Medicinal chemistry

Review Article Open Access

Drug Targets for Cancer Treatment: An Overview

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Abstract

Cancer is one of the major cause of death worldwide. Malignant cells display metabolic changes, when compared to normal cells, because of both genetic and epigenetic alterations. Number of drugs being used for the cancer treatment follows different mechanisms of action. Therapeutic strategies include targeting of drugs at specific genes or proteins/enzymes found in cancer cells or the internal tissue environment which contributes to growth and survival of these cells. Targeted therapy is often used along with chemotherapy and other treatments to restrict the growth and spread of cancer cells. During the past few decades, targeted therapy has emerged as a promising approach for the development of selective anticancer agents. There is a class of targeted therapy drugs called angiogenesis inhibitors which focus on blocking the development of new blood vessels in tumor tissues. In addition, anticancer drugs also include DNA intercalators, DNA synthesis inhibitors, transcription regulators, enzyme inhibitors etc. This review focuses on major classes of anticancer drug targets and their therapeutic importance.

Keywords: Anticancer drug targets; Angiogenesis; Gene regulation; Enzyme; Microtubules

Introduction

Cancer is the second leading cause of death in Europe and America. Tremendous resources are being invested all around the world for developing preventive, diagnostic, and therapeutic strategies for cancer [1]. Several pharmaceutical companies and government/non-government organizations are involved in the discovery and development of anticancer agents [2]. Identification of novel cytotoxic compounds has led to the development of anticancer therapeutics for several decades. Boom of knowledge in molecular sciences, genomics and proteomics has also helped in creating new potential drug targets. This has changed the paradigms of anticancer drug discovery toward molecularly targeted therapeutics. There are unique challenges and opportunities in discovery of anticancer drug delivery which might reflect at each stage of the drug development process [3]. Cancer is primarily a disease of uncontrolled cell division, thus identification of anti-proliferative compounds and their effects on regression of tumor size are the main aims for therapeutic discovery. For this purpose murine models of cancer were developed and several clinically important anticancer compounds were identified [1]. Differentiated result outputs among fast growing and slow growing tumors led investigators to modify the screening protocols to include a variety of cell lines and tumor types. The rationale that cancer cells are more likely to be replicating than normal cells makes the basis for targeting cell division process by most of the chemotherapeutics. Unfortunately significant toxicity is associated with chemotherapeutics as they lack specific action [1-3].

Double-helical DNA consists of two complementary strands running anti-parallel having sugar-phosphate poly-deoxyribonucleotide backbone associated with specific hydrogen bonding between nucleotide bases [4]. In a given DNA sequence difference in chemical feature of the molecular surfaces in either groove forms the basis for molecular recognition by small molecules and proteins. B-form of the DNA i.e. biologically relevant double helix is characterized by a shallow wide major groove and a deep narrow minor groove [5]. DNA replication, transcription and protein synthesis are the major steps in cell growth and division. Being carrier of genetic information as well as central to tumorigenesis and pathogenesis, DNA is a major target for drug development. There is always a challenge for drug to achieve maximum specific DNA binding affinity. The other thing that needs consideration is that drug should not affect cellular and nuclear transport activity of the normal cells. Some of the most effective anticancer agents that target DNA are known to produce significant survival rate in cancer patients when used in combination with drugs having different mechanisms of action [6]. Besides DNA, RNA, enzymes and other proteins also contributes as major targets for anticancer drug development [7]. Structures of some anticancer drugs are depicted in Figure 1. In this review we have tried to discuss some molecular aspects of anticancer drug mechanisms.

Angiogenesis Inhibitors

Angiogenesis (AG) is the process by which tumour develops new blood supply (neovascularisation) for the growth and metastasis. Small tumours can obtain oxygen and nutrients by diffusion but as they become enlarged they need to develop new blood vessels for the fulfillment of required nutrients for growth, invasion and metastasis. Different anti- and pro-angiogenic factors are involved in the development of blood vessels in a complex equilibrium [8]. In physiological processes such as wound healing this equilibrium may go in favor of angiogenesis by inflammation or hypoxia. But on the other hand it may be the part of the pathological process in cancer or other chronic inflammatory diseases. Vascular endothelial growth factor (VEGF), angiogenin, transforming growth factor-β (TGF-β) and fibroblast growth factor (FGF) are some pro-angiogenic factors that are released in tumor associated angiogenesis which in turn induces the proliferation, migration and invasion of endothelial cells in new vascular structures [8]. Platelet derived growth factor receptor and cell adhesion molecules (e.g., integrins) play important role in the process of angiogenesis. Oxygen deprivation, oncogenic mutations, inflammation and mechanical stress are the stimulus that initiates growth of new vessels in tumor (angiogenic switch). This leads to vascularisation

