

# RECENT UPDATES ON PROMISING TARGETS IN ANTICANCER ACTION: A REVIEW

## Abstract

Cancer is a multifactorial disease that is characterized by the failure of the normal mechanism of cell regulation which consists of survival, proliferation, and differentiation of the cell. Traditional chemotherapeutic agents directly target the DNA of the cell while modern antiproliferative agents engage in targeting the proteins showing abnormal expression inside the cancer cells also known as molecular-targeted therapy. In comparison to molecular targeted therapy, traditional therapies are ineffective in the complete abolition of the cancer cells while targeted chemotherapy shows its effectiveness in many neoplasms but their effectiveness proves failure due to the resistance of single drug and adverse effects caused by these chemotherapeutic agents to the normal cell and tissues. Cross-resistance also creates problems in the specificity and selectivity of the current chemotherapeutic agents in the application of chemotherapy. Instead, these restrictions have provided a good insight into determining basic molecular mechanisms responsible for the extension of various stages in cancer. In the past few years, a lot of promising drug targets are recognized for their effective action against cancer. The radiance of this continuous work is to find out the identification and validation of newer anticancer agents. This chapter represents some of the important drug targets which may facilitate the process of anti-cancer drug development.

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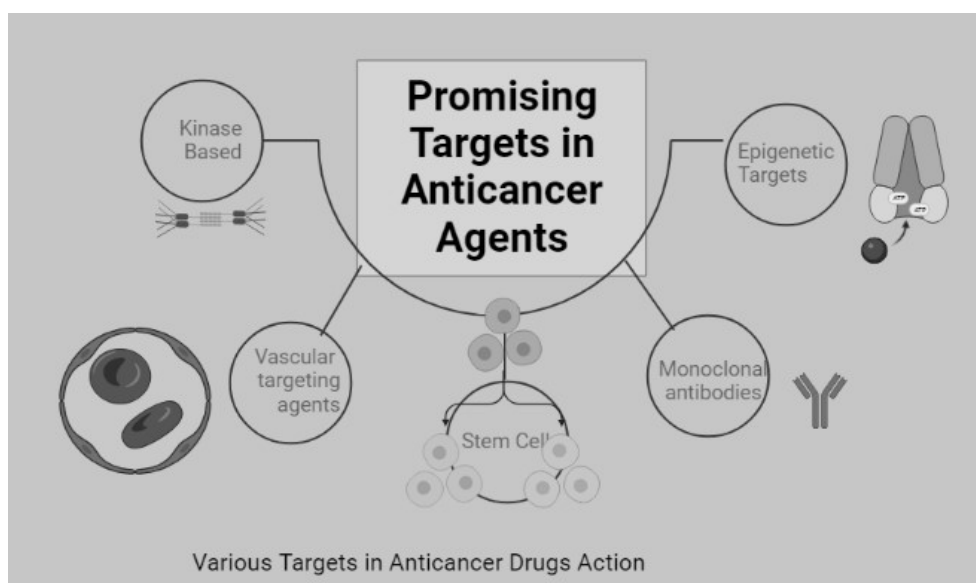
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## I. INTRODUCTION

The uncontrolled growth of cells for the development of cancer is the major cause of death throughout the world. There are more than 200 different kinds of cancers affecting around 60 human body organs [1]. The foremost confront for the development of anticancer drugs is to design the specific target cancer cells having good specificity and selectivity. It is very tough to determine most of the cancer in the early stage and as time passes the later stages cause the tumor metastasis may result in carcinoma-related deaths [2-3]. For the treatment of cancer, there are various strategies engaged including radiation and chemotherapy alone or in combination depending on the severity of the disease. Conventional anticancer drugs act on the DNA of cells directly while modern drug therapy includes targeting the normal and abnormal expression of proteins inside the cancer cells[4]. In comparison to traditional drugs action of targeted drugs is to selectively kill the cancer cells by reducing toxicity toward the normal cells and prohibiting the signaling pathway of specific cells that are required for the malignant phenotype of cancer cells [5-6].

