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Protein Kinase Signaling in Drug Resistance and Cancer Progression

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Abstract

Kinases are enzymes that transfer a phosphate group to a protein while phosphatases remove a phosphate group from protein. Together, these two enzymatic processes modulate numerous activities of proteins in a cell, often in response to an external stimulus. Approximately 538 known kinases are encoded in the human genome, and these kinases maintain cellular function by turning protein function on, while corresponding phosphatases reverse this action. These counter mechanisms greatly improve the plasticity of epigenome by regulating protein activity in virtually every imaginable way. Biochemically, protein kinases catalyze the following reaction.

Introduction

The human genome encodes 538 protein kinases that transfer a γ-phosphate group from ATP to serine, threonine, or tyrosine residues. Many of these kinases are associated with human cancer initiation and progression [1]. The recent development of small-molecule kinase inhibitors for the treatment of diverse types of cancer has proven successful in clinical therapy. Significantly, protein kinases are the second most targeted group of drug targets, after the G-protein-coupled receptors. Since the development of the first protein kinase inhibitor, in the early 1980s, 37 kinase inhibitors have received FDA approval for treatment of malignancies such as breast and lung cancer. Furthermore, about 150 kinase-targeted drugs are in clinical phase trials, and many kinase-specific inhibitors are in the preclinical stage of drug development. Nevertheless, many factors confound the clinical efficacy of these molecules [2]. Specific tumor genetics, tumor microenvironment, drug resistance, and pharmacogenomics determine how useful a compound will be in the treatment of a given cancer. This review provides an overview of kinase-targeted drug discovery and development in relation to oncology and highlights the challenges and future potential for kinase-targeted cancer therapies.

MgATP1−+protein−O:H→protein−O:PO32−+MgADP+H+

(Figure 1)

(Table 1)

Role of kinases in cancer

Targeting the kinases harboring oncogenic transformational capacity and metastasis has led to a notable change in the clinical management of cancer. Hundreds of kinases play overlapping and intricate roles in cell transformation, tumor initiation, survival and proliferation [3]. Diving kinases while justifying their coinciding functionalities is difficult. However, in order to understand and discuss their oncogenic undertakings, they can be vaguely categorized based on their hallmark roles in cancer. The first group is the kinases that play a fundamental role in the primary oncogenic transformation and thus present themselves as prospective drug targets [4]. Cytoplasmic tyrosine kinases are critical conveyers of extracellular signals, and mutations in these kinases have been reported to occur in various oncogenic conditions. This category includes the PI3K family of dual specific protein/lipid kinases, which are the most frequently mutated kinases implicated in 30–50% of human cancers. PI3KCA, perhaps the most notable member of PI3K family is associated with the pathology of colorectal cancer, breast cancer, ovarian cancer, endometrial carcinoma, and hepatocellular carcinoma [5]. The PI3KCA kinase catalyzes the production of PIP3, a phospholipid which activates downstream signaling components such as protein kinase AKT and promotes tumor cell growth and survival . Similarly, active form of the protein kinase Akt/PKB contributes to oncogenic transformation of cells . Likewise, V599E and V600E mutations in BRAF kinase are associated with various carcinomas while BRAF somatic missense mutations occur in 66% of malignant melanomas. The oncogenic mutations in JAK2 kinase such as single point mutation (Val617Phe) and JAK2 exon 12 mutations are implicated in both myeloproliferative disorders and myelodysplastic syndromes. Similarly, genetic alterations in other kinases such as ALK, IGF-1R, c-Kit, FGFR1–4, c-Met, c-Ret, c-SRC, regulate fundamental molecular mechanisms for tumor cell growth and development. Apart from tumor initiation, kinases are also vital for tumor cell survival and proliferation and may be present as downstream members of oncogenic kinase pathways [6]. This category of kinases includes EGFR, a receptor tyrosine kinase, which has been shown to prevent autophagic cell death by maintaining intracellular glucose levels through interaction and stabilization of the sodium/glucose cotransporter 1 (SGLT1) . Oncogenic alterations in EGFR make up approximately 45% of mutations in the tyrosine kinase domain . This leads to the loss of the inhibitory regulatory domains for dimerization resulting in hyper-proliferation of cancer cells via G1/S cell cycle progression. Other crucial members of the kinase family are aurora kinases (Aurora A-C). Aurora kinases are strategic kinases involved in defective spindle pole organization, and their pathophysiology correlates strongly with their oncogenic functions. Aurora-A is an oncogenic kinase, and its amplification is documented in 10–25% of ovarian cancers

