Present and Future Prospect of Small Molecule & Related Targeted Therapy Against Human Cancer

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Abstract

Cancer is uncontrolled cell growth guided by deregulation of cell growth network. Subsequently, alteration in genes occurs which influences expression (down-regulation of tumor suppressor genes and/or up-regulation of proto-oncogene) of these prominent cell growth proteins. Protein targeting has emerged as a hope against cancer. These therapies work by inhibiting or up regulating the target proteins through agents specific for treatment of deregulated proteins. Targeted cancer therapies are more favorable for cancers like lung, colorectal, breast, lymphoma and leukemia as they focus on particular molecular changes unique to a specific cancer. As researchers scrutinize and comprehend the cell changes that initiate cancer, they are better able to design promising therapies targeting these changes or nullify their effect. In present study we have assessed prospects of significant proteins which are known to be targeted by number of small molecules and related drugs for effective treatment of various forms of cancer. Moreover, we also addressed the efficacies of these drugs toward the cancer treatment and future challenges in their development as this information is lacking in previously published work.

Keywords- Cancer, Therapy, Small-molecules, Protein-targeting

Introduction

Cancer has become one of the leading health problems worldwide. 8.8 million deaths occur every year due to it (World Cancer Report: WHO, 2014). Since long time large amount of money have been spent around the world for finding cure with limited or no success. Conventional chemotherapy and radiotherapy offers partial cancer treatment with adverse side effects (Hoelder *et al.,* 2012).

Cancer is multi-genetic disorder that begins with mutations in genes encoding significant signaling pathway control proteins. These proteins control and regulate normal cellular processes like growth, apoptosis, DNA repair, division, checkpoint, etc. and thereby prevent the cells from becoming cancerous. These mutation leads to production of protein with impaired activity, thus possibly modifying cancer risk. Targeted therapies have emerged as a promising approach against cancer that primarily work by targeting deregulated protein which supports survival of cancer cells (Sever *et al.,* 2015). Small molecule targeted therapies are often advantageous as these molecules can interact with the target inside the cell as well as surface receptor, modulating the function of target proteins (Table 1) (Zhang *et al.,* 2009). Moreover, such targeted therapies are beneficial as they have potential of curing several forms of cancer where significant proteins play common role.

Kinases

Kinase receptors mediate significant events in normal cell growth and survival. They are also known to be closely linked with cancer cell survival and proliferation as well. Majority of cancer growth receptor are kinases in nature (Zhang *et al.*, 2009). Kinases are reported to be deregulated in several cancers, making them an important target for cancer therapy. Several kinase inhibitors are available for treatment of cancer and many are under different levels of clinical trials for final approval (Takeuchi *et al.*, 2011). Kinases activities are known to be affected by several genetic changes like mutations. Cancer is known to harbor mutations in their domain region, hence affecting their functionality.

Polo-Like Kinase

Polo-like kinases (PLK) are a serine/threonine kinases. PLK-1, being a regulator of mitotic checkpoint, is the most prominent PLK amongst all others (Lee *et al.*, 2014).Apart from that it plays role in chromosome segregation, cytokinesis and centromere maturation (Donaldson *et al.*, 2001). Higher PLK1 expression results in defective cell cycle checkpoints function and genetic instability, which may results in cancer (Wolf *et al.*, 1997, Knecht *et al.*, 1999, Kanaji *et al.*, 2006). Due to its crucial role in carcinogenesis, PLK1 inhibitors could be used as promising target for designing therapy against cancers.

Amongst all PLK inhibitors, Rigosertib is the most promising drug candidate. It is a potent PLK1 inhibitor which is currently under phase-3 clinical trials for development. This drug primarily shows anti-tumor properties by blocking cell cycle in cancerous cell at G2/M phase (Costa-Cabral *et al.*, 2016). In initial stages of clinical trials, it is found to be useful for treatment of Myelodysplastic syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML), Ovarian Cancers, Acute Myeloid Leukemia (AML) and Acute Lymphocytic Leukemia (ALL).

