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The Human Kinome: Its Role and Importance in Cancer and the Associated Therapeutic Strategies

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ABSTRACT

Background and Objective: Kinome refers to the complete set of protein kinases encoded in the genome. The most common type of post-translational modification is phosphorylation, with more than two-thirds of all human encoded proteins being phosphorylated by protein kinases. Phosphorylation as an important regulatory factor in the activity of proteins greatly expands the flexibility of the epigenome. Thus, protein kinases often promote cell proliferation, survival, and migration by participating in intracellular pathways and are associated with carcinogenesis when overexpressed or activated. The main goal of this study is to investigate the role of kinase enzymes in causing cancer and to investigate their potential as drugs in the treatment of various types of cancer.

Methods: In this review, by searching Scopus, PubMed, Web of Science and ScienceDirect databases, articles published between 2010 and 2022 were selected and analyzed using the keywords "cancer, human kinome, kinase and kinase inhibitor".

Findings: 64 articles were selected according to the research topic and 11 articles were excluded due to the lack of relation to the main keywords. In this study, the role of kinases in cell proliferation and human cancers has been investigated, and kinase inhibitors in combination with other common treatments such as chemotherapy or radiation therapy can be mentioned as a new and promising approach in cancer treatment.

Conclusion: Based on the results of this study, kinases are known as one of the most important components of cell growth and proliferation, so that they play an important role in the cancer process with excessive activity. This study shows that controlling and inhibiting the kinase family to overcome cancer cell growth has good benefits.

Keywords: *Human Kinome, Kinase, Post-translational Modifications, Cancer, Kinase Inhibitor.*

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Introduction

The kinome is known as the complete set of kinases encoded in the genome (1). Between 1.7 and 2.5% of the genome (approximately 500 genes) are responsible for coding the human kinome. Kinome is one of the largest superfamilies of homologous proteins with 538 kinase enzyme members (2). Kinases are enzymes that catalyze the transfer of gamma phosphate from adenosine triphosphate (ATP) to alcohol groups of serine, threonine, or tyrosine amino acids in proteins (3). Changes in protein activity, different intracellular orientation, and different relationships with other proteins are the result of phosphorylation in the protein substrate (4). Figure 1 shows the phylogenic tree of the human kinome (5).

