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Review Article

Review on: Signal Transduction Pathways as Therapeutic Targets in Cancer Therapy

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Abstract: Cancer is the second leading cause of mortality and it is a worldwide public health issue and has severe social and economic consequences. Cancer arises through a multistep, mutagenic process whereby cancer cells acquire a common set of properties including unlimited proliferation potential, self-sufficiency in growth signals, and resistance to anti-proliferative and apoptotic signals. Chemotherapeutic and cytotoxic drugs are widely used in the treatment of cancer. In spite of the improvements in the life quality of patients, their effectiveness is compromised by several disadvantages. Better understanding of the pathogenesis of this disease, identification of molecular targets for therapeutic intervention and availability of promising molecularly targeted therapies may change this dismal picture. These demands lead for developing new effective strategies with focusing on tumor cells and minimum side effects. Targeted cancer therapies have been defined as a new type of emerging treatments. This article provides an overview of: the characteristics and function of signal transduction pathway and emerging RTKs for targeted cancer therapies and therapy targeted at Ras/Raf/MEK/ERK Pathways and PI3k-Akt-mTOR-pathways. Future research in this area will maximize clinical benefit while minimizing the toxicity and cost through utilization of novel targeted agents.

Keywords: Cancer, Targeted Therapies, Small Molecule Inhibitors, Monoclonal Antibodies, Ras Pathways

1. Introduction

The first description of cancer is found in an Egyptian papyrus and dates back to approximately 1600 BC [1]. It is a cluster of diseases involving alterations in the status and expression of multiple genes that confer a survival advantage and undiminished proliferative potential to somatic or germinal cells [2]. Cancer is a leading cause of death worldwide and it is the second leading cause of mortality in the U.S with most of the deaths resulting from metastatic tumor formation at secondary sites [3]. Cancer accounts for about 7 million deaths/year (12.5% of deaths worldwide). It has been estimated that there will be more than 16 million new cancer cases every year by 2020. The main types of cancer leading to overall cancer mortality are lung, stomach, liver, colon and breast cancer. Nearly all cancers are caused by abnormalities in the genetic material which may occurs due to the effects of carcinogens, such as tobacco, smoke, radiation, chemicals or infectious agents [4].

Over time it was realized that neither surgery nor radiation or the two in combination could adequately control the metastastic cancer and hence, for treatment to be effective, therapy needed to reach every organ of the body [1] and chemotherapy treatments for locally advanced or metastatic cancer had little or no efficacy. This type of treatment does not discriminate between rapidly dividing normal cells and tumor cells, thus leading to severe systemic side effects, while attempting to reduce the tumor mass [5]. Therefore, nowadays, advances in understanding the molecular basis of cancer made possible by the identification and functional analysis of tumour-specific genetic alterations have opened exciting new opportunities for the design of therapies that specifically target the molecular pathways involved in promoting tumour cell growth and circumvent death pathways [2]. Such therapies have the ability to target a variety of cancer relevant molecules, including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and its receptor. In addition,

protein tyrosine kinases have been proven to be good targets to develop small molecule inhibitors. These inhibitors have clinically effective responses [6]. In this review, current status of targeted therapies in the treatment of cancers with in monoclonal antibodies (MoAbs), tyrosine kinase inhibitors (TKIs) and cytoplasmic signaling intermediates targeted was described in detail.

2. Background of Cancer

2.1. Epidemiology of Cancer

Cancers are complex and heterogeneous disorders of different organ of host [7] and it is the leading cause of death worldwide. Cancer is a worldwide public health issue and has severe social and economic consequences. According to the International Agency for Research on Cancer, a total of 14.1 million new cases of the disease and 8.2 million cancer-related deaths were reported in 2012. Projections based on these results indicate that the worldwide incidence of cancer will reach approximately 19.3 million by the year 2020 [8]. The most frequent types of cancer among men as worldwide are: lung, stomach. liver, colorectal, esophagus and prostate; while in women: breast, lung, stomach, colorectal and cervical [9]. In 2018, approximately 18.1 million new cancer cases and 9.6 million cancer deaths were reported. Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death in both sexes. Lung cancer is the most frequent cancer and the leading cause of cancer death among males while Among females, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death [10].

