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# Some Important Targets For Development Of Anticancer Drugs

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***ABSTRACT:***

***Among the non-communicable diseases (NCDs) cancer is a major global health burden with low survival rate. According to WHO's Globocan-2018 report, the developing countries of Africa and Asia are contributing more to 7 million new cases and 6 million figures of death due to non-availability of targeted and affordable treatment. The selective targeting of biological targets in cancerous cells or tissue is a crucial criterion for successful treatment of cancer. The continuous findings in the area anticancer therapeutic development have been provided variety of potential targets such as receptors, proteins, enzymes, nucleic acids etc. which are present in cancer cells. Here, we provided detail on different biological targets and their biological role in cancer. Additionally, some clinically used as well as novel molecular agent acting on these anticancer targets have been included along with updation. This paper will be helpful in the target specific design and development of novel anticancer therapeutics.***

***Keywords: Anticancer drugs, new targets, cyclooxygenase,antineoplastic enzyme***

## 1. INTRODUCTION:

As per WHO's report, cancer is one of the leading worldwide causes of high mortality rate among humans and it is found to be responsible for an approximately 9.6 million deaths in 2018. In low and middle income countries (including India), ~70% of deaths occur from various types of cancers [1]. The process of anticancer drug development starts after finding the suitable potential biological target. These biological targets include body proteins and receptors. Each body protein plays a major role in maintaining the cell homeostasis by regulating different physiological and biological processes. These processes include cell apoptosis, cell growth, cell migration, cell proliferation, DNA replication, transcription etc [2, 3].

Whenever there is any dysregulation in these proteins' functions, whether they are suppressed or overexpressed, it leads to change in biological processes contributing to body illness (diseases). Cancer is a non-communicable disease that also results from functional dysregulation of various biological proteins. The biological proteins that are overexpressed in various malignancies include COX-II, Mdm2, MELK, PRMT5, TOPK, etc. whereas proteins such as apoptotic proteins are suppressed in cancer disorders. Mutations in receptors like Trk, PDGFR, VEGFRs, EGFRs etc. have also been observed in various cancers that result in modification of their biological functions. Hence, these proteins and receptors have been used as biomarkers as well as potential therapeutic targets for diagnosis and treatment of cancer [3-11].

The scientific studies from several years provided a plethora of drugs that have been designed to act on these proteins and receptors to change their structure and functions. Thus, structural and functional changes in the proteins cause regain of their natural or routine activity in malignant cells to suppress tumor growth and increase patient's life span. Drugs like bortezomib, vorinostat, celecoxib, imatinib, vemurafenib, etc. have been clinically approved by FDA for treatment of different types of cancers. These drugs target different biological proteins and receptors to treat cancers. Such drugs exhibit their anti neoplastic activity by enhancing cell apoptosis and inhibiting processes like cell growth and proliferation, angiogenesis, cell migration, cell maturation, and by acting on various signaling pathways including MEK, cyclin D1, MAPK, p53 etc [12-20].

This work gives an insight on different biological proteins and receptors which are root cause of cancer or target of anticancer drugs and how they alter bodily processes to induce cancer.

## 2. ANTICANCER DRUG TARGETS

There are several biological target have been identified to develop the different types of anticancer therapeutics. Among these, some important targets described in following sections.

### *2.1. Cyclooxygenase-II (COX-II)*

Cyclooxygenase-II, also known as COX-II, is an inducible enzyme which is over expressed in various types of cancers. COX-II is a cytoplasmic enzyme which catalyzes the synthesis of prostanoids such as prostaglandin E2 (PGE2) from arachidonic acid. PGE2 is a mediator of inflammation and has a major role in biological processes such as pain, angiogenesis and cancer initiation [21, 22].

In cancer, due to uncontrolled expression of COX-II in cancerous cells, PGE2 biogenesis is increased leading to angiogenesis, metastasis and apoptosis resistance. In several types of cancer such as breast, prostate, lung, colon, bladder and cervical cancer, there is an over expression of COX-II enzyme which causes proliferation of cancer cells. Various studies have shown that there is an over expression of COX-II enzyme in approximately 42% of breast cancers [21, 22].

Drugs such NSAIDS and COXIBS are employed to inhibit the over expression of COX-II. While NSAIDS has less selectivity for COX-II, COXIBS are highly selective towards this enzyme. These drugs mainly show their effect by inhibiting COX-II enzyme and decreasing the synthesis of PGE2. PGE2 depletion helps in reducing the development and growth of malignancies by inhibiting cell proliferation and angiogenesis. FDA has approved celecoxib (COX-II inhibitor) in treatment of familial adenomatous polyposis (FAP) as an adjunct [23, 24].