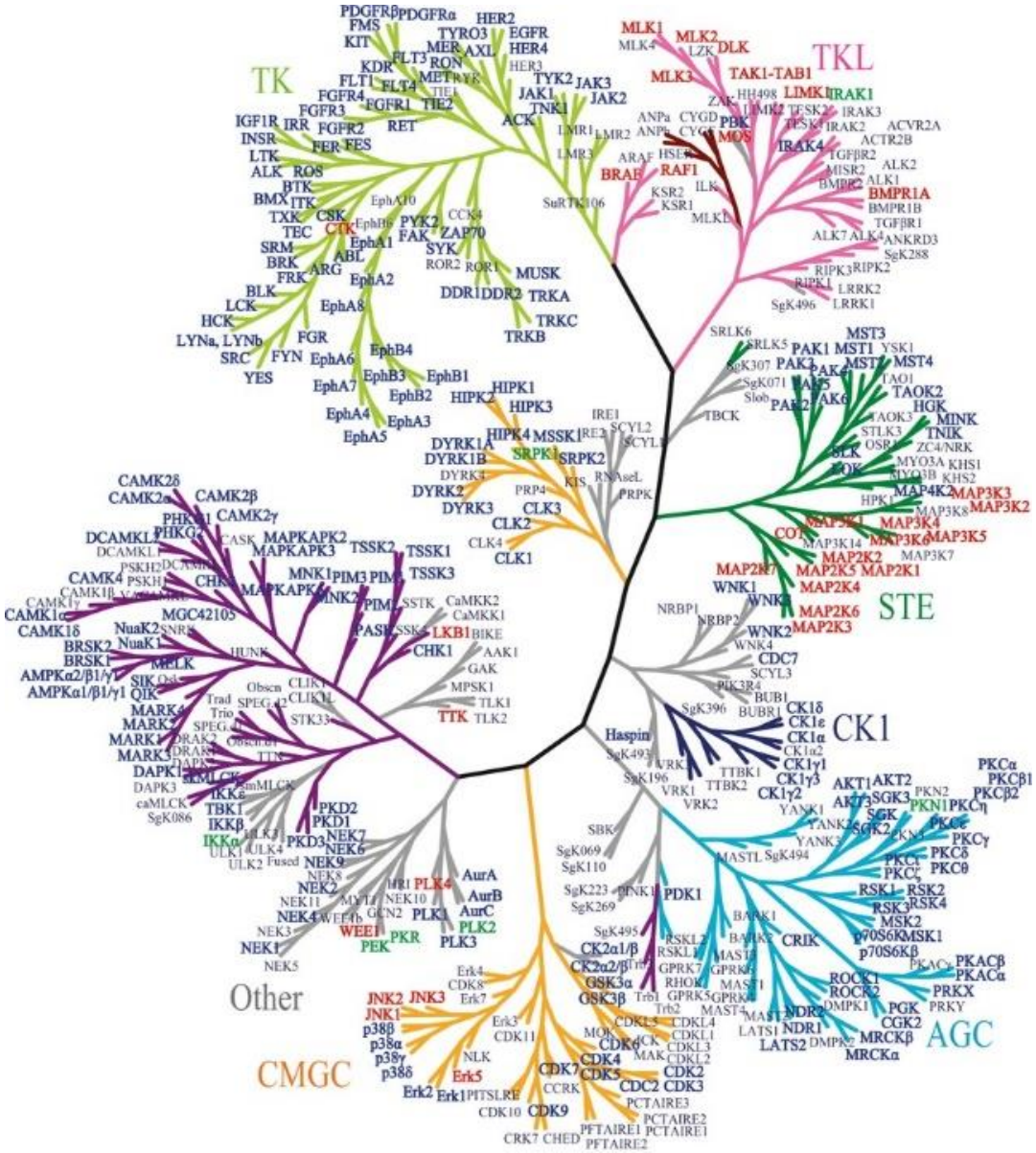


Figure 1. Phylogenetic tree of human kinome and its families (5). **The human kinome has at least 8 major subfamilies, and each subfamily contains several kinase enzymes.**

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UniProt, PhosphoSitePlus and PhosphoNET online databases are used to identify phosphorylation and its different locations. According to statistics and data reported in the UniProt database, the most common type of post-translational modification (PTM) is related to phosphorylation, and more than two-thirds of all human encoded proteins are phosphorylated by kinases (6, 7). More than 200,000 phosphorylated regions on proteins have been reported in the PhosphoSitePlus and PhosphoNET databases, and 760,000 regions with a high potential for phosphorylation have been predicted (8). As a result, phosphorylation as an important regulatory factor in the activity of proteins greatly expands the flexibility of the epigenome (9).

The human kinome consists of two main subgroups of lipid kinases and protein kinases (Figure 2) (10). Lipid kinases have approximately 20 members and members of this group include sphingolipid kinase and phosphoinositide kinases and play an important role in the downstream signals of many protein kinases (11). Protein kinases have two subgroups, eukaryotic (Eukaryotic Protein Kinase, ePK) and atypical (Atypical Protein Kinase, aPK) (12). Eukaryotic protein kinases include 478 kinase enzymes and have 8 subfamilies (Table 1) (13). Unusual protein kinases are not similar in sequence to the eukaryotic group and include 40 kinase enzymes (14).