2.2. Etiology of Cancer

Several factors, both intrinsic and external to the body, can contributed to the cancer risk. Exposure to environmental pollutants like many chemicals, industrial effluents, some therapeutic drugs, and mutagenic agents, including ionizing radiation, can increase the incidence of cancer [11]. In addition, Occupational factors are thought to account for 6% of cancers, while lifestyle and diet may account for up to 30%-50%. Genetic predisposition is also a factor in some types of cancer. Some infections can act as a stimulus to induce and promote cancer development [12].

2.3. Pathophysiology (Formation of Cancer Cells)

Cancer results from an accumulation of genetic mutations and carcinogenesis and is a multi-step process reflecting genetic mutations that drive the normal human cells into malignant derivatives [13]. Although loss of genomic stability and evading immune destruction are two milestone events that may be observed throughout the occurrence and development of tumors, the pathogenesis of tumors differs widely among different cancers and individuals. Dramatic advances in basic research over the last 30 years have enabled practitioners to understand the pathogenesis of malignancies at the molecular level and provided solid bases for the prevention and treatment of tumors [14]. The process of carcinogenesis consists of three major steps: initiation, where an irreversible change is affected in the cellular genes; promotion, where the initiated cells expand by self-proliferation leading to abnormal growth and further mutations; and progression, where the cells detach from the primary tumor and invade other organs and tissues, forming metastatic growths [11]. With each step reflecting genetic changes that promotes the progressive transformation of healthy cells into tumor cells. Studies show that the genes of tumor cells are frequently modified at many different sites, ranging from disruptions as subtle as point mutations (DNA base-pair change) to more obvious problems such as chromosomal translocations [12, 15, 16]. Different types of cancer genes oncogenes and tumor suppressor genes are involved in cancer development. Gain of function mutations in the oncogenes, leading to abnormal cell proliferation, and loss of function mutations in the anti-oncogenes leading to suppression of cell differentiation and apoptosis, are the major events leading to cancer development. Angiogenesis plays an important role in the tumor metastasis [11].

Currently, eight hallmarks explain the typical capabilities acquired by tumor cells in the process of tumorigenesis, these properties are sustaining proliferation, evading growth suppressors, resisting cell death, enabling replicative immortality, activating invasion, metastasis, evading from the immune system, and reprogramming energy metabolism. Recently, other features including epigenetic alterations have been introduced [17].

3. Signal Transduction Pathways as Therapeutic Targets in Cancer Therapy

Signal transduction is the process by which a cell converts an extracellular stimulus into an intracellular signal [18]. The mitogen-activated protein kinase (MAPK) cascade is a key intracellular signaling pathway that regulates diverse cellular functions including cell proliferation, cell cycle regulation, cell survival, angiogenesis, and cell migration [19]. Each cascade consists of three core kinases (MAP3K, MAPKK, and MAPK). Within each of the cascades, the signal is propagated by sequential phosphorylation and activations of the sequential kinases, and they eventually lead to the phosphorylation of target regulatory proteins by the MAPK. At present, four different mammalian MAPK cascades have been identified, and named according to their MAPK components: extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), p38, and ERK5 [20]. In general, growth factors, cellular stresses, and either growth factors or stresses are considered as the main activator of ERK1/2, JNK/p38-MAPKs, and ERK5 cascade, respectively. However, accumulated evidence has suggested cross talks between various components of the pathways. These multiple interactions between the different MAPK cascades serve to provoke more diverse and precise cellular responses to various intra- and extra-cellular stimuli [21].

Classic activation of the MAPK cascade occurs following ligand binding to a receptor tyrosine kinase (RTK) at the cell surface, but a vast array of other receptors has the ability to activate the cascade as well, such as serpentine receptors, heterotrimeric G-proteins, and cytokine receptors. Many receptor tyrosine kinases are capable of initiating MAPK signaling including receptors important in cancer, such as the human EGFR family, plate-derived growth factor receptors (PDGFR), VEGF, and c-Kit. The EGFR pathway serves as a relevant model for examining the activation and targets of MAPK signaling [19].

Tyrosine kinase is a subclass of protein kinase. It is enzymes that transfer a phosphate group to tyrosine residue in a protein this have important faction in signal transduction [22]. There are about 58 known tyrosine kinase receptors in humans, classified into 20 subtypes or families, according to structural aspects and the ligands that activate them and 30 of them have been shown to be necessary for oncogenesis in various tumors. Some examples include the EGFR, the VEGFR and PDGFR family [17].