Types of kinase inhibitors

They are categorized according to their capacity to catalyze the transfer of the terminal phosphate of ATP to the substrates that usually contain a serine, threonine or tyrosine residue. Many reviewers have

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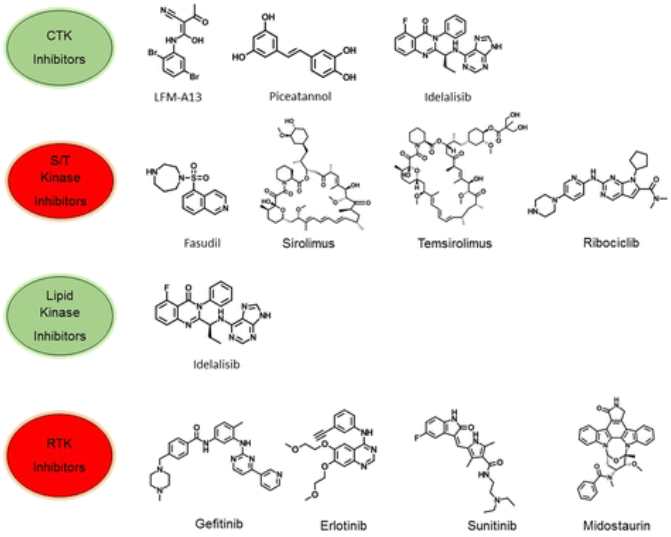

Figure 1: Chemical structures.

Table 1: Chemical structures of representative kinase inhibitors used for treatment of various human cancers.

Drug target	Protein substrate	Drug
ALK	Tyrosine	Crizotinib, Ceritinib, Alectinib, Brigatinib
BCR–Abl	Tyrosine	Bosutinib, Dasatinib, Imatinib, Nilotinib, Ponatinib
B-Raf	Serine/threonine	Vemurafenib, Dabrafenib
BTK	Tyrosine	Ibrutinib
CDK family	Serine/threonine	Palbociclib, Sorafenib, Ribociclib
c-Met	Tyrosine	Crizotinib, Cabozantinib
EGFR family	Tyrosine	Gefitinib, Erlotinib, Lapatinib, Vandetanib, Afatinib, Osimertinib
JAK family	Tyrosine	Ruxolitinib, Tofacitinib
MEK1/2	Dual specificity	Trametinib
PDGFR α/β	Tyrosine	Axitinib, Gefitinib, Imatinib, Lenvatinib, Nintedanib, Pazopanib, Regorafenib, Sorafenib, Sunitinib
RET	Tyrosine	Vandetanib
Src family	Tyrosine	Bosutinib, Dasatinib, Ponatinib, Vandetanib
VEGFR family	Tyrosine	Axitinib, Lenvatinib, Nintedanib, Regorafenib, Pazopanib, Sorafenib, Sunitinib

categorized types of kinase inhibitors according to their mechanism of action. Initially, small molecule protein kinase inhibitors were divided into three classes, termed as types I, II, and III kinase inhibitors [7]. Dar and Sakot defined the type I kinase inhibitor as "a small molecule that binds to the active conformation of a kinase in the ATP pocket," the type II inhibitor as "a small molecule that binds to an inactive (usually Asp-Phe-Gly (DFG)-OUT) confirmation of a kinase," and the type III inhibitor as "a non-ATP competitive inhibitor" or allosteric inhibitor. Later on, Zuccotto et al. introduced a new class of kinase inhibitors, i.e. type I½ inhibitors, which bind to the protein kinases with the DFG-Asp in and C-helix out conformation. Later, Gavrin and Saiah further divided the allosteric effectors into two subclasses (III and IV) where the type III inhibitors bind within the cleft between the small and large lobes adjacent to the ATP binding pocket and type IV inhibitors bind outside of the cleft and the phosphor-acceptor region. Afterwards, bivalent molecules that span two regions of the protein kinase domain were labeled as type V inhibitors. Finally, small molecules that form covalent adducts with the target enzyme were recently termed as covalent inhibitors. The classification described herein uses these parameters with added subdivisions and criteria, labeling them as types I, II, allosteric, and substrate directed and covalent inhibitors.(Table 2)