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Received February 24, 2015; **Accepted** March 17, 2015; **Published** March 19 2015

Citation: Kumar S, Ahmad MK, Waseem M, Pandey AK (2015) Drug Targets for Cancer Treatment: An Overview. Med chem 5: 115-123. doi:10.4172/2161-0444.1000252

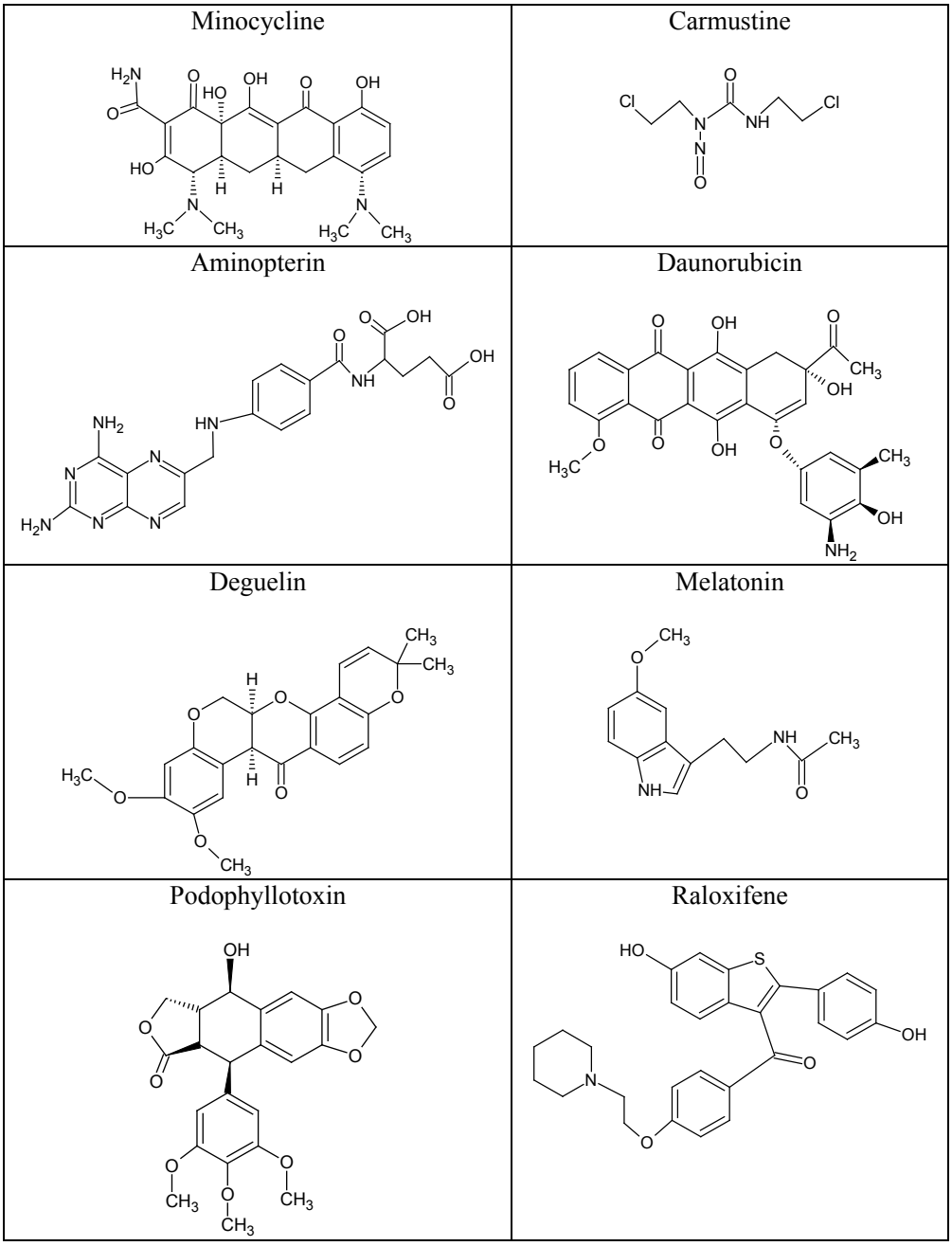

Figure 1: Structure of some anticancer drugs.