All RTK are transmembrane proteins, whose amino-terminal end is extracellular. Their general structure is comprised of an extracellular ligand-binding domain, a small hydrophobic transmembrane domain and a cytoplasmic domain, which contains a conserved region with tyrosine kinase activity, regulate catalytic function. This region consists of two lobules (N-terminal and C-terminal) that form a hinge where the ATP needed for the catalytic reactions is located. Activation of RTK takes place upon ligand binding at the extracellular level [18].

Binding of ligand induces oligomerization of receptor monomers, usually dimerization. Dimerization-driven stimulation of the intrinsic tyrosine kinase leads to the phosphorylation of tyrosine residues in the intracellular domain of the receptors that serve as docking sites to recruit a number of signal adapter proteins that link RTKs to different cellular signalling pathways such as phospholipase C, PI3K-Akt (involved in the survival of tumor cells), MAPK, and STAT pathways (mainly involved resistance to apoptosis), [19, 23]. Other signaling pathways associated to the process of EGFR activation are those of the phospholipase C-g and the JNK; these pathways have been found to be involved mainly in processes of cell migration, and cell proliferation and transformation, respectively. Together, these pathways control gene transcription, cell cycle progression, cell proliferation and survival, adhesion, angiogenesis, and cell migration [24, 25].

Many kinases have been found to be intimately involved in the processes leading to tumour cell proliferation and survival [26]. Deregulation of RTK activity is the major mechanism by which tumor cells escape from physiological constraints on survival and growth. Aberrant RTK activation due to receptor over-expression, chromosomal translocation, gene amplification, mutations, and impaired receptor down regulation contribute to the development of various forms of cancer in human [17]. In multiple tumor types this family of RTKs has been found to be deregulated, thus leading to an overexpression and amplification of *EGFR* and ensuing inappropriate cellular stimulation. Receptor overexpression has been correlated with a more aggressive clinical course in multiple tumor types [27].

Many chemotherapy-naive and nearly all drug resistant tumors are characterized by RTK signaling. The underlying mechanisms of this overactivation are diverse and comprise at least the following mechanism. Formation of a self-sustaining autocrine loop with secreted growth factors such as EGF, VEGF, PDGF, amphiregulin or others, Expression of intrinsically active RTK in the cell membrane, Over-activation of downstream signaling by imbalance of tumor-suppressor genes (p53) and (proto-) oncogenes (PI3K, monomeric G Proteins such as RAS, RAF and others) [28].

4. Treatment

A variety of anticancer compounds for the treatment of many different malignancies have been developed. These compounds comprise the classic cytotoxic and cytostatic agents, as well as the newer agent directed at particular cellular structures or targets and the agents that interrupt or interfere with intracellular processes [29]. In this review mainly concentrate on the current status of molecular targeted therapies in the treatment of cancers based on experience with in monoclonal antibodies, tyrosine kinase inhibitors and cytoplasmic signaling intermediates acting in signaling pathway.

Conventional anticancer drugs, such as DNA–alkylating and cross-linking agents, antimetabolites, topoisomerase inhibitors, and others agents, have been traditionally focused on targeting DNA processing and cell division. Although these drugs can be very efficacious, their lack of selectivity for tumor cells versus normal cells usually leads to serious side effects, such as bone marrow suppression and gastrointestinal, cardiac, hepatic, and renal toxicities, which limit their use [12]. For tumors of the same phases and stages, treatment responses and prognoses may differ vastly among patients even after application of the same therapeutic strategy. In fact, malignant tumors are highly heterogeneous at the molecular level. Tumors with the same morphology may contain varied changes in molecular genetics, resulting in diversity in treatment responses and prognoses [14].

Molecularly targeted drugs interact with a specific target, mostly a protein, in a selective way. This protein is a growth factor, a growth factor receptor, a signaling molecule, a cell cycle protein, an apoptosis mediator, a molecule involved in the initiation, progression and spread of cancer and angiogenesis [30]. Recognizing these families enables us to think rationally about which pathways to manipulate in order to suppress the disease [31] by direct and/or indirect approaches.

Many current targets involve the signal transduction pathways associated with changes in oncogenes and tumour suppressor genes. Accordingly, newer molecular targeted agents are classified as: targeting pathways of tumorigenesis like EGFR inhibitors and targeting angiogenesis and cell

proliferation [13, 32, 33].