Classification of small molecule kinase inhibitors

Type I kinase inhibitors

Type I kinase inhibitors represent ATP-competitors that mimic the purine ring of the adenine moiety of ATP. Functionally, they interact with the conformational phosphorylated active catalytic site of the kinases. These kinase inhibitors bind to the active conformational site and alter the structural conformation otherwise favorable to phosphotransfer [8]. Type I inhibitors usually contain a heterocyclic ring system that occupies the purine binding site, where it serves as a scaffold for side chains that occupy adjacent hydrophobic regions. These hydrophilic regions of the enzyme occupied by the ribose moiety of ATP may be used to exploit the solubility of the drugs or other active compounds. To date, many Type I kinase inhibitors for the treatment of cancer have been approved by the FDA viz. bosutinib, crizotinib, dasatinib, erlotinib, gefitinib, lapatinib, pazopanib, ruxolitinib, sunitinib, and vemurafenib. Apart from the large-scale clinical success, Type I kinase inhibitors also come with adverse side-effects. Type I inhibitors display an inclination for low kinase selectivity as the targeted ATP pocket is conserved through the kinome; therefore, increasing the potential for off-target side effects. This little selectivity for targeted kinases may result in cardiotoxicity and possible deterioration in cardiac function.

Table 2: Classification of small molecule kinase inhibitors.

Class of Kinase Inhibitor	Mechanism of Action	Examples
Type I	Competes for the substrate and binds in the ATP-binding pocket of the active conformation	Bosutinib, Cabozantinib, Ceritinib, Crizotinib, Gefitinib, Pazopanib, Ruxolitinib, Vandetanib
Type II	Type II inhibitors bind to the DFG-Asp out protein kinase conformation, which corresponds to an inactive enzyme form	Imatinib, Sorafenib, Axitinib, Nilotinib
Type III (Allosteric Inhibitor)	Occupy a site next to the ATP-binding pocket so that both ATP and the allosteric inhibitor can bind simultaneously to the protein.	Trametinib, GnF2
Type IV (Substrate Directed Inhibitors)	Undergo a reversible interaction outside the ATP pocket and offer selectivity against targeted kinases	ONO12380
Type V (Covalent Inhibitor)	Bind covalently (irreversible)to their protein kinase target	Afatinib, Ibrutinib, HK1–272

Type II kinase inhibitors

Type II kinase inhibitors act by targeting the inactive conformation of kinases and interact with the catalytic site of the unphosphorylated inactive conformation of kinase. Type II kinase inhibitors exploit new interactions inside the lipophilic pocket derived from the change of confirmation of the phenylalanine residue of the "Asp-Phe-Gly (DFG)" N-terminal loop conformation of kinases [9]. These inhibitors interact reversibly with the target kinase which leads to the formation of single or multiple hydrogen bonds with the protein in the 'hinge region' and also causes extra interactions in the open DFG-out conformation. These lipophilic interactions have a high degree of selectivity towards unwanted kinases affecting an increase in the safety profile of Type II kinase inhibitors. Type II inhibitors also display a high conservation of distinctive H-bond pattern between the inhibitor and the glutamic and aspartic acids of the kinase. Due to the exclusivity of inactive protein kinase conformations, it was theorized than type II kinase inhibitors would be more selective. However, there is considerable overlap of selectivity between type I and type II inhibitors. The discovery of Type II kinase inhibitors such as imatinib and sorafenib was serendipitous, and it wasn't until much later that their mode of action was discovered. The role of imatinib in the consequent development of small molecule protein kinase inhibitors cannot be overstated. All Type II inhibitors share a similar pharmacophore and hydrogen bonds that interact with DFG-out kinase conformational structure as revealed by the discovery of the Type II kinase inhibitor co-crystal structure. Since canonical ATP-binding sites of activated kinases, the target sites of Type I inhibitors, do not share these features, this pocket is conserved to a lesser extent across the kinome, and hence promises better prospects for the rational design of selective inhibitors. Overall, Type II kinase inhibitors display high selectivity towards kinase inhibition as compared to Type I kinase inhibitors along with the profound impact on cellular activity.