and expression of pro-angiogenic factors in tumor [8]. Some of the angiogenesis inhibitors and their mode of action are shown in Table 1.

VEGF signaling through its receptor tyrosine kinase is the major inducer of angiogenesis. VEGFR-1, 2, and 3 are the three receptor tyrosine kinases of VEGFR family which mediate the angiogenic effect [9]. In endothelial cells stimulation of VEGFRs, other tyrosine kinases, G-proteins and serine/threonine kinases cause massive activation of signaling pathways. Src homology 2 (SH2) and b-cell (Shb) protein act as adapter molecules in VEGFR mediated signaling in angiogenesis. Endothelial cell migration, proliferation, and survival are the important processes involved in angiogenesis. These event takes place by the activation of PI3K (phosphatidylinositol 3-kinase) and Akt/PKB (serine threonine kinase/protein kinase B), by virtue of Shb protein interaction with VEGFR-2 phosphorylation site. For last three decades AG has been taken as an appealing target for anticancer drugs [9]. Till know about thirty AG inhibitors are in clinical trials and some of them have been approved for the treatment of malignancy. AG inhibitors play role as cytostatic rather than cytotoxic drugs. The anti-angiogenic drugs have capability to reduce the production of pro-angiogenic factors as well as their binding efficacy to respective receptors which results into their blockage of action [8,9].

DNA Intercalators and Groove Binding Agents

Intercalation and groove binding are the major mechanisms underlying drug-DNA interaction. Insertion of a planar molecule between DNA base pairs is known as intercalation which results

Name	Mode of Action	References
Angiostatin K13	Inhibitor of endothelial cell growth and angiogenesis.	[10]
DLαDifluoromethylornithine	Inhibition of ornithine decarboxylase (ODC) and blocks angiogenesis	[11]
Endostatin	Inhibits endothelial cell proliferation; Potent inhibitor of angiogenesis and tumor growth as well.	[12]
Fumagillin	Inhibitor of endothelial cell proliferation and angiogenesis.	[13]
Genistein	Down regulates the transcription of genes involved in controlling angiogenesis.	[14]
Minocycline	Inhibits endothelial cell proliferation and angiogenesis.	[15]
Staurosporine	Blocks angiogenesis by inhibition of up regulated VEGF expression in tumor cells.	[16]
(±)Thalidomide	Inhibits biosynthesis of tumor necrosis factor α (TNFα); inhibits angiogenesis.	[17]

Table 1: Angiogenesis inhibitors and their mode of action as anticancer agent.

in the reduction of lengthening and helical twist of the DNA [18]. Approximately 4 kcal per mol free energy is used to establish the intercalation cavity. Some favorable contributions *viz.,* hydrophobic, ionic, hydrogen bonding, and vander Waals forces are also involved [18]. DNA intercalating agents may be divided into mono (e.g. ellipticine, actinomycins and fused quinoline compounds) and bi/poly (e.g. ditercalinium and echinomycin) functional intercalating molecules. The two intercalating units (usually cationic) in bifunctional intercalators are separated by a spacer chain that must be long enough to allow double intercalation [19]. Recognition and function of DNA-associated proteins (polymerases, topoisomerases, transcription factors and DNA repair systems) are disturbed by DNA intercalating agents. Bi/tricyclic fused or non-fused ring structures have been traditionally used as DNA intercalating agents. They are known to be used as antimalarial, antibiotic, antitumor and antineoplastic agents. The intercalators may be toxic or non toxic depending on the presence/absence of various functional groups *viz.,* basic, cationic, or electrophilic required for genotoxicity [20,21]. Groove binding molecules (usually crescent-shaped) unlike intercalators bind to the minor groove of DNA as a standard lock-and-key model and do not induce large conformational changes in DNA. Here, for the creation of binding site, cost of free energy is not required and the associations are stabilized by intermolecular interactions [22]. DNA intercalators are less sequence selective and show a preference for G-C regions. On the other hand groove binding molecules are more sequence selective and do not show G-C region preference [23]. Intercalators and groove binders have proven clinical utility both as anticancer and antibacterial agents. For example mitomycin and anthracyclines are exemplified both as DNA crosslinker as well as groove-binding molecules [24]. Table 2 shows some more example of DNA intercalators used as anticancer agents.