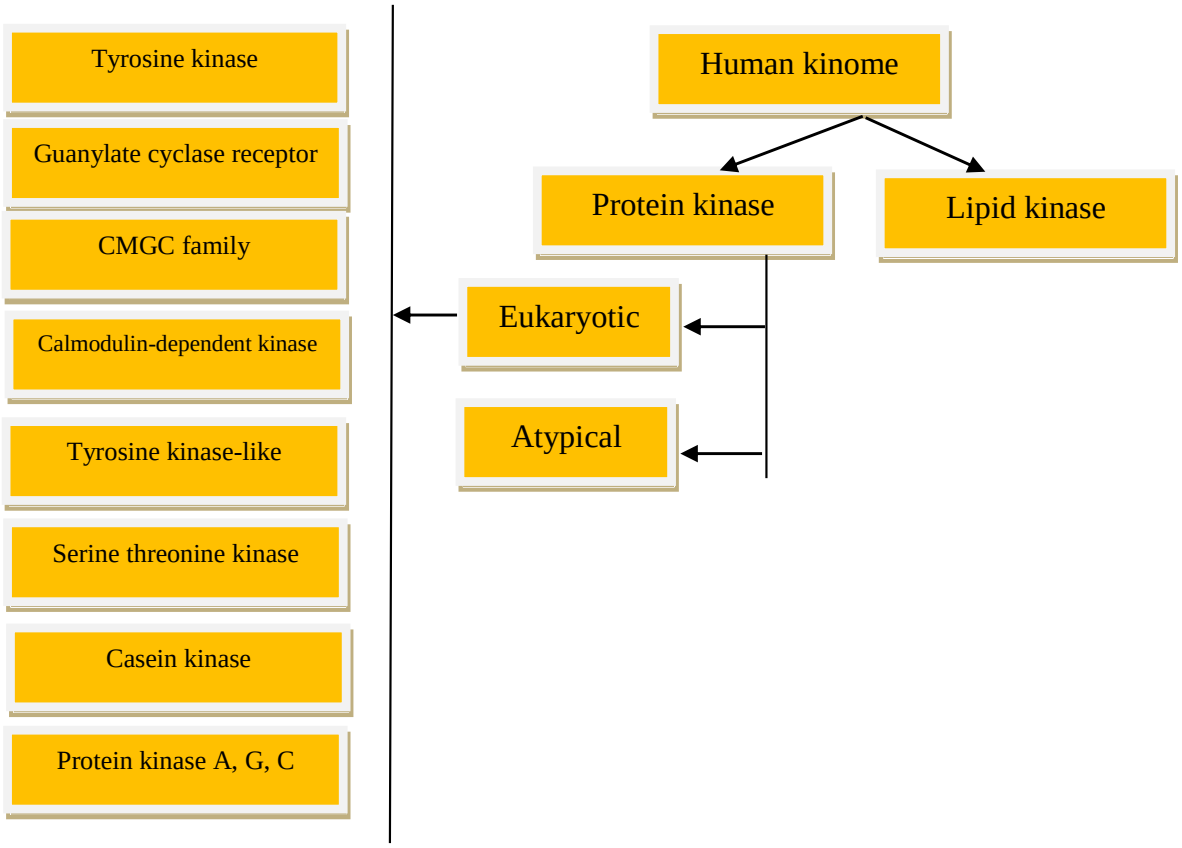


Figure 2. Classification of human kinome with subfamilies. **The human kinome consists of two main subfamilies, protein kinase and lipid kinase.**

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Table 1. Subfamilies of eukaryotic protein kinases (14-21)

Subfamilies of protein kinases	Origin of the name	Details	Reference
STE	Sterile kinase	It includes many protein kinases that are involved in MAP kinase cascades and activate each other sequentially.	(14)
AGC	From protein kinases A, G and C (PKA, PKG, PKC)	A subgroup of serine/threonine kinases is divided based on the sequence of their catalytic domain. PKA is dependent on cAMP, PKG is dependent on cGMP and PKC is dependent on calcium.	(15)
CAMK	Calcium-calmodulin-dependent protein kinases	Serine/threonine kinases that act in response to increased intracellular calcium ion concentration and actually control the expression of several transcription factors in different pathways.	(16)
CK1	First Casein kinase 1 and now Cell kinase 1	Serine/threonine kinases that act as regulators of signal transduction pathways.	(17)
CMGC	From the family members of CDK, MAPK, GSK3 and CLK	CDKs regulate cell cycle progression at different stages. MAPK kinases play a key role in the processes of proliferation, differentiation and death. GSK3 was first identified as a key enzyme in glycogen metabolism and now regulates a range of functions including the WNT pathway. CLK phosphorylates proteins involved in pre-mRNA processing and releases them into the nucleoplasm.	(18)
TK	Tyrosine Kinase	Members of this group specifically phosphorylate amino acid tyrosine on protein. TKs are located as receptors on the cell surface (RTK) or act in the cytosol (CTK).	(19, 20)
TKL	Tyrosine Kinase-Like	This group is similar to tyrosine kinases in terms of sequence, but they are serine threonine kinases in terms of function.	(14)
RGC	Receptor Guanylyl Cyclase	These are single-transmembrane receptors and have an active guanylate cyclase domain and a catalytically inactive kinase domain on the intracellular side. The guanylate cyclase domain makes the messenger cGMP, and the kinase domain may have a regulatory role, leading to ATP binding.	(21)