Type III or allosteric inhibitors

The third class of kinase inhibitors bind outside the catalytic domain/ATP-binding site and modulates kinase activity in an allosteric manner. Some authors have divided the allosteric inhibitors into two subtypes where type A inhibitors bind to an allosteric site next to the adenine-binding pocket whereas the type B inhibitors bind elsewhere. Overall, Allosteric or Type III inhibitors exhibit the highest degree of target kinase selectivity as they exploit binding sites and physiological mechanisms that are exclusive to a particular kinase [10]. With respect to ATP, these drugs are steady-state noncompetitive or uncompetitive inhibitors because ATP cannot prevent their interaction with the target kinase. One of the earliest allosteric inhibitors was CI-1040, an orally active, highly specific, small-molecule inhibitor of the MEK1/MEK2 pathway. A recent chemical proteomics study confirms the allosteric activity of type III inhibitors as they showed a higher selectivity, but also stated that these are special cases as most of them are designated MEK1/2 inhibitors that bind to a particular cavity adjacent to the ATP-binding site. Another allosteric kinase inhibitor GnF2 binds to the myristate binding site of BCR–ABL1. GnF2 also displays sound IL-3 reversible anti-proliferative and apoptotic effect on two mutants identified as E255V and Y253H. Likewise, TAK-733 binds to the MEK1-ATP complex in the gate area and the back cleft adjacent to the ATP-binding pocket; however, it cannot bind to the adenine pocket owing to its occupation by ATP. Other examples include RO0281675 and analogs thereof. Overall, targeting kinases using allosteric inhibitors is thought to be a crucial approach for overcoming hurdles in kinase inhibitor research, such as limited selectivity, off-target side effects, and drug resistance. In future, more active and target specific allosteric inhibitors will be discovered as larger stress is placed on cell-based assays in which kinases are explored in their native cellular context.

Substrate-directed inhibitors

These are also called Type IV kinase inhibitors and undergo a reversible interaction outside the ATP pocket, located in the kinase substrate-binding site. These inhibitors don't compete with ATP and offer a higher degree of selectivity against targeted kinases. Substrate-directed inhibitors include ATP-noncompetitive inhibitors such as ON012380 which are targeted against Philadelphia chromosome-positive leukemias. More importantly, ON012380 was found to override imatinib resistance at physiologically relevant concentrations of < 10 nM.

Type V or covalent inhibitors

The covalent kinase inhibitors form an irreversible covalent bond with the kinase active site and target a catalytic nucleophile cysteine within the active site of the enzyme. The chemical rationale for developing Type V inhibitors is based on exposed cysteine side chain in the ATP site which can be targeted for covalent reaction with a drug candidate with an electrophilic Michael acceptor in the right position. This type of kinase inhibition takes place via trapping of a solvent-exposed cysteine residue either by SN2 displacement of a leaving group or by reacting with a Michael acceptor incorporated within the kinase inhibitor. Covalent inhibitors target respective kinase by formation of a rapidly reversible collision complex followed by an irreversible enzyme-inhibitor complex. Afatinib (targets EGFR (ErbB1), ErbB2, and ErbB4) and ibrutinib are currently FDA-approved drugs that form a covalent bond with their target kinase. Afatinib, unlike the first-generation EGFR-TKIs such as gefitinib and erlotinib, is a mutant-selective EGFR inhibitor with low toxicity profile despite its irreversible mechanism. Similar to Afatinib, ibrutinib also targets mutant-EGFR kinase with a distinct binding conformation . Both of these kinase inhibitors initiate Michael reaction with the addition of a nucleophile (the -SH of