Apart from Rigosertib, other drugs candidates including Volasertib (Goga *et al.*, 2016), TKM-080301 and CFI-400945, are under different stages of clinical trials. Volasertib is a highly selective PLK-1 inhibitor (Rudolph *et al.*, 2009) leading to cell cycle arrest as well as apoptosis. It shows anti-tumor activity against xenograft model of neuroblastoma (Gorlick *et al.*, 2014) and ALL (Rudolph *et al.*, 2015), as monotherapy. Volasertib also demonstrate anti-tumor activity when used in combination with Cytarabine or Quizartinib, Fulvestrant and Vincristine against ALL (Rudolph *et al.*, 2015), breast cancer (Bhola *et al.*, 2015) and rhabdomyosarcoma (Hugle *et al.*, 2015) respectively.

Aurora Kinase

Aurora kinase family boasts of its importance as a prominent cell cycle regulatory serine/threonine kinase that plays role in cytokinesis and mitosis. Precisely, Aurora kinase A and B act as best candidates for targeted cancer therapy. Aurora kinase A promotes CDK1 activation and mitotic entry, especially after DNA damage checkpoint-dependent G2 phase arrest (Mac• rek *et al.*, 2008, Seki *et al.*, 2008) by phosphorylating and activating PLK1. Moreover, it also promotes centromere maturation, as spindle assembly and spindle orientation.

Aurora kinase B is present in chromosome, where it controls its condensation and orientation, and at mitotic spindle. Overexpression of Aurora A and B causes DNA damage inactivation of checkpoint and spindle assembly during G2 phase (Marumoto *et al.*, 2002) and mitosis (Anand *et al.*, 2016) aneuploidy due to inept parting of chromosome. Overexpression of Aurora A and B has been reported in breast, prostate, ovarian, cervical, colon, thyroid, lung, liver and several other cancers.

Aurora A and Aurora B are being used extensively to develop inhibitory drugs for cancer treatment. These inhibitors include Alisertib, ENMD-2076, Danusertib and AMG-900. Alisertib have high selectivity for Aurora A (Manfredi *et al.*, 2011), inducing mitotic arrest and polyploidy, that results in senescence or apoptosis (Görgün *et al.*, 2010, Qi *et al.*, 2011).

An ongoing study reports that Alisertib when used in combination with paclitaxel shows a response rate of 29% in patients suffering from recurrent ovarian cancer (Melichar *et al.*, 2016). Moreover, in case of solid tumors, response

rate is 21% and 18% for small cell lung carcinoma and breast cancer, respectively (Melichar *et al.,* 2015). Combination of Alisertib and Docetaxel shows approximately 50% response rate against castration-resistant prostate cancer (Hwang *et al.,* 2012). Its usage with proteasome inhibitor (e.g. Bortezomib) inhibits multiple myeloma upto 30% (Barr *et al.,* 2015). Presently, over 30 clinical investigations are going on for the use of Alisertib as a treatment for a wide range of cancers.

Table 1: Showing Medicine along with their targeting molecule and associated cancer

Medicine	**Mechanism**	**Cancer Target**
Afatinib	Inhibitor of the receptor tyrosine kinases epidermal growth factor receptor (EGFR)	Non-small cell lung carcinoma (NSCLC) (Keating *et al.,* 2012)
Axitinib	Tyrosine Kinase Inhibitor	Renal Cell Carcinoma (Rini *et al.,* 2005)
Bosutinib	Tyrosine Kinase Inhibitor	Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) (Cortes *et al.,* 2011)
Cabozantinib	Small Molecule Inhibitor of the Tyrosine Kinases	Thyroid cancer (Keating *et al.,* 2012)
Certinib	Anaplastic Lymphoma Kinase (ALK) inhibitor	Non-small cell lung cancer (NSCLC) (Shaw *et al.,* 2014).
Crizotinib	ALK (anaplastic lymphoma kinase) inhibitor	Non-small cell lung cancer (NSCLC) (Forde *et al.,* 2014)
Dasatinib	Tyrosine Kinase Inhibitor	Chronic myelogenous leukemia (CML), prostate cancer (FDA. "FDA approves additional medical indication for Sprycel". www.fda.gov. FDA)
Erlotinib	Tyrosine Kinase Inhibitor , EGFR Inhibitor	Non-small cell lung cancer (NSCLC), pancreatic cancer
Gefitinib	EGFR Inhibitor	Non-small cell lung cancer (NSCLC)
Ibrutinib	Bruton's Tyrosine Kinase (BTK) Binder	Mantle cell lymphoma, chronic lymphocytic leukemia
Imatinib	Stopping the Bcr-Abl Tyrosine Kinase	Chronic myelogenous leukemia (CML) and acute lymphocytic leukemia (Burris 2004)
Lapatinib	Syrosine Kinase Inhibitor, Tyrosine kinase Inhibitor	Breast cancer and other solid tumours (Burris 2004)
Lenvatinib	Multiple Kinase Inhibitor	Thyroid cancer (Matsui *et al.,* 2008)
Osimertinib	Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor	Metastatic non-small-cell lung cancer (NSCLC) (Ayeni *et al.,* 2008)
Pazopanib	Tyrosine Kinase Inhibitor	Renal cell carcinoma and advanced soft tissue sarcomas (Négrier *et al.,* 2017)
Ponatinib	Tyrosine-Kinase Inhibitor	Chronic myeloid leukemia, acute lymphoblastic leukemia (Massaro *et al.,* 2017)
Regorafenib	Tyrosine Kinase Inhibition	Metastatic colorectal cancer (Yoshino *et al.,* 2015)