The major limitations of these therapies are drug resistance and toxicity to normal cells and tissues. In the path of complete eradication of cancer and multidrug resistance (MDR) is the major hindrance[7]. The problem with the development of new drugs in cancer eradication is the higher difference between investment and success rate and effectiveness of drugs. There is a requirement for higher efforts by scientists for the permanent abolition of cancer [8]. The main reason for the failure of drug treatment in human carcinomas is the partial perspective regarding the pathogenesis of the disease and the underestimation of the target over the expression. Failure of anticancer chemotherapeutics by determining the role of cancer stem cells is needed to be sincerely investigated[9-10]. In the concern of toxicity, many anticancer agents having molecular targets are proven ineffective. Recent research in the molecular biology field for determining the pathology of cancer at the molecular level has a big challenge to focus on drug targets for the complete eradication of cancer [11-12]. In this article the most promising drug targets are summarised as follows:



**Figure 1:** Promising Targets in Anticancer Agents

**1. Kinase-Based Drug Targets:** Kinase-based drug targets are the class of anticancer agents that bind with the active site of the target enzyme kinase and block the kinase enzyme function. In the human genome, there are around 2000 kinases that are either threonine /serine or tyrosine-based[13]. A lot of anticancer drugs today explode as kinase inhibitors and around 60-80 drugs are under clinical trials. protein kinase regulates most of the cellular activities by reversibly phosphorylating the proteins in post-translational modifications and thus regulates signal transduction [14]. Protein kinases play an important role in cell apoptosis, proliferation, cellular metabolism, and various cellular processes required for the survival of cells. They are ATP-dependent phosphotransferases that transport the phosphoryl group from the ATP to the hydroxyl group of amino acids such as tyrosine, threonine, or serine.  $Mg^{++}$  ions are catalyzed in this reaction to ATP binding [15-16]. The details of some important protein kinases required for various anticancer drug development are listed below

- **Cyclin-Dependent Kinases:** Cyclin-dependent kinases (CDKs) are the group of protein kinase family that first recognized their role in cell cycle regulation. They participate in the regulation of transcription, processing of mRNA, and nerve cell differentiation [17]. CDKs bind with cyclin which is a regulatory protein to form an active cyclin-CDK complex to phosphorylate their substrate on threonine and serine that's why they are known as a serine-threonine kinase[18].

The mammalian genome contains 12 types of CDKs out of which CDK1-CDK5 are actively involved in the cell cycle process. In cell division CDK4 and CDK1 enhances passage through G1 and S phase while CDK1 improves G2 and the mitosis process [19]. Thus this cyclin-dependent kinase is very crucial for blocking the cell cycle in sarcoma cells and it may also under observation the effect of inhibition of CDKs in cell division in normal cells [20]. Many subunits of CDKs are found severely mutated in various types of tumors eg. CDK4 is highly overexpressed in blood cancer, lymphosarcoma, colon cancer, prostate, and breast cancer [21]. Thus cyclin-dependent kinases may be a good target for new drug development for anticancer agents. Many molecules that block the cell cycle-dependent kinases are synthesized and under clinical examination for antiproliferative agents[22].