DNA Synthesis Inhibitors

It is well established that without purines, pyrimidines, serine, and methionine the de novo synthesis of DNA in mammalian cells can not be possible. Folates belong to the family of B9 vitamins that are essential to mammalian cells. Folic acid is not a naturally occurring folate, it is composed of a pteridine ring, para-aminobenzoic acid (pABA) and glutamate [33]. In cells folic acid undergoes reduction process mediated by dihydrofolate reductase (DHFR) which ultimately leads to production of folate polyglutamates. These polyglutamates serve as one-carbon donors in de novo synthesis of purines, thymidylate, and polyamines [34]. The understanding of the role of folate derivatives in humans has led to the identification and development of antifolates as therapeutic agents. This idea got support from the observation of serum folate deficiency among patients with acute leukemia in the early 1940s leading to new postulation that acute leukaemia might be the result of folate deficiency [33]. Ribonucleotide reductase (RNR) is an enzyme responsible for the de novo conversion of ribonucleoside diphosphate (NDP) to deoxyribonucleoside diphosphate and also regulates the supply of intracellular dNTP [35]. The consequences of imbalance in the substrates for DNA synthesis may lead to mutagenesis and cell death. Thus maintenance of a balanced dNTP pool is a fundamental cellular function by RNR shows its importance in cell survival. Because of this activity differential expression of RNR is tightly regulated during cell cycle [36,37]. Aberrant replication forks, activation of S-phase checkpoint, and cell-cycle arrest are the some key goals that might be achieved by targeted inhibition of RNR [37]. RNR is expressed at relatively low level in normal cells while in cancer cells its expression level is very high for maintaining high dNTP pools required for DNA synthesis and proliferation. Using a structure and mechanism based approach scientist have designed and developed novel class of RNR inhibitors with potential clinical use. Recently COH29, an RNR inhibitor was discovered that showed activity in tissue culture and human tumor xenografts in mice [38]. S-phase arrest was observed in cell cultures treated with COH29 which is consistent with inhibition of RNR and its established role of catalyzing the rate-limiting step in dNTP synthesis and therefore DNA synthesis [39,40]. Novel binding pocket in RNR have been identified which is located on such a position that makes it potentially capable of multiple functional and biologically relevant effects. Gemcitabine (2',2'-difluoro-2'-deoxycytidine, dFdC) is metabolized intracellularly to 5'diphosphate (dFdCDP). It is another potent inhibitor of ribonucleotide reductase and a very promising anticancer drug [41]. Several DNA synthesis inhibitors have been enumerated along with their mode of action in Table 3.

Transcription Regulators

In all living cells transcription is required for the growth and survival. However, tumor cells require excess levels of transcription, including ribosomal RNA and mRNA transcription by RNA polymerase I and RNA polymerase II respectively. Mutations are responsible for the enhanced transcription in cancer cells. DNA transcription is dependent on the spatially and temporally coordinated interaction between transcriptional machinery and transcriptional regulatory components. Different transcription factors (TFs) have been reported to associate with cancer. Transcription deregulation can occur by aberrant activation, repression, temporal/spatial dyscoordination, structural changes including mutations, translocations, and fusion. Dysregulation of transcriptional and thereby post-transcriptional processes contributes to cancer initiation [51]. The TF nuclear factor (NF)-kB is a family of five reticuloendotheliosis (REL) proteins. The protein influences gene transcription that allows its translocation into the nucleus. Its inhibition sequesters the complex (NF-kB and its inhibitor IkBα) in the cytoplasm in an inactive conformation. Activation of NF-kB transcription factor may lead to IkBα degradation. NF-kB has been known to be active constitutively in several cancer types. It is associated with the regulation of cell survival, cell proliferation, invasion, metastasis and apoptosis inhibition. Thus inhibition of NF-kB transcription factor may result into retarded tumor formation [51]. Targeting of a TF might inhibit several cancer related genes, since