Rucaparib	PARP Inhibitor	Metastatic breast and ovarian cancer (Dockery *et al.*, 2015)
Ruxolitinib	Tyrosine Protein Kinases	Advanced renal cell carcinoma, hepatocellular carcinoma (Kong *et al.*, 2017)
Sunitinib	Receptor Tyrosine Kinase Inhibitor	Renal cell carcinoma (Blay *et al.*, 2009)
Vandetanib	Kinase Inhibitor (EGFR) Inhibition	Medullary thyroid cancer (Ayeni *et al.*, 2008)

Receptor Tyrosine Kinase

Receptor tyrosine kinases (RTKs) are the membrane covering proteins that display inherent phosphotyrosine kinase action. Once the ligand is bound to the receptor, a conformational change is induced leading to transphosphorylation of receptor present in that specific tyrosine residue. This phosphorylated residue is recognized by signaling proteins that transfers signal from receptor to inside the cell (Peschard *et al.*, 2003). RTKs activation is linked to various significant cellular events like cell growth morphogenesis of organs, repairing certain tissue and cell regeneration.

Gene expressing RTKs can become potent oncogenes as a result of mutation, chromosomal translocation or genomic amplification. Various cancers are caused due to aberrant degradation of RTKs emphasizing the importance of mechanism regulating RTKs (Pawson *et al.*, 2005, Bache *et al.*, 2004). Receptor tyrosine kinases activity is controlled in normal cells but deregulation of RTK is reported in numerous cancers like breast cancer, lung cancer, head and neck cancer, gastrointestinal stromal tumor and chronic myeloid leukemia. The deregulated RTK signaling provides the rationale for anti-RTK drug treatment.

By inhibiting the catalytic activity of RTK with the help of small molecule inhibitors, aberrant signaling can be blocked. Non-small cell lung cancer with mutant EGFR and Gastrointestinal stromal tumor with KIT gene (c-kit) encoded mutant receptor tyrosine kinase protein can be treated using small molecules, Imatinib, and Gefitinib and Erlotinib respectively (Minkovsky *et al.*, 2016). Multiple RTKs like vascular endothelial growth factor receptor (VEGFR) (which plays a vital role in tumor angiogenesis and tumor cell proliferation) and kinases of platelet-derived growth factor receptor (PDGFR) are effectively inhibited by Sunitinib. Drugs like Brivanib and Sorafinib have been approved for the treatment of hepatocellular carcinoma (Mendel *et al.*, 2003).

Cell Cycle Regulatory Protein and Cancer

Uncontrolled cell proliferation, a very significant indicator of cancer can be instigated by the loss of cell cycle regulatory control. A very large number of proteins are known to function in cell cycle regulation. However, some proteins that have more significant role in cell division and maintaining cell cycle, can be targeted for the treatment of cancer.