In a study by Zhang et al. (4), the intracellular map of the human kinome was reported. The highest percentage of kinome is related to cytosol (50.2%), nucleus (16.4%) and plasma membrane (10.3%), respectively, while mitochondria, endoplasmic reticulum, Golgi, and vesicle each contain less than 5% of the kinome (4). Table 2 shows the distribution of kinases in the cell according to their function (22). For example, the protein IGFBP-3 (Insulin-like growth factor-binding protein 3), which is known as the main transporter of IGF (Insulin-like growth factor), can also act independently of IGF (TMEM219, EGFR and

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LRP pathways) in regulating growth, survival and cell death (23-26). Phosphorylation of IGFBP-3 at serine-156 by the casein kinase 2 is necessary to inhibit cell growth and promote apoptosis, and also phosphorylation of IGFBP-3 is required for its entry into the nucleus and interaction with nuclear components (26). Indeed, phosphorylation of IGFBP-3 results in the loss of its affinity for IGF-I and ensures its release from the IGFBP-3/IGF-I complex before entering the nucleus. Therefore, post-translational modifications can change the three-dimensional composition of IGFBP-3 protein and regulate its IGF-dependent and independent processes (23-26).

The main purpose of this review article is to study the role of kinase enzymes in cancer and the need to investigate its potential as a drug in the treatment of all types of cancer.

Table 2. Distribution of kinases in the cell according to their function (22)

Row	Cell location	Protein kinase family	Cell function	Example
1	On cell membrane	Receptor tyrosine kinase (RTK) family	They play the role of receptors for hormones and growth factors to regulate cell responses such as proliferation, survival and migration.	INSR, ERBB, EPH, FGFR, PDGFR, VEGFR, MET, RET, etc.
		Transforming growth factor β (TGF-β) receptor	By affecting cell proliferation, cell migration and recruitment, they are mainly involved in cell cycle arrest.	ACVR1B, ACVR2A, ACVR2B, TGFβR2, BMPR2, etc.
2	In the cytoplasm and close to the cell membrane	Cytoplasmic tyrosine kinases (CTK) family	These kinases usually act downstream of specific cell surface receptors that lack catalytic activity.	JAK1, JAK2, JAK3, ABL1, SRC, etc.
3	Cytoplasm	Phosphatidyl-inositol 3-phosphate kinase (PI3K)	They are involved in the control of cell growth, proliferation and survival.	PI3KCA, mTOR, AKT, etc.
		MAPK family	They control proliferation, differentiation, cell survival, apoptosis and inflammation.	MAPK cascade
		Kinases associated with the cytoskeleton	They control cell migration and contractions.	DCLK1, KALRN, MYO3A, TRIO, BRSK1, etc.
		Cell cycle related kinases	They play a role in controlling the cell cycle and proliferation.	CDK4, CDK6, PLK2, AURKA, NEK9, etc.
4	Nucleus	DNA related kinases	They control DNA repair.	ATM, ATR, CHEK.
		Transcription-related kinases	They play a role in controlling The transcription and expression of certain genes.	TAF1, CDK12, BRD4, etc.

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Methods

In this review article, the studies available in Scopus, PubMed, Web of Science and ScinceDirect databases were reviewed during the years 2010 to 2022 using the keywords "cancer, human kinome, kinase and kinase inhibitor".

Results

64 articles were found according to the research topic and 11 articles were excluded from the study due to the lack of relation with the main keywords.

Kinases mediate signal transmission in the cell and thus control many cellular processes including proliferation, differentiation, survival, transcription, cell migration, metabolism, interaction with the immune system and differentiation of the cytoskeleton (27). Therefore, when kinases are overexpressed or activated, they are associated with carcinogenesis or oncogenesis (9). Furthermore, genome-wide studies have shown that mutations of kinases are associated with the initiation, promotion, progression and recurrence of cancer (9). In 2004, the Cancer Gene Census (CGC) reported 291 genes involved in cancer as "cancer genes" and showed that protein kinases (27 genes) were the most common genes involved in cancer (22). Hundreds of kinases have overlapping and complex roles in cell transformation, tumor initiation, survival, and proliferation (9). More than 450 kinases are involved in the development or progression of diseases, and it is worth noting that 448 kinases are related to the genetics and signaling of cancers, and 230 kinases are potentially involved in the development of other diseases as well (10).

Several mechanisms lead to dysregulation of kinases that increase their oncogenic potential, including overexpression, translocation and fusion, point mutations, or dysregulation of upstream signals (28, 29).