Name	Mode of Action	References
Bleomycin	Inhibits DNA synthesis; causes cleavage at specific base sequences. Induces apoptosis and inhibit angiogenesis.	[25]
Carboplatin	Forms DNA adduct and induce apoptosis.	[26]
Carmustine	DNA alkylating/crosslinking agent effective against glioma and other solid tumors.	[27]
Chlorambucil	Alkylates DNA; In leukemia cells induces apoptosis by p53dependent mechanism.	[28]
Cyclophosphamide (nitrogen mustard)	Crosslinks DNA and causes strand breakage.	[29]
cisDiammineplatinum(II) dichloride (Cisplatin)	Induces apoptosis by forming cytotoxic adducts with the DNA dinucleotide d(pGpG).	[30]
Melphalan	Forms DNA intrastrand crosslinks by alkylation of 5'(GGC) sequences.	[31]
Mitoxantrone	Inhibits DNA synthesis by intercalating DNA.	[32]

Table 2: DNA intercalators/groove binding agents and their mode of action as anticancer agent.

Name	Mode of Action	References
(±)Amethopterin (Methotrexate)	Blocks thymidine biosynthesis via inhibition of dihydrofolate reductase (folic acid antagonist)	[42]
3Amino1,2,4benzotriazine 1,4dioxide	Hypoxia activated antineoplastic agent	[43]
Aminopterin	Mechanism same as methotrexate but more potent.	[44]
Cytosine- β D-arabinofuranoside	Selective inhibitor of DNA synthesis.	[45]
5-Fluoro5' deoxyuridine	Inhibits proliferation of cancer cells transformed by HRas or Trk oncogenes	[46]
5-Fluorouracil	Depletes dTTP and inhibits thymidylate synthetase; it forms nucleotides that can be incorporated into RNA and DNA and induces p53dependent apoptosis	[47]
Ganciclovir	In suicide gene therapy of solid tumors, the gene for *Herpes simplex* virus thymidine kinase is delivered to tumor cells and expressed, which in turn activates ganciclovir cytotoxicity.	[48]
Hydroxyurea	Blocks the synthesis of deoxynucleotides by inactivating ribonucleoside reductase resulting into inhibition of DNA synthesis and induction cell death.	[49]
Mitomycin C	Inhibits DNA synthesis, nuclear division, and proliferation of cancer cells.	[50]

Table 3: DNA synthesis inhibitors and their mode of action as anticancer agent.

it regulates different downstream target genes. In cancer therapy, the drugs that targets TFs are less known than inhibitor molecules targeting the signal transduction. Recently novel immunotherapies have been documented against some transcription factors. For example transcription factor WT-1 and PML-RARα are the targets for the treatment of leukemia and acute promyelocytic leukemia respectively [52,53]. Drugs that potentially target the transcription machinery include cyclin-dependent kinases (CDKs), RNA polymerases or components of associated transcriptional complexes. Inhibitor such as triptolide, that targets the general transcription factors TFIIH and JQ1 to inhibit BRD4 are administered to target the high proliferative rate of cancer cells [54]. Tumor suppressor genes or oncogene antagonists have been used as an attempt at cancer therapy targeting TFs. It is reported that ETS transcription factors, especially Ets-1 have capability to inhibit cell growth, metastasis and tumor angiogenesis. But no reports are available regarding trials of gene therapies targeting ETS transcription factors. Considering that TFs that regulate growth, apoptosis, angiogenesis, invasion and metastasis related genes in tumor cells could be molecular targets for cancer gene therapy [54]. Some examples of transcription regulators are shown in Table 4.