Cyclins and Cyclin Dependent Kinases (CDKs) are the proteins which are important in progression of cell cycle through different phases. They are divided into two categories: G1/S cyclins and G2/M cyclins, which include CDK2/4/6 and CDK1, respectively. Cyclins acts as regulator of CDKs which controls their activity and specificity. In recent decades, several strategies have been analyzed to develop a possible therapy against cancer targeting cyclins and CDKs.

CDK4 and CDK6

CDK4 and CDK6 are known to control G1 phase of cell cycle in complex with cyclin D. The gene encoding these proteins are very commonly mutated in human cancers suggesting there major role in cancer prevention. Several promising cancer therapies like Palbociclib, Ribociclib and Abemaciclib, are under clinical trials targeting CDK4/6 proteins. Breast cancer, is currently being treated by the use of these therapeutic drugs (Otto *et al.*, 2017). Pablociclib when used in combination with Letrozole is reported to increase the survival rate in patients with

breast cancer. Apart from breast cancer, these drugs are also reported as potential candidate for treatment of lung, ovarian, hepatocellular, prostate, pancreatic and several other cancers as well (Finn *et al.,* 2016).

CDK1

CDK1 is activated by cylins B2 and B-protein. During cell cycle, phosphorylation and dephosphorylation of CDK1 plays an essential role in transition from G1 to M phase which affects cell proliferation in the course of M-phase. Therefore, CDK1 inhibitors can be a useful therapy against cancer. TG-02, Flavopiridol, Roscovitine, Dinaciclib, AT7519, Milciclib and RGB-286638, inhibits G1 cell cycle arrest and apoptosis (Goh *et al.,* 2012). Moreover, TG-02, a multi-kinase CDK1 inhibitor is also reported to have an anti-proliferating affect against tumor cells (Goh *et al.,* 2012). All of these potential drugs are under various stages of clinical trials. It is very likely that some of these will be used for the treatment.

Tumor Suppressor Proteins

Proteins encoded by various tumor suppressor genes are known to prevent cancer by different mechanism. Gene mutation can lead to loss of function and higher cancer risk.

BRCA1

The BRCA1, a caretaker gene, is located on chromosome number 17. The BRCA1 is a 220 kdalton protein, believed to work as a cell protector by repairing and preventing DNA strand break. Certain functions like apoptosis, cell checkpoint, DNA repairing, transcription and protein ubiquitination contributes to the tumor suppressing activity of BRCA1. Protein BRCA1 along with BRCA2 helps in stabilizing the human genome by interacting with the RAD51 (Boulton *et al.,* 2006). This very gene displays a significant participation during double strand break repair in homologous recombination of DNA. The BRCA1 gene is found to be the principal component in the process of transcription and also in RNA polymerase II holoenzyme (Scully *et al.,* 1997).

The mutations in BRCA1 gene mainly results in the Breast and Ovarian cancer. Inherent mutation of BRCA1 gene is also a cause of cancer in most of the women. EMSY is a protein known to bind with BRCA2 protein and result in its inhibition (Wilkerson *et al.,* 2011). This protein causes gene amplification and can be considered as a primary factor in non-familial breast cancer, that is, in sporadic breast cancers (De Leeneer *et al.,* 2012).

Poly (ADP-ribose) polymerase 1 (PARP1) is found to take the major leads in the treatment of the BRCA mutant genes. It is capable in post transcription modification of histone and DNA damage and repairing DNA single strand breaks (Hoeijmakers *et al.,* 2001). Human PARP inhibitor sensitizes tumor cells, leading to cell-cycle arrest and apoptosis (Farmer *et al.,* 2005) causing a big breakthroughs in less toxic cancer treatments. Various clinical trials indicates PARP inhibitors including Valiparib, Olaparib and Rucaparib (Kaufman *et al.,* 2016)that help in treatment of ovarian, breast and some of prostate and pancreatic cancers with BRCA1/2 mutation (Kaufman *et al.,* 2016). Olaparib is found to have 26.2% of response rate in various advance cancers associated with the BRCA 1/2 mutations. This drug in combination with chemotherapy and other hormonal therapies is found to be very effective in ovarian, breast and pancreatic cancer (Abbas *et al.,* 2009).

p21 Protein

Human p21 protein is a potent CDK inhibitor, activated by p53 gene. It maintains cell growth and respond to DNA damage, also modulates the repair process. Proliferating cell nuclear antigen (PCNA) (Abbas *et al.,* 2009) is interacted by it, resulting in promotion of suppression of cell cycle and DNA replication. Other functions of p21 includes regulation of cell morphogenesis, motility, survival, gene transcription, apoptosis, hormone signaling mediated by PAK family of activated kinases. The mutated p21 gene or subsequent down regulation of p21 protein enhance the chances of breast cancer.