4.1. Tyrosine Kinase Inhibitors (TKIs)

Small-molecule TKIs (SMIs) are another class of RTK-targeted agents. TKIs are small molecules that inhibit the enzymatic activity of the target protein. SMIs are among the most effective drugs for targeted cancer therapy. These agents prevent and block vital pathways through targeting signaling molecules which are necessary for cell survival. TKIs can translocate through the plasma membrane and interacting with the cytoplasmic domain of RTKs. Most of the current RTK–TKIs are multi-targeted and inhibit a variety of molecules in a non-specific manner. Multi-targeted inhibition has been shown to have several disadvantages due to targeting various RTKs compared to selective/specific TKIs. Only a few specific/selective TKIs have been approved by authorities for cancer treatment or are in preclinical and clinical settings [17, 34, 35].

4.1.1. Small Molecule Targeted EGFR (EGFR TKIs)

EGFR TKI's act by binding to the intracellular EGFR TK domain, and inhibit receptor phosphorylation and downstream signalling. The first generation of EGFR TKI's bind reversibly to the ATP binding site of the EGFR TK domain, and have higher binding affinity for EGFR with activating mutations, resulting in inhibition of RTK activity. Erlotinib and Gefitinib were the best example of drugs that target this pathway and been approved for the treatment of cancer. Lapatinib and AE788 are dual kinase inhibitors, which in addition to EGFR inhibit HER2 and VEGF receptors respectively [25].

Prolonged use of first-generation EGFR-TKI's leads to drug resistance due to common secondary mutation of the target action of the drugs. These types of resistance can be overcome by second generation (irreversible EGFR TKI's irreversible EGFR TKI's), such as Afatinib and Dacomitinib. These second generation have some advantages over the first generation TKI's, like higher affinity for the EGFR TK domain, longer suppression of some signalling pathway due to irreversible binding and are also effective against the mutation that cause resistance against first generation drugs [36, 37]. Currently several other second generation TKI's such as PK1166, EKB569, Canertinib, HKI-272, HKI-357, CL 387.785 and BIBW 2992 are currently under investigation [25].

4.1.2. Small Molecules Inhibitors Targeted VEGF

Several anti-angiogenics which are TKI's like sorafenib (targets Raf and VEGF and PDGF receptors) and sunitinib (targets VEGF) agents were approved for cancer [6]. There are also several SMIs of VEGFR that are currently in clinical trials. For example, vitalanib (PTK 787), SU 11248, AG 013736, and AZD 2171 are in Phase I clinical trials [13, 17].

Table 1. *Small molecules kinase inhibitors of anticancer drugs [38- 40].*

Agent	Target	Indication
Afatinib	HER2, EGFR	NSCLC, carcinoma of the head and neck, breast cancer
Canertinib	EGFR, HER2, 4	Head and neck, breast, and NSCLC, ovarian cancer
Dacomitinib	EGFR	NSCLC, gastric, head and neck cancer, glioma
Erlotinib	EGFR	NSCLC, pancreatic cancer
Gefitinib	EGFR	NSCLC in carriers of activating EGFR-mutations
Lapatinib	HER-2, EGFR	HER-2 positive breast cancer
Vandetanib	EGFR, VEGFR2,	NSCLC, medullary thyroid Cancer
XL647	EGFR, VEGFR2	NSCLC
Sorafenib	VEGFR-2/3	Renal cell carcinoma, hepatocellular Carcinoma
Pazopanib	VEGFR, PDGFR	Renal cell carcinoma,
Ponatinib2	BCR-ABL	Patients with CML for which Imatinib, Nilotinib, and Dasatinib are not appropriate
Sunitinib	VEGFR 1/3, KIT PDGFR-A/B	Renal cell carcinoma
Cediranib	VEGFRs	NSCLC, kidney and colorectal cancer
Lenvatinib	VEGFR2, 3	Approved for thyroid cancer
Tivozanib	VEGFR1, 2, 3	RCC, breast cancer
Vatalanib	VEGFR2	NSCLC, DLBCL, colorectal adenocarcinoma
EKB-569	EGFR, ErbB2	NSCLC, colorectal
BIBW2992	EGFR, ErbB2	NSCLC, breast

4.2. Cytoplasmic Signaling Intermediates

4.2.1. Ras/Raf/MEK/ERK Pathways

Ras is the most frequent oncogene in human cancers, with mutational activation being detected in approximately 30% of human tumors [41]. The three human RAS genes encode four highly related 188 to 189 amino acid proteins, designated as H-RAS, N-RAS and K-RAS (K-RAS4A and K-RAS4B). The Ras family members are anchored to the cytoplasmic side of the plasma membrane by carboxylterminal farnesylation. This localization places the Ras in close proximity to adaptors, the growth factor receptor bound protein 2 (Grb2) and the nucleotide exchange factor son of seven less (SOS), to mitigate the exchange of nucleotide guanosine diphosphate (GDP) bound to Ras with guanosine triphosphate (GTP) in the cytosol. This exchange activates Ras conformationally, allowing its interaction with a number of downstream effectors [42].