cysteine) to an α, β unsaturated carbonyl compound . C481 within hinge region of the Bruton tyrosine-protein kinase is hypothesized to form a covalent link with ibrutinib. A recently approved kinase inhibitor, neratinib (HKI-272), inhibits Herceptin-2 (HER-2), and prevents recurrence in patients with early-stage HER2-positive breast cancer . Overexpression of HER-2 is seen in 25–30% of breast cancer patients and predicts a poor outcome in patients with primary disease. Likewise, CL-387785, a covalent inhibitor, overcomes resistance caused by T790 M mutation of the epidermal growth factor receptor (EGFR). These kinase inhibitors also display an extended dissociation half-life which minimizes off-target side effects. Other advantages include prolonged pharmacodynamics, suitability for rational design, high potency, and ability to validate pharmacological specificity through mutation of the reactive cysteine residue. The approved covalent kinase inhibitors (Ibrutinib, Afatinib, and Neratinib) have shown that small molecules containing weak reactive electrophiles can be mutant specific in action with low toxicity. These kinase inhibitors have initiated resurgence of interest in covalent inhibitors, and feature an acrylamide functionality to specifically target the cysteine side chains of kinases. Example include a recent study showing nine irreversible EGFR and two BTK inhibitors with higher kinase inhibitory selectivity than reversible compounds. The Type V or covalent kinase inhibitors have substantial potential for exploration as 200 different kinases have a cysteine chain located near the ATP pocket.

Biochemical Mechanism

Biochemically, kinase inhibitors are classified according to the activation state of the protein kinase target including the nature of DFG-Asp (active in, inactive out), the C-helix (active in, inactive out), and the regulatory spine (active linear, inactive distorted). Apart from type III or allosteric inhibitors, all the FDA-approved kinase inhibitors form hydrogen bonds with one or more hinge residues. Overall, most kinase inhibitors form: (i) hydrophobic contacts with catalytic spine residues; (ii) contact with the RS3 R-spine residue within the C-helix; (iii) interaction with the gatekeeper residue; and (iv) residues that occur just before the DFG-D of the activation segment. The following section briefly discusses the biochemical mechanism of action of FDA-approved kinase inhibitors.

Frequent mutations in various protein kinases present specific kinase inhibition as a therapeutically relevant approach in oncology. Kinase inhibitors have evolved to target many different regulatory and inhibitory mechanisms. There are various mechanisms by which kinase inhibitors bind to their target kinases broadly classified into kinase inhibitors that bind either covalently or non-covalently to or around the ATP binding site. Primarily, kinases bind with ATP in a cleft between the N- and C-terminal lobes of the kinase domain. In this domain, the adenine group of ATP is bound by two hydrophobic surfaces and interact via hydrogen bonds to the connector of two lobes, called the "hinge region". The cleft of ATP contains various elements such as the flexible activation loop (A-loop), along with closed conformations which are responsible for the catalytic activity of the kinase. The active or inactive state of the protein kinase is determined by the position of the A-loop, including the DFG motif at its N-terminal, which has various conformations. The only component of kinases that does not vary between the active and inactive states is the catalytic loop. The active state of the protein kinase when the Asp in the DFG motif coordinates one magnesium ion, which prepares the phosphates of ATP for the transfer of the phosphoryl group. The Phe in the DFG motif packs under the helix-C positioning both helix-C and A-loop for catalysis. Protein kinases return to their inactive conformation once kinase transfers the phosphoryl group from ATP to tyrosine, serine or threonine of the substrate protein. This process also involves the returning of the A-loop to the closed position by the change of A-loop from the DFG-in to the DFG-out conformation. However, ribose binding and the phosphate binding site of ATP usually remains unexplored by the majority of kinase inhibitors. Based on the biochemical mechanisms of action, kinase inhibitors are categorized as covalent and non-covalent kinase inhibitors. The non-covalent kinase inhibitors are classified into those who either bind or do not bind to the hinge region of the kinas. The DFG-in or Type I kinase inhibitors bind to hinge region and represent the vast majority of non-covalent kinase inhibitors. In these kinase inhibitors, the Asp in the DFG motif coordinates the phosphates of ATP, and the Phe in the DFG motif stabilizes the position of helix-C and the A-loop for catalysis. However, the ATP-binding pocket is highly preserved among members of the kinase family, and it is hard to find highly selective Type I kinase inhibitors. Moreover, the pre-clinical to clinical translation of Type I kinase inhibitors is hindered as they compete with high levels of intracellular ATP leading to a discrepancy between biochemical and cellular analysis. Contrary to the Type I inhibitors, Type II inhibitors bind to the DFG-out confirmation of kinases. These inhibitors induce a conformational shift in the target enzyme such that the target kinase is no longer able to function. Type II inhibitors use an additional hydrophobic pocket adjacent to the ATP site exposed by the movement of A-loop from DFG-in to DFG-out conformation. This gives the Type II inhibitors higher selectivity as they recognize novel regions of the active cleft outside the highly conserved ATP-binding site. Like Type II kinase inhibitors, the allosteric inhibitors or Type III inhibitors also display high selectivity as they explore binding sites and regulatory mechanisms that are unique to a particular kinase. They contain a heterocyclic system that forms one or two hydrogen bonds with the kinase hinge residue. Like Type II inhibitors, they also induce the DFG-out confirmation and move phenylalanine side chain to a new position. Examples include compounds such as CI-1040, which inhibit MEK kinase by occupying a pocket adjacent to the ATP-binding site. Interestingly, exploration of allosteric kinase inhibitors also helps to recognize unique kinase activation targets, which could be explored for therapeutic intervention in other diseases states. Recently, there has been an increased interest in the development of irreversible (covalent) kinase inhibitors that form covalent bonds with cysteine or other nucleophilic residues in the ATP-binding pocket. These inhibitors have typically been developed by incorporation of an electrophilic moiety into an inhibitor that already possesses submicromolar binding affinity to the target of interest. The covalent kinase inhibitors bind to a cysteine residue in or around the active site, thus preventing the binding of ATP to the protein kinase. These kinase inhibitors undergo the "Michael reaction", which is a reaction that triggers the addition of a nucleophile, such as a cysteine, to an α, β unsaturated carbonyl functionality. Nucleophile additions cause the formation of adducts at the electrophilic β-position and inactivate kinases by irreversibly blocking the binding of ATP to kinase. These kinase inhibitors are highly selective as they overcome endogenous ATP competition and target a specific cysteine at the corresponding position in a kinase. Various covalent kinase inhibitors target kinases such as BTK , Fes , VEGF-R2 , and RSK2 through their ability to bind to a cysteine residue.