In the study of Wilson et al., 122 kinases with a significant amount of mutation and 78 kinases with changes in the number of gene copies in all types of cancer were reported (10). Figure 3 shows the distribution of mutations and changes of all types of kinases in each family.

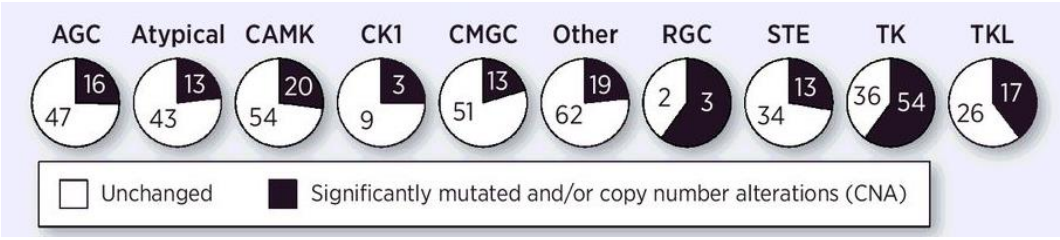


Figure 3. Mutations and copy changes of various kinase families in cancer (10). Black color indicates mutation or changes in the number of enzyme copies in that family, and white color indicates no change.

Most changes in human malignancies are related to the tyrosine kinase family (10). Mutations in tyrosine kinase receptors lead to receptor activation followed by uncontrolled activation of signal transduction pathways (30). Non-receptor tyrosine kinases such as Janus kinase (JAK) and Src family play an important role in cancer cell proliferation, survival and invasion (31). In fact, c-Src was proposed as the first known proto-oncogene in 1978 (32). Among serine/threonine kinases, protein kinase A, MAPK, RAF, protein kinase B, mTOR, GSK-3, and cyclin-dependent kinases (CDKs) are among the most common drivers of cancer in humans (33). It is activated by binding of cAMP to the regulatory subunits of protein kinase A

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and can then phosphorylate and regulate a variety of target proteins. It has also been shown that overexpression of cAMP-dependent protein kinase A is associated with cell proliferation and neoplastic changes (34, 35). MAPK is a complex series of signal transduction pathways that connect extracellular signals into the cell and its function is to regulate important processes such as cell proliferation, differentiation, and death (36). RAF kinase is activated by growth factors and its function is to stimulate cell division and growth and forms part of the RTKs/RAS/RAF/MEK/ERK pathway (37). Most solid tumors are clearly characterized by mutations along the above signaling pathway genes (38). By phosphorylating GSK-3, protein kinase B or Akt targets it for proteasome degradation (39). Akt is often activated in human cancers, so GSK-3 is often inactivated (33). Cyclin-dependent kinases are intracellular serine/threonine kinases whose central activity is cell cycle regulation and responsible for cell progression through its various checkpoints (40). Dysregulation of various cyclin-dependent kinases such as CDK1, CDK2, CDK3, CDK4, and CDK6 are a well-known hallmark of cancer (33).

Investigating the kinome as the complete set of protein kinases encoded in the genome has not only contributed to the advancement of the field of cancer biology, but also led to the emergence of targeted therapy in cancer and has become an attractive target for the treatment of many types of cancer (41). In fact, targeting the kinases that play an important role in oncogenic changes and metastasis has led to a significant change in the clinical management of cancer (9). Nowadays, various types of kinase inhibitors are proposed as targeted therapeutic strategies in human malignancies (9). Kinase inhibitor drugs have a broad spectrum and are also less toxic to non-cancerous cells, thus selectively eliminating tumor cells with much lower toxicity (9). As a result of inhibiting the activity of kinases in patients under treatment, several anti-proliferative mechanisms have been established that have led to clinical improvement of cancer (9). Currently, 35 kinase inhibitor drugs have been approved by the Food and Drug Administration, and the list is shown in Table 3 (9).

Table 3. List of kinase inhibitor drugs approved by the Food and Drug Administration

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

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Types of kinase inhibitors are divided into five categories based on the mechanism of action: I, II, III, IV and V:

Type I kinase inhibitors compete with ATP in binding to the enzyme due to their similarity to the purine ring of the ATP molecule (42). These inhibitors interact with the active conformation of kinases and actually change its structure so that phosphate transfer does not take place (42). The types of drugs in this family include Bosutinib, Cabozantinib, Ceritinib, Crizotinib, Gefitinib, Pazopanib, Ruxolitinib and Vandetanib (42). Type I kinase inhibitors have had good clinical success on a large scale, but adverse side effects have also been reported. This family has less selectivity for the kinase, so the potential for off-target side effects such as cardiotoxicity and problems in cardiac tissue function has been observed (9, 42, 43).