Drugs used as COX-II inhibitor in treatment of cancer are NSAIDS such as aspirin and COXIBS like celecoxib, rofecoxib. Clinical application of these COX-II inhibitors in treatment of various cancers (such as breast, prostate, lung, pancreas, osteosarcoma, and head and neck squamous cell carcinoma) reduces the mortality rate and further development of these cancers [21, 23].

### *2.2. DNA Topoisomerases*

DNA topoisomerases are nuclear enzymes which are involved in management of topology of DNA. Inhibition of topoisomerase causes cell apoptosis by blocking ligation part of cell

cycle. These enzymes are required in various biological processes such as transcription, replication, recombination etc. In cancer, there is an over expression of topoisomerases enzymes which leads to rapid cell division. In addition to their anti cancer property, topoisomerases are also a target for anti bacterial drugs [25-27].

In humans, six types of topoisomerases are found which is categorized into Type IA, Type IB and Type IIA. Type IA is further classified into TOP3α and TOP3β which carry out cleavage of single DNA strand to cause negative supercoiling. TOP2α and TOP2β are subtypes of Type IIA that cause double strand breakage on single DNA molecule to permit the passing of another DNA strand. Type IB consists of TOP1mt and nuclear TOP1. TOP1mt is involved in maintaining the integrity and metabolism of mitochondria while TOP1 by cutting one DNA strand commences the relaxation of DNA [28].

Naturally derived TOP2 inhibitors such as riccardin D and wedelolactone are employed in the treatment of prostate cancer and breast cancer respectively [26]. Drugs like valrubicin, mitoxantrone, etoposide, doxorubicin act as TOP2 inhibitors, while phenanthriplatin is a TOP2 poison [27-29].

Camptothecin derivatives such as irinotecan, belotecan and topotecan (TOP1 inhibitors) have been clinically approved by the FDA for treatment of colorectal and ovarian cancer while derivatives like exatecan, lurtotecan, gimatecan and diflomotecan are under clinical trials. These drugs act by accelerating DNA breaks accumulation and inducing cell apoptosis. Non camptothecins like indolocarbazole (BMS-250749 and edotecarin) and indenoisoquinolines (indotecan and indimitecan) are currently in clinical trials. Topovale (phenanthroline ARC-111) showed antineoplastic activity in Wilm's tumor and colon cancer. Derivatives of Artemisinin cause DNA damage in vitro and in silico by targeting DNA TOP1. [26, 27, 28, 30].

*2.3. B-RAF Kinase*

B-RAF mutation is found in 5-10% of malignant tumors and nearly in 50% of melanomas. B-RAF (a serine and threonine protein kinase) works by activating MAP/ERK pathway. A fundamental component of RAS-RAF pathway, B-RAF is involved in the cell proliferation regulation. In neoplastic diseases, the mutation of B-RAF gene leads to excessive cell proliferation due to dysregulation of MAPK/ERK pathway resulting in development of cancer [31-33].

BRAF oncogene mutation is associated with 8-10% colorectal cancer, 30% ovarian cancer and 30-70% papillary thyroid carcinoma. V600E (valine to glutamate transition) is the most common BRAF mutation [33, 34]. Anti neoplastic activity of BRAF inhibitors has been observed in 60% patients and 5% patients with BRAF induced melanomas and colorectal cancer respectively. Dabrafenib and vemurafenib has been approved by the USFDA as BRAF inhibitors in the treatment of melanomas caused due to BRAF mutation [35, 36].

Enhanced anti tumor activity can be achieved by the addition of vemurafenib to bevacizumab, capecitabine, erlotinib, irinotecan and cetuximab. RAF709 has a high selectivity and potency for BRAF and KRAS mutations in xenograft models [32, 37].

*2.4. Mouse Double Minute 2 (Mdm2)*

Mouse double minute 2 over expression is found in several forms of malignancies. Also known as murine double minute 2, it is an oncoprotein which is involved in the negative regulation of p53. Mdm2 inhibit p53 transcription activity. p53 is an important factor in

controlling cell proliferation as it leads to cell apoptosis via arrest of cell cycle and is involved in DNA damage repair. Due to over expression of Mdm2, activity of p53 is inhibited leading to excessive cell proliferation and ultimately cancer [38, 39].

Nearly 30% cancers are related to Mdm2 over expression. Over expression of Mdm2 is found in various types of cancers such as breast cancer, endometrial cancer, ovarian cancer, lung cancer, liver cancer, liposarcoma, glioblastoma, pediatric rhabdomyosarcoma, acute myeloid leukemia and colon cancer [38-45].

