of the mouth, nasopharynx, oropharynx, pharynx, hypopharynx, and other buccal areas. Oral cancer is frequently associated with Chromosomal alterations in chromosome 8. Chromosomal gains in 8q and losses in 8p are the common alterations present and have been shown to be involved in the lymph node metastasis of oral cancer. c-MYC (8q24) in chromosome 8 is frequently amplified in various cancers. Frequently deleted regions are 8p21, 8p22 and 8p23 [26-28].

Lung Cancer

Lung cancer is one of the most common human cancers representing most common form of cancer death worldwide, and tobacco smoke is the major risk factor for this disease. Collaborative, genome-wide association studies have identified common gene variants involved in lung cancer. Three separate loci associated with lung cancer (5p15, 6p21, and 15q25) are identified including the genes that regulate acetylcholine nicotinic receptors and telomerase production. Mutations in Epidermal Growth Factor Receptor (EGFR) tyrosine kinase identified in patients with lung cancer who have never smoked. Prevalence of mutations in *KRAS* and *P53* genes differ in patients with tobacco-associated lung cancer and patients who have never smoked [29-32].

Soft Tissue Sarcoma

Soft-tissue sarcoma is a heterogeneous group of neoplasms arising in mesenchymal tissue and comprises more than 35 histologic subtypes, often associated with distinctive clinicopathologic features. These types of sarcomas are rare, but generally aggressive tumours mainly affecting children and young adults. These types of tumours arise from muscle, connective tissue, supportive tissue and vascular tissue with high propensity for local recurrence. Soft-tissue sarcoma can be divided into two groups: Rhabdomyosarcoma (RMS) and Non-Rhabdomyosarcoma Soft-Tissue Sarcomas (NRSTS). Frequently mutated genes in soft tissue sarcoma included *TP53* (17% of pleomorphic liposarcomas), *PIK3CA* (18% of myxoid/round-cell liposarcomas) and *NF1* (10.5% of myxofibrosarcomas and 8% of pleomorphic liposarcomas) [33-35].

Signal Transduction in Cancer

Cancer is not a single disease it is a syndrome with many disease phenotypes involving massive army of genes involved in it. During the course of tumour initiation and progression tumour cells acquire a number of characteristic alterations which allow them to proliferate, survive, and invade other tissues. All these cancers associated phenotypes are associated and dependent on each other and regulated by network of the genes. Cellular signalling pathways are interconnected to form complex signalling pathways. Cancer cells receive information from many different growth factor receptors and from cell-matrix and cell-cell contacts and then integrate this information via signal transduction and cellular signalling. This integrated network regulates protein synthesis and cell growth, cell architecture and polarity, motility, differentiation, and programmed cell death capacities. There are many pathways regulating these processes are dysregulated leading cancer progression and survival e.g. Src and FAK in cell motility and invasion, The Ras/MAP kinase pathway: Targets and scaffolds, PI 3-kinases and the regulation of cell growth, motility, Survival, Rho family GTPases etc. PI3K-Akt and

Ras-ERK Pathways is an important signalling pathway responsible for cancer is described here [36,37].

The PI3K-Akt and Ras-ERK Pathways: The phosphatidylinositol 3-kinase-mammalian target of rapamycin (PI3K-mTOR) and ras-extracellular signal-regulated kinase (Ras-ERK) signalling pathways are the chief mechanisms for controlling cell survival, proliferation, differentiation, metabolism, and motility in response to extracellular signals. These pathways play key roles in the transmission of proliferative signals from membrane bound receptors. Activation of these pathways can induce cellular immortalization, proliferation, survival, metabolism of cancer cells and resistance to anticancer therapeutics, for example, epidermal growth factor receptor inhibitors and chemotherapy. The PI3K signalling pathway is dysregulated almost in all cancers due to the gene amplification, genetic mutations of PI3K gene and the components of the PI3K pathway. These pathways are activated by growth factors, polypeptide hormones, neurotransmitters, chemokines, and phorbol esters, which signal through their cognate RTKs (receptor tyrosine kinases) and GPCRs (G protein-coupled receptors). Many of the genes commonly mutated in cancer encode components or targets of the Ras-ERK and PI3K-Akt pathways. Normally these pathways are transiently activated in response to growth factor or cytokine signalling and ligand occupancy of receptors, but genetic changes can lead to constitutive signalling even in the absence of growth factors [38,39].

Cancer Therapy

Cancer is one of the biggest challenges and facing the absence of right effective drug for the treatment. Surgery is the most effective method of treatment for the localized primary tumours and associated regional lymphatics. With the emergence of radiation therapy and chemotherapy, surgery has become conservative for the cancer treatment. Chemotherapy and radiation therapy are only capable of killing a fraction of tumour cells and complementary to each other [40]. With the tremendous advances achieved in the understanding of cancer biology molecularly targeted cancer therapy come into the scene. Targeted cancer therapies are drugs or other substances that target specific molecules and block the growth and spread of cancer, for example, Monoclonal antibodies: Anti-HER2 (Trastuzumab), Anti-EGFR (Cetuximab), Anti-VEGF (Bevacizumab); Chemotherapy: Altretamine, Cisplatin, Carboplatin; Endocrine therapy: Tamoxifen, Fulvestrant, Aromatase Inhibitors; Small molecule: Sunitinib, Imatinib, Lapatinib, Erlotinib [41]. Tumour heterogeneity is the main factor behind limited response against targeted therapy therefore targeted cancer therapy remains challenged by a high failure rate and an extremely small proportion of patients benefited. Oncolytic viruses are the class of anticancer agent emerging as a promising tool for cancer therapy. These viruses replicate within, and ultimately lyse, cancer cells sparing normal cells. Many oncolytic viruses have been developed, for example, adenoviruses, herpesviruses (HSV), reoviruses, retroviruses and Vesicular Stomatitis Virus (VSV) and measles virus. US FDA has approved the oncolytic herpesvirus talimogene laherparepvec in advanced melanoma, a major breakthrough for the oncolytic virus as cancer therapeutics [42]. Immunotherapy is the treatment that uses body's own immune system to fight cancer and this can be achieved by stimulating immune system to work harder or smarter to attack cancer cells or exogenously giving immune system components or proteins. Immunotherapy includes monoclonal antibodies, immune checkpoint inhibitors, cancer vaccines. Gene therapy (an experimental technique using genes to treat or prevent disease) is emerging as a field of cancer research which offers a number of potential treatments. This technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery. The term gene therapy includes a wide range of treatment types that all use genetic material to modify cells to cure cancer. Gene therapy of cancer includes transfer of genetic material through viral (or bacterial) and non-viral vectors into cancerous cell or the surrounding tissue to cause cell death or slow down the cancer growth. In recent development of gene therapy clustered regularly interspersed palindromic repeats (CRISPR) technique is used for human diseases including cancer [43].

Conclusion

During the last two decades and half, more than 2000 gene therapy clinical trials have been undertaken worldwide. Almost 95% of the trials were in early phases of development and 72% were ongoing [44]. The majority of gene therapies clinical trials identified targeted cancer diseases. Regulators are defining path for rapid access of those new therapies. Major steps forward are expected in the field of gene therapies in the future.

Acknowledgement

None.

Conflict of Interest

None.

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