Type II kinase inhibitors act by targeting the inactive conformation of the kinases and reversibly interact with the unphosphorylated catalytic site of the kinases (42). In fact, these inhibitors lead to the formation of single or multiple hydrogen bonds with the hinge region of the kinase (44). The types of drugs in this family include Imatinib, Sorafenib, Axitinib and Nilotinib (9). Compared to type I kinase inhibitors, type II kinase inhibitors have a higher selectivity in inhibiting the enzyme and thus will cause less risk to other non-cancerous cells (9, 42, 43).

Type III kinase inhibitors inhibit the enzyme in the allosteric region, outside the catalytic site and the ATP pocket, and are also known as allosteric inhibitors (43). Types of drugs in this family include Trametinib and GnF2 (44). Type III or allosteric inhibitors show the highest degree of kinase selectivity; that's because the allosteric site is unique in each kinase (43). In general, targeting kinases using allosteric inhibitors is a critical approach to overcome obstacles in kinase inhibitors such as limited selectivity, off-target side effects, and drug resistance (9, 43, 45).

Type IV kinase inhibitors bind at the substrate site of the enzyme and are also known as direct substrate inhibitors. The main drug of this family is ONO12380. Type IV kinase inhibitors do not compete with ATP and provide a higher degree of selectivity against type I and II kinases (9, 43, 46).

Type V kinase inhibitors form an irreversible covalent bond with the active site of the kinase, effectively targeting the active site nucleophile cysteine; therefore, they are also known as covalent kinase inhibitors (47). The types of drugs in this family include Afatinib, Ibrutinib and HK1-272 (9, 43). Type V kinase inhibitors have a longer half-life, thereby minimizing off-target side effects (9, 43). Covalent inhibitors have significant potential for discovery; because 200 different kinases have a cysteine chain that is located near the ATP pocket in the active site (9, 43).

Recently, it has been reported that kinase inhibitors cause drug resistance in some cancers, which can be a major challenge in these patients. As an example, in lung cancer (due to mutation in ALK kinase [Anaplastic Lymphoma Kinase]), after a period of using a type I kinase inhibitor such as Crizotinib or type II such as Alectinib, resistance mutations in ALK by tumors have been observed (48). A new strategy to overcome the drug resistance of kinase inhibitors is the use of a new system of targeted proteolysis of ALK (ALK-PROTAC). PROTAC or Proteolysis Targeting Chimera, by entering the target cell as an interface, creates a complex of ALK and E3 ubiquitin ligase, and ALK is exposed to polyubiquitination, and finally the delivery of the system is degraded and its amount decreases in the target cell (48). Currently, the PROTAC technique has been successfully used to selectively degrade various protein targets such as BCR-ABL, TBK1, epidermal growth factor receptor (EGFR), HER-2, and c-MET. In conclusion, the proteolysis system provides a promising strategy to treat cancer patients and overcome drug resistance in the future (49-51).

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Discussion

After numerous pathophysiological changes and as a result of the dysregulation of kinases, uncontrolled cell proliferation and the process of metastasis occur. In a study by Chu et al. (52), the important role of protein kinase signaling pathways in tumor development, cancer recurrence, metastasis, and treatment resistance has been discussed, and it is in line with the findings of this study.

Targeted therapies, such as kinase inhibitors, block specific cancer-inducing pathways or pathways that are specifically activated in cancer cells by different mechanisms, and are of great importance. Compared to the toxic effects of chemotherapy on non-targeted tissues, they can have a more effective approach and improve the patient's quality of life (53).

Kinases represent an important targeting strategy for the development of anticancer drugs, so that today about one-third of all protein targets being researched in cancer are based on kinase inhibition. Kinase inhibitors mainly differentiate between non-malignant cells and proliferating cancer cells, overcoming these fundamental drawbacks of traditional cancer treatments.

Common anti-cancer treatments such as chemotherapy (such as Taxol) or radiation therapy are used simultaneously in combination with kinase inhibitors, as a new and promising approach in cancer treatment (53).

Conflict of interest: None of the authors of this study have any conflict of interest for publishing the article.

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