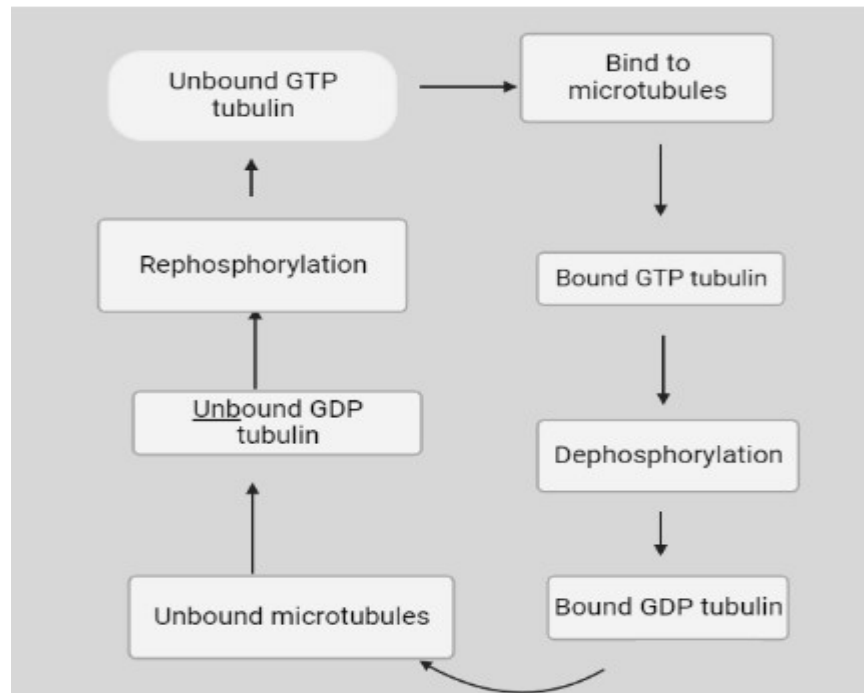
- **Tyrosine Kinase:** Tyrosine Kinase (TKs) show a distinctive role in controlling cell growth, proliferation, survival, and metabolism [23]. There are around 30 families of RTKs including vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and nerve growth factor receptor (NGFR) that share a similar structure and an active site for improving the dimerization of receptor results in enhancing the RTKs activity. In human genome around 90 tyrosine kinase genes are identified which are subdivided into non-receptor tyrosine kinase (NRTK) and receptor tyrosine kinase (RTK) in which RTKs having extracellular ligand binding protein (LBD) [24-25]. The improvement of TKs results in the activation of various signaling pathways as the TKs are having an ATP binding site which is divided into three sub-divisions i.e. sugar region, the phosphate binding region, and the adenine binding site. The phosphorylation of TKs leads to the activation of P42/44 Mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK). This activated MAPK provokes the formation of various transcription factors and controls cell proliferation [26]. Some other pathways are activated by tyrosine kinase,

for example, focal adhesion kinase(FAK), Phosphoinositide-3-kinase(PI3K), Rapidly accelerated fibrosarcoma kinase (FAS), receptor tyrosine kinase (RAS)and Focal Adhesion kinase (FAS) depend for the reorganization and cell proliferation and migration which may lead to cancer metastasis [27-28]. Thus the role of tyrosine kinase is highly important and by targeting TKs the new drug development for carcinoma treatment shows good potential.

- 2. Microtubules based drug target :** In cancer, the cells divide and grow very rapidly in comparison to normal cells [29]. Microtubule is the key component of cell division and growth thus targeting the microtubules for developing anticancer drugs is very crucial [30]. Microtubules are made by the association of alpha and beta tubulins which is of a universal cytoskeletal structure that shows an important role in cell division and cell development [31-32]. both  $\alpha$  and  $\beta$  subunits have guanosine tri Phosphate (GTP) molecules in which the GTP molecule of the  $\alpha$  subunit is bound irreversibly and can-not hydrolyzable to GDP while the GTP of the  $\beta$  subunit attaches reversibly and is easily hydrolyzable to GDP [33]. These alpha and beta-tubulin act as monomer unit and the  $\beta$  polypeptide of one monomer is attached with the  $\alpha$  subunit of another monomer in head to tail way to form protofilaments, These 13 protofilaments binds together to form a cylindrical wall of microtubules [34].

After that polymerization of microtubules is performed with the help of GTP to give conformational changes gives depolymerization of microtubules with the formation of GDP-tubulin unit. This depolymerization of microtubules is helpful for the growth and disassembly of tubulin dimmers [35]. Any alteration in dynamic instability of microtubules blocks the cell division which may cause cell apoptosis [36]. Chemical compounds may attach to the tubulins and interrupt microtubule dynamics and control the destabilized state. These are four binding sites for molecules to bind with microtubules like colchicine binding site, taxane binding site, vinca alkaloid, and laulimalide binding site [37].

In the cell division process microtubules participate in proper movement and attachment of chromosomes. Microtubule targeting agents bind to tubulin in polymeric form and block the depolymerization process [38]. These polymerization inhibitors thus inhibit polymerization and induce many conformational changes in tubulin to inhibit microtubule growth [39]. This tubulin target gains attraction towards further anticancer development. The blocking action of anticancer agents causes disruption of microtubule dynamics that inhibits cell division at mitosis which gives result in the death of the cell thus inflection in the microtubule dynamics gives an important target for the progress of antiproliferative agents.