Recent clinical developments

Traditional cancer therapies follow palliative as well as off-targeted approaches in oncology. In contrast, kinase inhibitors symbolize a class of targeted cancer therapeutic agents with limited nonspecific toxicities. So far, 28 inhibitors with activity targeted to one or multiple

kinases have been approved for clinical use. With over 500 members, the kinase family has received a high degree of attention from academic researchers as well as pharmaceutical industries . After the clearance of possible hindrances, owing to the high degree of active site similarities and possible off-target activity, kinase inhibitors have gained scientific limelight. In a 13-year summary of targeted therapies including kinase inhibitors, the clinical success rate of kinase inhibitors was superior to other cancer therapies. Nevertheless, this clinical success does come with exceptions; attempts to control cytotoxicity during treatment, particularly with sunitinib and EGFR/VEGF-system targeting drugs have yielded disappointing results. Overall, during the last 5 years, Aurora kinases, casein kinase II, cyclin-dependent kinases, focal adhesion kinase, protein kinase B, phosphatidylinositol 4,5-bisphosphate 3-kinase delta and gamma, polo-like kinase I, tyrosine-protein kinase SYK, high affinity nerve growth factor receptor family and Wee1-like protein kinase have been targeted in Phase I clinical trials. Although recent developments have shown Aurora kinases as major new targets in kinase inhibitor development. After initial hurdles, two compounds palbociclib and ribociclib have passed the phase III clinical trials and are in clinical use.