Gossypol is a Mdm2 inhibitor as well as VEGF inhibitor. Nutlin-3 acts as p53-Mdm2 interaction inhibitor and induces cell cancer apoptosis. Pyrido[b]indole CPI-7c is a chalcone based molecule which not only inhibit p53-Mdm2 interaction but also promote degradation of Mdm2 [38, 40, 42, 46].

DIMP53-1 is p53 activator and p53-Mdm2 interaction inhibitor which increases p53 tumor suppressing activity. ALRN-6924 can be suggested in treatment of acute myeloid leukemia. It induces cell apoptosis leading to inhibition of cell proliferation in xenograft models. Idasanutlin and venetoclax combination treatment results in synergistic antineolastic activity in in-vitro studies with established acute myeloid leukemia cell line [47-49].

MK-8242 and NVP-CGM097 have been entered in phase one trials as Mdm2 antagonist. JapA, lead compound of a newly discovered class of Mdm2 inhibitor decreases cell proliferation and inhibits cell growth in in-vivo and in-vitro studies by inhibition and degradation of Mdm2. Inulanolide A showed anti-cancer activity by inhibiting both Mdm2 and NFAT1 in breast carcinoma cells in in-vivo and in-vitro studies [50-52].

### *2.5. Wnt/β-Catenin*

In various biological processes such as cell proliferation, cell differentiation and cell apoptosis, Wnt/β-catenin signaling pathway plays an essential role. Wnt pathway can be divided into two types: β-catenin dependent signaling (also known as canonical) and β-catenin independent signaling (or non-canonical) [53, 54].

Modifications in β-catenin dependent signaling (or canonical) lead to activation of oncogenes such as Jun, Cyclin D1 and c-Myc, inactivation of tumor suppressor genes and are also known to cause variations in many proteins involved in this pathway. β-catenin nuclear localization and high cytoplasmic activity triggers tumorigenic traits and promotes tumor proliferation by suppression of T-cell responses [53, 55].

A multifunctional protein, β-catenin plays an important role in physiological homeostasis. Abnormal activation of Wnt/β-catenin leads to increased concentration of β-catenin in nucleus and transcription of various oncogenes like Cyclin D1 and c-Myc is promoted. Over expression of this β-catenin leads to various carcinomas such as ovarian cancer, colon cancer, lung cancer, melanoma, leukemia, pancreatic cancer and hepatocellular carcinoma [55].

Cysteine rich glycoproteins WNTs are secreted into extracellular matrix by the cells. Wnt binds to Frizzled receptor and interrupts the β-catenin destruction leading to increased accumulation of β-catenin in cytoplasm. Alteration of Wnt/β-catenin pathway is also found in

bone cancer and gastric cancer. Over activation of β-catenin increases cell metastasis by over expressing the oncogene [56-59].

Compounds targeting Wnt pathway such as ETC-159, LGK974, PRI-724, Foxy-5, OTSA101, OMP-54F28, OMP131R10 and OMP18R5 are currently under clinical trails for their antineoplastic activity [54]. Atractylochromene is a natural product which inhibits the Wnt/β-catenin signaling pathway in colon carcinoma cells by modulating nuclear translocation of galectin-3 and β-catenin. It also inhibits activity of TOPFlash and proliferation of SW-480 cells [59].

Reishi (*Ganoderma lucidum*) shows its anitineoplastic effect by obstructing signaling of Wnt/β-catenin through inhibition of phosphorylation of LRP6 (a Wnt co-receptor). It is a Chinese medicine used in breast carcinoma to reduce cell migration and proliferation [60].Fibulin-3 and fibulin-5, both extracellular proteins, block Wnt/β-catenin signaling in lung cancer and suppress tumor invasion [61, 62]. Prodigiosin and gigantol are inhibitors of signal pathway in breast cancer while SMAR1 prevents colorectal carcinoma progression [63-65].

*2.6. Glucose Related Protein 78 (GRP78)*

Glucose related protein 78 is a member of family of heat shock protein 70 which is localised to endoplasmic reticulum. It is a heavy chain binding protein which is involved in several cellular processes such as ER calcium binding, misfolded proteins proteosomal degradation, proper assembly and folding of proteins and transmembrenal ER stress sensor activation. GRP78 deregulation has been related to progression and occurrence of tumor. An important chaperone in ER, GRP78 is expressed on stressed carcinoma cells surface and has a major role in regulating oncogenic signaling pathway. GRP78 as an autoantigen causes stimulation of autoimmune responses and serves as an important biomarker in hepatocellular carcinoma [66, 67].