Human p21 exert oncogenic as well as tumor suppressor activities. By the induction and accumulation of p21 expression using histone deacetylase (HDAC) inhibitors (. Drummond *et al.,* 2005, Mercurio *et al.,* 2010) and

proteasome inhibitors (Voorhees *et al.,* 2006, Zavrski *et al.,* 2016) respectively, the situation of increase in cellular level of protein can be effectively exploited.

Various anti-cancer agents, including the HDAC inhibitors like Vorinostat, Romidepsin, Valproic acid, Belinostat, Panobinostat and Givinostat (Fig 1) (Kahnberg *et al.,* 2006) promotes p21 activation (Ocker *et al.,* 2007), resulting in inhibition of cancer cells (Pecuchet *et al.,* 2010), demonstrating benefits in cutaneous T-cell lymphoma and other distortions like solid tumor (Mercurio *et al.,* 2010). Bortezomib (Velcade), the first proteasome inhibitor to undergo clinical testing, showed efficacy against non-Hodgkin's lymphomas, human mesothelioma, breast cancer cells, hematologic and other solid malignancies (Matta *et al.,* 2016). MG-132, MG-115, Lactacystin and Epoxomicin stabilizes the protein levels, involved in checkpoints (e.g. p53 and p21) and apoptotic pathways (e.g. Bax).

Human p21 can act as a therapeutic target in breast and other cancers characterized by chemotherapy resistance. Tumor cells can be sensitized by anti-proliferative drugs using p21 deletion (Weiss *et al.,* 2003) through antisense oligonucleotide that attenuate p21 expression in myeloid leukemia (Freemerman *et al.,* 1997), renal carcinoma (Park *et al.,* 2008) and breast cancer cells (Fan *et al.,* 2016).

Adenomatous Polyposis Coli (APC)

The human APC not only works as a negative regulator of the Wnt/beta-catenin signaling pathway but also facilitates mediation of cell migration, DNA replication, cell cycle and repair along with apoptosis.

This tumor suppression gene mainly causes colorectal cancer along with lungs, breast, liver and many other cancers. Mutations in other genes often result in mutations in APC as they can be inherited or arise sporadically in somatic cells. The production of abnormally short non-functional APC protein which is unable to suppress the cellular overgrowth leading to formation of polyps in intestine is caused by an inherited, inactivating mutation (Groden *et al.,* 1991). Mutations in APC have been found in around 60% of adenomas besides sporadic carcinomas (Powell *et al.,* 1992). Mutation cluster region (MCR) is known to harbor most Cancer linked APC mutations. This leads to C-terminal truncation of the protein (Beroud *et al.,* 1996) which, in turn leads to loss of domains required for binding to beta-catenin and signaling pathway along with activities like DNA repairing and replication, regulation of cell cycle, apoptosis and cell signaling pathways.

Several therapeutic approaches have been explored to treat APC-mutant cancers and contribute to the mechanism by which APC mediates tumorigenesis. PKF 115-584 and CGP049090, two small molecule inhibitors, have been developed against colorectal cancer cells with active Wnt/beta-catenin pathway. These compounds are found to disrupt beta- catenin/TCF binding, thus, inhibit proliferation. But they are cytotoxic in nature (Lepourcelet *et al.,* 2004). The ICG-001 molecule weakens the interaction of transcriptional co-activator CREB-binding protein (CBP) and beta-catenin (Emami *et al.,* 2004). This drug inhibits the expression of cell survival gene survivin, suppressing colorectal cell growth (Ma *et al.,* 2005). Another small molecule, FH535 prevents beta-catenin from interacting with TCF. Resulting in inhibition of proliferation through the mechanism that involves peroxisome proliferator-activated receptor (PPAR) (Handeli *et al.,* 2016).