Ras is activated by cellular stimuli to a GTP-bound state, leading to the recruitment of Raf from the cytosol into the cell membrane where it becomes activated. Activated Raf leads to the activation and phosphorylation of MEK1 and MEK2, which then activates ERK1 and ERK2. When ERK is activated, it translocates into the nucleus and phosphorylates

transcription factors that can promote cellular growth and prevent apoptosis [43]. Termination of Ras activation occurs on hydrolysis of the GTP to GDP, but Ras proteins have intrinsically low GTPase activity. Thus, the GTPase activity is stimulated by GTPase-activating proteins such as NF-1 GTPase-activating protein/neurofibromin and p120 GTPase activating protein thereby preventing prolonged Ras stimulated signaling [19].

Ras activation through the Raf/MEK/ERK pathway modulates the activity of nuclear factors such as Fos, Jun and AP-1, which regulate the transcription of genes that are required for proliferation [44]. Aberrations in the RAS-MAPK complex are implicated in several human cancers; render them an attractive therapeutic target [51]. Because of the cross talk at the cellular level, aberrant upstream EGFR signaling and other receptor signaling (*i.e.* VEGFR and PDGFR) may cause activation of Ras/Raf/MEK/ERK signaling. Thus, an effective blockade of the Ras/Raf/ MEK/ERK pathway can be achieved using small molecules, such as sorafenib, selumetinib (AZD6244), and regorafenib [43].

A variety of agents that disrupt signalling through Ras and downstream proteins are under development. They can be functionally characterized as those agents that inhibit Ras protein expression (such as the oligodeoxynucleotide ISIS 2503), those that inhibit Ras processing (in particular, the farnesyl transferase inhibitors R115777, SCH 66336 and BMS 214662), and those that inhibit the downstream effectors Raf (such as the oligonucleotide ISIS 5132 and the small molecule BAY 43-9006) and MEK, which is inhibited by CI-1040 [44, 45]. PD98059 is an important inhibitor of MAPK cascade that lies downstream of Ras pathway and thus is effective in many tumors [22]

MEK inhibitors are sub-divided into two major classes, ATP non-competitive and ATP competitive inhibitors. Most of the known MEK inhibitors are noncompetitive i.e. they do not directly compete for the ATP–binding site. Rather they bind to a unique allosteric site adjacent to the ATP site. This explains the high specificity of the non-competitive MEK inhibitors. MEK1/2 inhibitors are currently being evaluated in phase I clinical trials of advanced cancer patients are AZD8330, RO5126766, RO4987655, TAK-733 and AS703026, XL518. Other novel MEK1/2 inhibitors such as RO4927350, RO5068760 and PD318088 have recently been reported on preclinical models [36].

Compounds like CI-1040/PD-184352, RDEA-119, PD-0325901, RO4987655, TAK733, Pimasertib, Cobimetinib, RO5126766, PD098059, SL-327, UO126, MEK162 (Binimetinib), RO5068760, Trametinib, Refametinib molecules were found to be MEK inhibitory and potential option for cancer treatment [46]. Other findings indicated that Tan-IIA have a potential to inhibit MiaPaCa-2 human pancreatic cancer cells; the molecular mechanisms underlying this inhibitory effect may be involved in downregulating EGFR, IGF1R and VEGFR expression, and dual blockade of the Ras/Raf/MERK/ERK and PI3K/AKT/mTOR pathways [47]. Everolimus and sirolimus (mTOR inhibitor) that is used for the treatment of several tumors, and it has been tested in combination with anti-cancer drugs against cancer of different types and found to be stabilize the disease. Other study reported that Copanlisib and BKM120 (PI3K inhibitor) has been used for patients with solid tumors, resulting in high toxicity rates [48].