GRP78 plays an important role in carcinoma cell proliferation, angiogenesis, metastasis and drug resistance. GRP78 is involved in survival of cells under damaging conditions. In case of endoplasmic reticulum stress, GRP78 binds with unfolded proteins which activate UPR sensors. GRP78 expression is increased due to ATFs acting on ERSE. By recognizing extracellular ligands such as T-cadherin, kringle 5, $\alpha_2$-microglobulin, MHC-I and PAR-4, it transduces corresponding signals. Binding of ligands to N-terminal site of GRP78 stimulate antiapoptotic response as well as cell proliferation while binding of ligands to C-terminal site prevents cell proliferation and induces cell apoptosis [68].

GRP78 overexpression has been found in various carcinomas such as human osteosarcoma, lung cancer, brain cancer, prostate cancer, breast cancer, colorectal cancer, hepatocellular carcinoma, gastric cancer and ureter tumors along with ovarian cancer, mutilple myeloma, esophageal squamous cell cancer, pancreatic cancer and endometrial cancers [69-74].

Versipelostatin (VST) alone or in combination with cisplatin inhibits GC cell tumor growth in gastric carcinoma. Other anti GRP78 agents include GMBP1, GRP78BP and tk/GCV [68]. Bioconjugates like BMTP78 and Mab159 target GRP78 and show antimetastatic effects in lung cancer. Ruthenium containing IT-139 suppresses GRP78 induction in various carcinomas [75, 76]. BMTP78 therapy suppresses primary tumor growth as it kills breast carcinoma cells which express surface GRP78 [77].

*2.7. DNA Repair Helicases*

DNA helicases are omnipresent enzymes which are engaged in the maintenance of genome integrity and nucleic acid metabolism. They cause disruption of hydrogen bonds between complementary DNA double helix strands and unwind the nucleic acids. DNA helicases play an essential role in various cellular processes such as DNA repair, DNA transcription, DNA replication and maintain cellular homeostasis. Mutations in DNA helicase genes are observed in several types of tumors and genetic disorders [78-80].

The RecQ helicase family consists of five different DNA helicases classified as: RECQL1 (RECQ1 or RECQL), Rothmund Thomson syndrome (RECQL4 or RTS), RECQL5, Werner syndrome (WRN) and Bloom syndrome (also known as BLM). These helicases are highly expressed in cell proliferation, DNA repair and DNA replication [81].

Mutations in different DNA helicases lead to various types of cancer. Mutations in WRN helicase cause osteosarcomas, thyroid neoplasms, meningiomas, melanomas, sarcomas, lymphoid neoplasms and haematological neoplasms. BLM mutations are found in lymphomas, leukaemias, paediatric tumors and epithelial tumors in adults. Lymphomas and osteogenic sarcomas are associated with RECQL4 mutation whereas RECQL1 mutation is found in pancreatic cancer. XPB and XPD mutation is linked with skin cancer and FANCJ mutation is associated with breast cancer and acute myeloid leukaemia [78].

NSC 19630 is an inhibitor of WRN helicase which increases the apoptosis process and decreases cell proliferation and growth. WRN-siRNA, RECQL1-siRNA, RTS-siRNA and BLM-siRNA are promising therapeutical inventions that inhibit DNA repair in cancerous cells [80, 81].

WRN NSC617145, BLM ML216, DNA2 NSC 105808, Mcm2-7 ciprofloxacin, Mcm4/6/7 heliquinomycin, DDX3 rhodamine based derivative 4 (RBD4) and DDX3 compound 1, compound 6 and compound 8, all are newly discovered small molecule human DNA helicases inhibitors which have shown their activity in in-vitro studies while DNA2 $C5^{b}$ is a FDA approved DNA2 helicase inhibitor. These all helicase inhibitors decrease cancerous cell proliferation and cause DNA damage [79].

*2.8. Apoptotic Proteins*

Apoptosis is a suicidal and programmed cellular process in which unhealthy and unnecessary cells are eliminated from the body. Caspases, belonging to cysteine proteases family, is the initiator of the apoptotic process. Different caspases such as caspase-2, caspase-8, caspase-9 and caspase-10 are activated whenever there is an apoptotic stimulus [82].

This process plays a crucial role in keeping the balance between cell growth and cell death. During this process, several morphological changes like chromatin condensation, cell volume reduction (or pyknosis), nuclear fragmentation, breakdown of protein and DNA, and caspase activation take place. Modifications in membrane surface helps in recognition of apoptotic cells and its engulfation via phagocytic cells [83].