APC function in mutant cells is restored using Tylosin, an aminoglyceride. Tylosin is found to be non-toxic, showing reduction in tumor growth and oncogenic phenotypes (Zilberberg *et al.,* 2010). Colorectal cancer cells containing a non-sense APC mutation can be targeted using the Tylosin. Cyclooxygenase-2 (COX-2) inhibitor, Celecoxib in combination with EGFR inhibitor, Erlotinib decreases 96% of polyps. Celecoxib was replaced by NSAIDS in this combination as they were found to have cardiovascular side effects (Buchanan *et al.,* 2007). AZD0530 and SKI-606 are Src inhibitors that decrease proliferation, invasion and metastasis in breast cancer (Hiscox *et al.,* 2008).

p53 Protein

Human p53, also known as 'guardian of DNA', functions in controlling significant cell cycle checkpoints. Around 50% of human cancers including cervical, ovarian, lung, liver, bladder, skin, colorectal and brain are caused due to p53 gene mutation. Once DNA damage is detected, human p53 protein induces G1 arrest, thus, providing more time

for DNA to repair during cell cycle. However, in case of higher damage of DNA, p53 leads cell to apoptosis, by transactivating p21 as well as certain apoptotic genes like PIG3, CD95 (Fas), Perp and BH3-only proteins, Bax, Killer/DR5, p53 AIP1, Noxa and PUMA (Fig 1) (Gurzov *et al.*, 2010).

Various non-genotoxic molecules have been recognised for the treatment of cancers retaining wild type p53 which activates p53 and induces tumor cell death. Some drugs like nutlin (Graves *et al.*, 2012), RITA (Issaeva *et al.*, 2014), MI-219 (Shangary *et al.*, 2008) and RG7112 (Saha *et al.*, 2013) target MDM2 - p53 interaction. RITA and nutlin induces apoptosis in tumor cells and inhibits there growth, thus, preventing the interaction of MDM2 and p53 (Hong *et al.*, 2014). The p53 can be activated through targeting specific molecular pathways using drug combinations. The combination of CDK inhibitors (roscovitine and DRB) and nutlin-3 shows synergy in activating p53 and apoptosis in p53 wild-type tumor cells (Cheok *et al.*, 2007).

PRIMA-1 is promising clinical trials on drugs targeted at restoring mutant p53 proteins in cancerous cells. It is converted into a methylated form of a drug called PRIMA-1(MET) & acts by thiol group modification present in the central domain of mutated protein (Lambert *et al.*, 2009). Molecules like MIRA-1, STIMA-1 and CP-31398 have the ability to alkylate cystine residues present in mutant p53 (Cheok *et al.*, 2007). Thus, p53 protein is reactivated, regaining its potential to induce apoptosis.