Enzyme Inhibitors

In contrast to normal cells, the metabolic properties of cancer cells are different and they depend on aerobic glycolysis for their energy requirement. In addition they have dysregulated fatty acid synthesis, Warburg-like glucose metabolism and glutaminolysis. Studies have shown that several enzymes in metabolic pathways act as anticancer targets and their inhibition is responsible for mediating apoptotic death in cancer cells. Hence inclusion of inhibitors of metabolic enzymes (e.g. glucose transporters, fatty acid synthase, hexokinase, lactate dehydrogenase A, pyruvate kinase M2, pyruvate dehydrogenase kinase and glutaminase etc.) in cancer therapy regimen are also important to enhance the efficacy of chemo/radiotherapy [60]. Estrogens and its receptors (ERs) are known to play important role in the progression and development of breast cancer [61-62]. Estrogens influence breast cancer through the ERα pathway, increases genetic mutations, and/or effects on DNA repair pathway [63,64]. Biosynthesis of estrogens from androgens involves a cytochrome P450 enzyme known as aromatase, encoded by the aromatase gene *CYP*19. Its expression is regulated by tissue-specific promoters [65]. It has been found in all the tissues in body including breast, brain, skin bone and muscles. It is found that the expression of aromatase is increased many folds in breast cancer tissues. Inhibition of this enzyme has been shown to be responsible for the decreased level of estrogen. Thus in the progression and development of hormone responsive breast cancers aromatase enzyme may have significant effects and their inhibitors (AI) can be utilized as chemopreventive agent [66]. AIs can be divided into steroidal (Type I inhibitors) or nonsteroidal (Type II inhibitors). Type I inhibitors binds covalently while type II binds reversibly to the aromatase enzyme. Amino glutethimide (Ist generation); formestane and vorozole (IInd generation); anastrozole, letrozole, and exemestane (IIIrd generation) are some examples of AIs. Testolactone, a first generation AI and is approved for treatment of advanced breast cancer in the United States [67]. Due to the development of resistance to AIs there is need to develop new aromatase inhibitors that could offer less severe side-effects and increased clinical efficacy. Unwinding and rewinding of the DNA helix during various processes such as replication, repair, and chromatin remodeling, entanglement of DNA occurs. The enzyme DNA topoisomerases a nature's tool solve the problem by performing topological transformations in DNA. They form a covalent adduct with DNA resulting into a transient DNA break through which strand passage can occur. The two types of topoisomerases i.e., type I and type II enzymes involves a nucleophilic attack of a DNA phosphodiester

Name	Mode of Action	References
Actinomycin D	Inhibits cell proliferation by forming complex with DNA and blocks production of mRNA (RNA polymerase inhibition); Induces apoptosis.	[55]
Daunorubicin	Complexes to DNA and blocks production of mRNA by RNA polymerase.	[56]
Doxorubicin	Inhibits reverse transcriptase and RNA polymerase by binding to DNA.	[57]
Homoharringtonine	Binds to the 80S ribosome in eukaryotic cells and inhibits protein synthesis by interfering with chain elongation.	[58]
Idarubicin	Antileukemia agent with higher DNA binding capacity and greater cytotoxicity than daunorubicin	[59]

Table 4: Transcription regulators and their mode of action as anticancer agent.

Name	Mode of Action	References
S(+)Camptothecin	Binds irreversibly to the DNA topoisomerase I complex leading to the irreversible cleavage of DNA and the destruction of cellular topoisomerase I by the ubiquitin proteasome pathway. Induces apoptosis in many normal and tumor cell lines	[72]
Curcumin	Potent inhibitor of protein kinase C, EGFR tyrosine kinase and IκB kinase. Induces apoptosis in cancer cells.	[73]
Deguelin	Inhibitor of activated Akt. Does not affect MAPK, ERK1/2 or JNK.	[74]
Etoposide	Binds to the DNA topoisomerase II complex to enhance cleavage and inhibit religation; inhibits synthesis of the oncoprotein Mdm2 and induces apoptosis in tumor lines that over express Mdm2.	[75]
Formestane	Aromatase inhibitor	[76]
Fostriecin	Interferes with the reversible phosphorylation of proteins that are critical for progression through the cell cycle.	[77]
Hispidin	Potent inhibitor of protein kinase Cβ.	[78]
2Imino1imidazolidineacetic Acid (Cyclocreatine)	Creatine analog; decreases the rate of ATP production via creatine kinase and reduces the proliferation of tumor cell lines characterized by high levels of creatine kinase expression.	[79]
Mevinolin	Inhibits mevalonic acid production and induces apoptosis in numerous cancer cell lines, perhaps, in part, by inhibiting the isoprenylation of Rhofamily GTPases.	[80]
Trichostatin A	Histone deacetylase inhibitor that enhances the cytotoxic efficacy of anticancer drugs that target DNA.	[81]