Posttranslational modification of Ras

These modifications include prenylation, proteolysis, carboxymethylation, and palmitoylation. Posttranslational modification and is catalyzed by 3 different enzymes: protein farnesyltransferase (FTase), protein geranylgeranyltransferase type I (GGTase I), and geranylgeranyltransferase type II (GGTase II) [49]. The first modification is catalyzed by farnesyltransferase to cause covalent addition of the farnesol group from farnesylpyrophosphate FPP. Proteolytic degradation to remove the AAX residues, followed by carboxylmethylation of the farnesyl-cysteine residue donor: *S*-adenosyl methionine, SAM., complete the CAAX-signaled modifications. FTI inhibition of Ras farnesylation renders Ras completely cytosolic and nontransforming [45, 49, 50].

A. Farnesyltransferase inhibitors (FTIs)

FTIs are a new class of biologically active anticancer drugs. They inhibit farnesylation of a wide range of target proteins, including *ras*. It is thought that they block *ras* activation through inhibition of the enzyme farnesyl transferase, ultimately resulting in cell growth arrest. Although FTIs were originally designed to target the *ras* signal transduction pathway, it is now clear that several other intracellular proteins are also dependent on posttranslational farnesylation for their function [51]. The FTIs entered in clinical development, so far, are R115777 (Zarnestra), SCH-66336 (Sarasar), L-778, 123 and BMS-214662 [52]. Finally, inhibitors of GGTase I have also been considered, to block the activities of K-Ras and N-Ras when treated with FTIs [36].

B. RAF Inhibitors

Several small molecule inhibitors of BRAF have been prospectively developed over the last decade, including nonselective ones and more recently highly selective ones. Selective BRAF inhibitors are gaining exclusively interest as being significantly more effective clinically. The latest generations of highly specific and potent BRAF inhibitors offers a significant improvement for mutant BRAF and have fewer off-target effects and that have been evaluated currently under preclinical or clinical investigation include AZ628, XL281, GDC-0879, SB590885, LGX818, dabrafenib (GSK2118436), vemurafenib, and its analog PLX472 Of these, vemurafenib and dabrafenib are the most comprehensively investigated. Vemurafenib is a potent ATP-competitive RAF inhibitor [53].

4.2.2. PI3k-Akt-mTOR-Targeted Therapy

The PI3K/Akt/mTOR pathway is crucial in carcinogenesis. This pathway is activated when growth factors bind to membrane receptors, such as EGFR and IGF-R1, which engage and activate PI3K. When PI3K is activated, a cascade of downstream effectors such as Akt and mammalian target of rapamycin (mTOR) are produced. Once activated, Akt leaves the cell membrane to phosphorylate intracellular substrates.

Phosphorylation can lead to the promotion of cell survival as well as positively modulating mTOR function [43]. PI3K/AKT not only plays an important role in cell proliferation by acting on the anti-apoptosis and cell cycle, it also plays a role in protein translation and synthesis via mTOR as well as angiogenesis. It has been reported The PI3K pathway is aberrantly activated by a number of different mechanisms in cancers. These include genetic mutation and/or amplification of key pathway components, such as amplification or mutation of the PI3K catalytic subunit, mutation or deletion of the phosphatase PTEN, amplification or mutation of the gene encoding for the PI3K effector protein kinase AKT, as well as constitutive activation of RTKs or other less frequent events [54].

The significant role of the PI3K/Akt/mTOR pathway in the initiation and development of cancer suggests that this path way may be an appropriate target for cancer therapy. Such therapy may involve inhibiting cell proliferation, enhancing apoptosis, and restoring the sensitivity of cancer cells to chemotherapy. PI3K inhibitors may be classified into several functional categories: PI3K inhibitors, dual mTOR1/mTOR2 inhibitors, Akt inhibitors, mTOR1inhibitors, and dual PI3K/mTOR inhibitors. These inhibitors may exhibit differences in their affinity for different isoforms of these proteins. Derivatives of these inhibitors are more selective and are highly effective in targeting the PI3K/Akt/mTOR pathway [55].