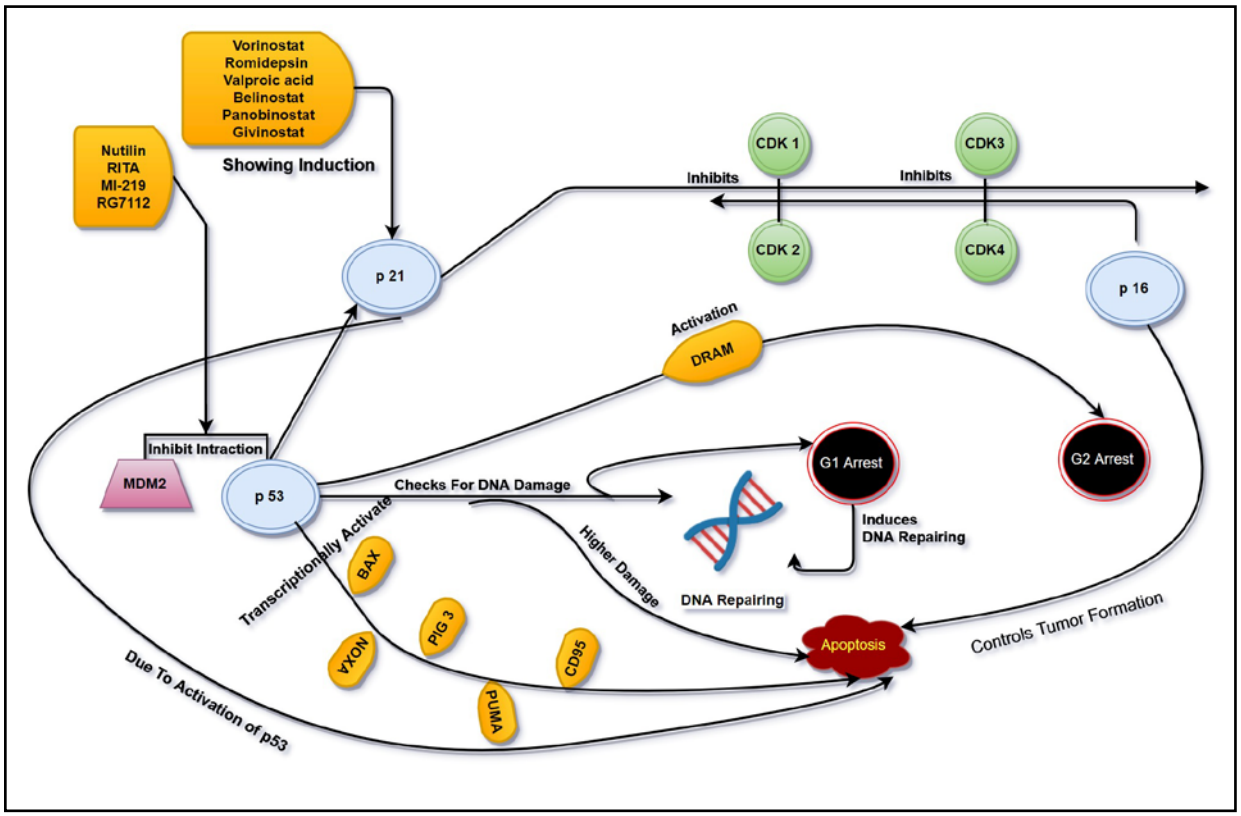

Figure 1: Interaction of some drugs with their respective protein. The interaction of Vorinostat, Romidepsin, Valporic acid, Belinostat, Panobinostat and Givinostsat with p21 protein, which helps in the inhibition of the Cell cycle by inhibiting Cyclin dependent Kinases (CDK1, CDK2,CDK4 and CDK4), this inhibition is also performed by p16 protein which further control tumor formation by apoptosis. Certain other drugs like Nutilin, RITA, MI-219, RG7112 inhibit the interaction of MDM2 with p53 which further helps in apoptosis and certain molecules which are transcriptionally activated by the p53 such as NOXA, BAX, PIG3, PUMA and CD95 further helps in apoptosis. P53

also interact with the DNA repairing mechanism by checking of any damage and in some conditions leads to G1 arrest, G2 arrest is also initiated by p53 by activating DRAM which helps in G2 arrest. In case of higher damage p53 causes apoptosis.

Resistance to Therapy

Cancer treatment has been revolutionized by small molecule therapy. Some of these therapies have helped in increasing survival rate amongst fair number of patients. But complete treatment is a major issue, as cancer relapse after certain period of time. On-target mutation accumulation and pathway alteration are predominant mechanism of drug resistance. Resistance is further influenced by drug factors like nature of drug & chosen target itself. Current research focuses on genomic studies of resistant cells to understand mechanism which helps cancer evade treatment. Understanding of such molecular events will help in designing second-generation therapies which can effectively deal with relapse of tumor (Gross *et al.,* 2015).

Conclusion

Protein targeted therapies against cancer by small molecules have progressed significantly in last few decades due to enhanced understanding of molecular events underlying cancer progression. These therapies have helped in improving overall patient life quality and saving many lives. Despite the recent advancement, for many patients the targeted therapies are not available. Designing targeted therapies are always difficult as cancer is result of multiple gene mutations. These mutations are not only different in diverse forms of cancer but varies greatly in individual cancer forms. Moreover, many potent proteins that have strong cancer linkage, like RAS, c-MYC and HIF. These are regarded as technically un-druggable by small molecules (Hoelder *et al.,* 2012). Nevertheless, with new and advanced discoveries we can hope that targeted therapies may become more efficacious and work as meaningful and primary strategy to treat cancer in upcoming future.

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