Caspases can be classified into two classes: (i) caspases involved in processing of cytokines during inflammation (e.g. caspase-1, caspase-4, caspase-5, caspase-13 and caspase-14) and

(ii) caspases involved in apoptosis (e.g. caspase-2, caspase-3, caspase-6. caspase-7, caspase-8, caspase-9 and caspase-10) [84].

Disruption of this process leads to ungoverned cell proliferation, cell development, tumor progression and cancer therapy resistance. Inhibitors of apoptosis proteins (IAP) are the negative regulators of caspases activity. This family constitutes of IAP-like protein 2 (ILP2-BIRC8), livin/ML-IAP (BIRC7), apollon (BRUCE, BIRC6), survivin (BIRC5), X-linked IAP (XIAP, BIRC4), cIAP2 (BIRC3), cIAP1 (BIRC2) and NAIP (BIRC1) [85].

Antiapoptotic protiens (such as Bcl-W, Bcl-xL, Bcl-2, Bf1-1/A1 and Mc1-1) inhibit cell apoptosis and promote cell survival. Bcl-xL or Bcl-2 overexpression is found in more than 50% of cancers [86].

Reduced caspase-3 activity is found in cervical tumors, ovarian cancer and breast cancer while caspase-9 downregulation is associated with colorectal cancer. Both caspase-8 and caspase-10 downregulation contribute to choriocarcinoma. Abnormal IAP expression occurs in pancreatic cancer while livin was overexpressed in lymphoma and melanoma. Apollon upregulation was found in gliomas and contributed to camptothecin and cisplatin resistance whereas survivin overexpression was associated with haematological malignancies [84].

Agents such as SH-130, JP-1201 and SH-122 target IAPs and are used in prostate cancer cell line whereas AEG35156 targets XIAP in advanced solid cancer and is in phase II. YM155 acts on survivin in advanced solid cancer and is in phase I and II. LY2181308 also targets survivin and is in preclinical trials, and used in colorectal cancer cell line [87]. Several endogenous IAP inhibitors like TWEAK, ARTS, Omi/HtrA2 and SMAC/DIABLO regulate the activity of IAPs [88].

*2.9. Breakpoint Cluster/Abelson (BCR/ABL)*

ABL1 and ABL2 belong to the family of Abelson tyrosine kinases which are involved in the regulation of cell survival, growth, migration, adhesion and invasion. Their enzymatic activity is controlled by tyrosine phosphorylation [89].BCR/ABL oncogene is a product of chromosomal translocation in which fusion of breakpoint cluster gene (from chromosome 22) with Abelson tyrosine kinase gene (from chromosome 9) takes place [90, 91].

ABL1 is involved in the repair of damaged DNA through DNA binding domain and localized nuclear signals while ABL2 enhances cytoskeletal remodeling through its microtubules and actin binding capability [92].

Cells with BCR/ABL mutation have high rate of cell proliferation, increased apoptosis resistance and altered adhesion properties. This mutation is associated with B-cell acute lymphoblastic leukemia (B-ALL) and chronic myeloid leukemia (CML) [93, 94].

HS-438, PBA2 and CD-200 inhibit the BCR/ABL signals in CML which have T315I mutation and are imatinib resistant. Another inhibitor of BCL/ABL signals, triptolide is used in CML with STI571 resistance and T315I mutation [95-98].

Ponatinib, dasatinib and imatinib are FDA approved BCR/ABL inhibitors for treatment of CML and Ph+ ALL (Philadelphia positive acute lymphocytic leukemia) whereas bosutinib and nilotinib has been approved FDA for treatment of CML only. Axitinib is another FDA approved drug which is used in the treatment of renal cell carcinoma [89].

*2.10. L-Asparaginase*

Belonging to the essential amino acids, extracellular L-asparagine is needed in ample quantity by the cancerous cells for their speedy growth and survival whereas normal cells are independent of this enzyme because they carry their own synthesis with the aid of enzyme known as L-asparagine synthetase. By reducing the quantity of asparagine in the circulation, tumor growth can be suppressed. L-asparaginase converts L-asparagine to its metabolites ammonia and L-aspartic acid [99, 100].

Approved by FDA, L-asparaginase is an antineoplastic enzyme which reduces the concentration of L-asparagine by converting it into its metabolites. L-asparaginase treament can be used to treat several cancers such as ovarian cancer, brain tumors, acute lymphoblastic leukemia and different blood cancers. By optimization of the dosing schedule of L-asparaginase, its antineoplastic activity was found to be improved in mice with breast tumors [101-106].

## 3. CONCLUSION

The study of various cancer related proteins concluded that these proteins plays significant role in the development and progression of cancer. They provide the potential targets for diagnosis of the cancer disorders and development of new molecular probes as potential anticancer agents.

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