A. PI3K Inhibitors

PI3K catalyzes the addition of a phosphate to phosphatidylinositol-4, 5-bisphosphate (PIP2) to form phosphatidylinositol-3, 4, 5-triphosphate (PIP3), which initiates many of its tumorigenic activities via Akt. Akt is recruited to the plasma membrane by PI3Kmediated formation of PIP3, leading to Akt phosphorylation at thr308 and Ser473 (via phosphoinositide dependent kinase-1 and phosphoinositide-dependent kinase-2, respectively). Akt phosphorylation at these 2 sites activates its kinase function, leading to downstream signaling that promotes proliferation and inhibits apoptosis. The PTEN tumor suppressor gene encodes a phosphatase that catalyzes the dephosphorylation of PIP3, thus inhibiting activation of the Akt pathway. When PTEN is altered, the Akt pathway can become constitutively active [35].

Several clinical trials targeting the PI3K/Akt/mTOR pathway are ongoing. The first PI3K inhibitors identified were LY294002 and wortmannin, a natural product from *Penicillium wortmannii*. However, these two inhibitors have been found to be toxic in animals. Several different types of PI3K inhibitors have also been tested against various tumor types in clinical trials. A phase I study on the safety of BYL719 and an HSP90 inhibitor, AUY922, in patients with advanced gastric cancer is ongoing [55].

B. AKT inhibitors

There are two main classes of AKT inhibitors in clinical development: ATP competitive and allosteric AKT inhibitors. ATP competitive AKT inhibitors are AKT kinase inhibitors. Because of the shared homology of the ATP binding pocket among various kinases. AZD5363 is a potent AKT kinase inhibitor that has pharmacologic properties consistent with AKT inhibition. It inhibited the growth of a range of human tumor. Allosteric AKT inhibitors bind to the PH domain of the AKT enzyme forming drug enzyme complexes. Due to conformational changes, translocation of AKT to the plasma membrane, a step essential for AKT activation, is disrupted. Such a conformation-based approach circumvents the issue of kinase selectivity often seen with ATP competitive AKT inhibitors. MK2206 is an allosteric AKT inhibitor that selectively inhibits AKT1, 2, and 3 isoforms [56].

C. mTOR Inhibitors

mTOR inhibitors either inhibit mTORC1 only, or are dual mTORC1/2 inhibitors. mTORC1 inhibitors including everolimus, temsirolimus, ridaforolimus, etc. which are approved as one of standard treatments for renal cell carcinoma and pancreatic neuroendocrine tumors. In hormone-receptor-positive breast cancer, the significant activity of mTOR inhibitor has been shown in a large randomised study. All these agents have similar structure and mechanism of action but different pharmacokinetic properties. Indeed, all these drugs are small molecule inhibitors that function intracellular, forming a complex with the FK506 binding protein-12 (FKBP-12) that is then recognized by mTOR. The resulting complex prevents mTOR activity, leading to inhibition of cell cycle progression, survival, and angiogenesis [57].

Second-generation mTOR inhibitors that target the catalytic sites of both mTORC1 and mTORC2 have been developed. In preclinical studies, the mTORC1/2 inhibitors AZD8055 and OSI-027 resulted in dose-dependent growth inhibition in a variety of cell lines including endometrial cancer models. AZD8055, OSI-027, and INK128 are currently in early-stage clinical trials in solid tumors [19, 58].

5. Conclusions and Future Directions

Better understanding of cell signaling pathways and their modulation by various negative and positive signals simultaneously activated by anticancer agents may prove particularly valuable in cancer therapy. Proteins involved in cell proliferation, survival, differentiation and death regulation could be used as new targets for anticancer drugs, and simultaneous signals may be manipulated to increase the efficacy of anticancer drugs. Thus, analysis of the molecular mechanisms of cell signaling pathways has dramatically increased the field of anticancer drug pharmacology and suggested new strategies for tumor cell sensitization or normal cell protection, some of which might be tested in clinics in the near future. As reflected in current review, cell surface available molecules and protein kinases continue to be the most favored targets for anticancer drug discovery. Additional inhibitors of the ERK MAPK cascade will provide effective antineoplastic agents for the treatment of a wild range of human cancers, including those where our current regimen of drugs are disappointingly ineffective. Many inhibitors of EGFR, VEGFR, Ras, Raf and PI3k-Akt-mTOR inhibitors

have been developed that target different components of ERK signaling, agents already approved and added to our expanding repertoire of anticancer agents.

It is expected that many more targeted therapies will come into routine clinical use. A future direction for small molecule tyrosine kinase inhibitors will be to combine them to overcome treatment resistance. Monoclonal antibodies will be modified to become carriers for radiation or cytotoxic drugs and will be enhanced to increase their immune effects.

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