Recent kinase developments include precision therapy based on tumor genomic data. The ability to perform genetic studies of tumors and follow-up treatment decisions based on the identification of tumorigenesis drivers has resulted in significant benefits for patients in need of effective systemic therapy. The detailed information regarding all the clinical trials is out of the scope of this mini-review; however, a few important developments are highlighted. A small number of small molecule tyrosine kinase inhibitors have recently received FDA approval for treatment of non-small cell lung cancer (NSCLC) with EGFR mutations or ALK translocations. Afatinib, a second-generation, non-competitive kinase inhibitor targeting all members of the ErbB family of receptors (also known as Her-2/neu) was approved in 2013 as frontline therapy for NSCLC patients with EGFR-deletion 19 and L858R mutations. Despite several challenges that need to be overcome, reviewed in, precision medicine has yielded important dividends for patients with advanced cancers. In order to counter currently undruggable targets and acquired resistance, immunotherapy has gained widespread recognition in recent years. Additionally, kinase targeted antibody therapy for hematological malignancies, and solid tumors have become established over the past 20 years. Key examples of antibody constructs targeting kinases include Trastuzumab and T-DM1 (targeting ERBB2/HER2) in breast and bladder cancer, Bevacizumab (targeting VEGF) in ovarian, metastatic colon cancer and glioblastoma , Cetuximab, Panitumumab and necitumumab (targeting EGFR) in colorectal cancer and NSCLC . Other experimental candidates include scFv, affibody and minibody (ERBB2/HER2 and FGFR1), Protein–Fc (VEGFR1 and VEGFR2) and Intact IgG (EGFR, ERBB2, and VEGF) in breast and lung cancer studies. Also, there is an increased development of PI3K and mTOR inhibiting compounds. Dual PI3K/mTOR inhibitors in advanced clinical trials include NVP-BEZ235 (glioblastomas), XL765 (breast cancer), GDC0980 (mRCC), PF04691502 (breast cancer), GSK2126458 (colorectal, breast, non-small cell lung, and pancreatic cancers), Quinacrine (various leukemias) and PKI587 (advanced solid malignancies). Also, buparlisib and idelalisib, both PI3K inhibitors, have entered phase III clinical trials. In line with PI3K/mTOR inhibitors, various kinase inhibitors have entered into clinical trials for gastrointestinal cancers, thyroid carcinoma , breast cancer, and endocrine tumors . Many previously approved kinase inhibitors are being tested in clinical trials against BRAF and cyclin-dependent kinases 4/6 mutations. BRAF somatic mutation, particularly BRAF V600E/K, drive tumorigenesis through constitutive activation of the downstream MAPK pathway. Multiple drugs including vemurafenib, dabrafenib, PLX3603, ARQ736, CEP-32496, BMS-908662, BGB283, encorafenib in combination with other chemotherapies are being targeted for BRAF-mutated cancers. It is now suggested that dabrafenib, a selective BRAF inhibitor may target other kinases indicating polypharmacology (that is, drugs that act on more than one target) . A paper published by Klaeger and colleagues explains the potential of 243 clinically evaluated kinase drugs . Although multiple new kinases have been targeted during the last 5 years, a large share of the cancer kinome is still untargeted. Furthermore, use of these targeted therapies is not without limitations. Reservations on the use of kinase inhibitors include the development of resistance and the lack of tumor response in the general population and these constraints still need to be resolved.

Natural Bioactives as Kinase Inhibitors

Overexpression of kinases is observed in multiple carcinomas. In recent years, there has been a major paradigm shift in discovery and screening of natural compounds as potential kinase inhibitors. Emerging data has revealed numerous mechanisms by which natural compounds mitigate kinase mutations. Classically, many of the biological actions of small molecule compounds, especially polyphenols, have been credited with their antioxidant properties, either through their reducing capacities or their possible influence on intracellular redox states. These small molecule bioactives can directly bind receptor tyrosine kinases and alter their phosphorylation state to regulate multiple cell signaling pathways . Elevated levels of the EGFR and HER-2 have been identified as common components of multiple cancer types and appear to promote solid tumor growth EGFR inhibition is exhibited by multiple polyphenols including resveratrol, quercetin , curcumin , and green tea extracts . HER-2 overexpression in tumor cells is also attenuated by these bioactives. Fibroblast growth factors are involved in a variety of cellular processes, such as tumor cell proliferation, drug resistance, and angiogenesis. Oncogenic alterations of RTK kinases including FGFR1, FGFR3, and FGFR4 are inhibited by natural compounds .Similarly, curcumin and chrysin block expression of receptor d'origine nantais (RON) in tumor cells The product of the human SRC gene, c-Src, is found to be over-expressed and highly activated in a wide variety of human cancers . It is also accompanied by elevated levels of Abl and JAK-2 kinases . Interestingly, the overexpression and translocation of oncogenic cytoplasmic tyrosine kinases such as c-SRC , Abl, c-Met and JAK-2 are tempered by natural compounds. Serine/threonine kinases, within the kinase family, play vital roles regarding their involvement in human cancers. Akt, a crucial kinase modulates diverse cellular processes involved in the regulation of cell survival, cell cycle progression and cellular growth. Up to date, more than 50 proteins have been identified as the phosphorylation substrates of Akt. Resveratrol modulates expression of Akt in breast, uterine, prostate skin and glioma cells. It targets the kinases at ATP-binding site competitively and reversibly.

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