Table 5: Enzyme modulators and their mode of action as anticancer agent.

bond by a tyrosyl residue [68]. Type I enzyme is composed of N-terminal, core, linker and the C-terminal domains [69-71]. Different natural and synthetic molecules are known to target DNA topoisomerases represents the important class of antitumor drugs. The transesterification reaction involved in cleavage and relegation of DNA backbone is exploited by cytotoxic agents. Table 5 shows example of some enzyme modulators used as anticancer agents.

Gene Regulation

Epigenetic alterations in DNA are potentially reversible and hence are involved in the earliest steps of malignant transformation. Interventions using epigenetically active compounds are considered as promising targets for anti-cancer therapy [82,83]. Beside these a number of challenges remain prior to any epigenetic intervention against cancer. Massive deregulation of the epigenetic machinery including DNA methylation, histone modifications and non-coding RNAs contributes to all major cancer hallmarks [84]. In eukaryotic cells acetylation and deacetylation of histones is an important event for transcriptional regulation for which histone acetyltransferase (HATs) and histone deacetylases (HDACs) are responsible, respectively [85]. Acetylation to lysine group of chromatin produces relaxation which intern allows increased transcription of the gene. On the other hand deacetylation increases condensation of chromatin thereby decreasing the rate of transcription of particular part of the chromatin [86,87]. It is found that HDACs are over expressed in tumors and this inhibits expressions of tumor suppressor genes. Thus HDACs inhibition may be considered as a potential strategy for cancer treatment. Vorinostat and romidepsin are the two HDAC inhibitors that have been approved by the FDA (US Food and Drug Administration) as anticancer therapeutic [88,89]. Metal-binding compounds such as clioquinol (a zinc ionophore) are increasingly believed to be an important group of anticancer agents. It has been reported that clioquinol induces apoptosis by the inhibition of NF-κB signaling pathway in human cancer cells [90]. Clioquinol targets cyclin D1 gene at both transcriptional and post-transcriptional regulation level in cancer cells. It is believed that clioquinol promotes mRNA degradation of the cyclin D1 gene regulated by miR-302C. This implies that metal-binding compounds might affect gene expression at different regulatory levels. Out of which the post-transcriptional gene regulation may be a potential target for chemotherapy [91]. P-glycoprotein (P-gp) is a transmembrane permeability glycoprotein and member of ABC super family (ATP binding cassette). It functions as a carrier mediated primary active efflux transporter and widely distributed throughout the body. P-gp is encoded by MDR1/ABCB1 gene and was firstly identified in human cancer cells. It was found to be present in pancreas, elementary canal, kidney, capillary endothelial cells of blood brain barrier and in various other tissues like lungs, heart, adrenals, spleen and skeletal muscle [92]. The optimal P-gp expression is always required for its protective function as its over expression leads to multi drug resistance while toxic reactions occurs because of its low expression level [93]. In various cancers a correlation was found between increased P-gp expression and MDR1 gene mRNA transcription which shows its connection to MDR in cancer. A few novel antitumor drugs which are able to suppress P-gp expression are under development. Lanthanum, a new anticancer compound have been reported to block P-gp expression especially in MDR cancerous cells [94]. Gefitinib another compound is a selective tyrosine kinase inhibitor has capability to inhibited P-gp function and has been used in the treatment of lung cancer [95]. Some of the gene regulator and their targets are shown in Table 6.

Microtubule Inhibitors

Microtubules a component of cytoskeleton is composed of α and β tubulin. This heterodimer is involved in many biological process *viz.,* cell signaling, cytokinesis, intracellular transport, maintenance of cell shape, and polarity [104]. Due to their role in mitosis they become an important target for anticancer drug development. In eukaryotes during cell division mitotic spindle is responsible for the movement of chromosomes to the opposite sides of the cell. These mitotic spindles are nothing but are composed of microtubules having tubulin as its monomer [105-107]. Molecules that interfere with microtubule assembly are known as microtubule inhibiting agents. Currently these agents are used in clinical therapy as they are able to suppress

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