**Figure 2:** Tubule-microtubule dynamic instability

3. **Vascular Disrupting Agents:** For the treatment of carcinoma tumors vascular targeting is an important strategy [40]. As the division of cells in cancer is very rapid and it needs a constant supply of ATPs, essential nutrients, and oxygen so for the progression of the tumor the generation of blood cells is also very necessary and it is the main step for metastasis [41]. The newer anticancer agents are focused on interference in the blood flow in tumor cells to control the generation of new arteries. It is underdetermined that tumor vessels are divided differently from the normal cell division [42]. They look leaky, unorganized, and unstructured in comparison to normal cells. This difference is helpful for the anticancer agents to target them selectively. these vascular disrupting agents (VDA) act at the endothelial system to enhance vascular permeability and death of blood vessels[43]. The adverse effects are mild as compared to other cytotoxic agents. Various drugs with vascular disruption action are under clinical trials to provide newer antiproliferative agents in the future with lessened side effects [44].
4. **Stem Cells as Target:** Cancer stem cells (CSC) are found in the tumor having tumorigenic properties means they can create a cancerous tumor [45]. The main feature of these stem cells is their self-renewal and their ability to differentiate into various types of cells [46]. They can reproduce by themselves and maintain cancer in the body for a long thus can enhance the growth and metastasis of cancer. They are mostly found in the brain, breast, colon, ovarian, pancreatic, and prostate tumors [47].CSCs also initiate tumors and maintain the number of dividing cells in the tumorous area [48]. The most common CSCs are leukemia stem cells. It is also determined in a study that the capacity of stem cells to initiate a new tumor remains enhanced in breast carcinoma cells with differential potential[49]. Targeting these stem cells is very valuable for the development of new anticancer cells. It can control the generation, progression, and metastasis of cancer [50]. These CSs have unique properties that make them resistant to traditional anticancer therapies. These stem cells improve DNA damage repair and over-progression of anti-

apoptotic proteins and transport multidrug resistance [51]. There is a lot of research under investigation for the inhibition of these cancer cells [52-54]. The main target is to block cell signaling pathways for survival and generation of new stem cells and drug resistance too.

- 5. Targeting Monoclonal Antibodies:** Immunoglobulins are antibodies that help in the determination and control of foreign particles or antigens and They are synthesized by the immune system to control the antigens or foreign material [55]. They are heterodimers with two light and two heavy chains connected by multiple disulfide bonds. Targeting monoclonal antibodies (mAb) helps identify foreign harmful antigens and destruction of these abnormal cells or particles. The specificity of these mAbs based on the sequence of amino acids present in different areas [56-57].

These antibodies target cancerous cells by inhibiting receptor binding sites or enhancing apoptosis and improving the speed of anticancer drugs to target receptors. They can also act by improving T-cells regulation and antibody-dependent cellular cytotoxicity(ADCC) [58-60]. Rituximab is the first mAb drug approved for different kinds of cancer. now many other Humanized monoclonal antibodies (CD33) have also been approved for anticancer activity [61]. This target may give more opportunities in the development of new improved anticancer drugs in the future.

## II. CONCLUSION

Cancer is an abnormal disease and for the treatment of cancer is the chemotherapy. In chemotherapy drugs speedily targets on mitotic cells but unfortunately cancer as well as non cancerous cells are also targeted. As a result many patients face abnormal toxic effects such as alopecia or gastrointestinal infections. The treatment based on chemotherapy, surgery or radiation is highly costly as well as narrow therapeutic index also.

On the other hand targeted therapy includes interference with specific protein required for growth and progression of tumor. Multidrug resistance is also a big problem for treatment of carcinoma thus a better understanding of controlling of resistance is also required for good anticancer agent. By targeting various signalling pathways may escape secondary resistance and by improving drug potency and efficacy. By selecting multitargeted therapy against designed cancer cell line is found effective and improves the effects of multidrug resistance(MDR). In targeting cancer stem cells the destroying CSCs to reduce normal stem cell toxicity. Thus by selecting targeting therapy in anticancer agent development may provide a promising strategy for total eradication of various kinds of cancers in future.

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