

Advances in Kinase Inhibitors Anticancers: Highlights and Challenges

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History:

- Received: March 26, 2020
- Accepted: June 18, 2020
- Published: Sept 1, 2020

DOI: <https://doi.org/10.31838/ejmcm.07.02.02>

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INTRODUCTION

One of the major life-threatening diseases is the malignancy which has a high mortality and morbidity rates. However, the diagnosis and the treatment of this serious disease have been improved, there are a significant number of tumors that are considered resistance to the available treatment. This in turn necessitates the search and research for new, effective, and safe therapies. At the meantime, many of the utilized anticancers are considered relatively toxic as they possess a low selectivity pattern, profound adverse reactions, and ease of arising drug-resistance [1]. In the past few years, many of cellular processes have been revealed. For instance, in tumor cells the following cellular pathways were followed; tumor-cell signal transduction, regulatory processes of cell cycle, initiation of apoptosis, and many others [2]. Moreover, these clarified cellular processes can be utilized in producing anti-tumor drugs that targeting such processes. Consequently, utilizing the major cellular transduction's key enzymes concerning neoplastic cell multiplication has been considered a significant pathway to design and develop effective, safe, and hopefully specific anticancer drugs [3].

Protein tyrosine kinase (PTK) can be classified as one of the proteins that possess catalytic activity of the tyrosine kinase enzyme which is responsible for the transference of phosphate moieties from the ATP to the tyrosine amino acid residue that constituting many significant proteins, resulting in phosphorylating proteins, followed by regulating cell growth via the signal transduction, cell differentiation, and apoptosis [4]. Accordingly, any PTK disorders are able to cause a cascade of significant diseases leading to eventual tumorigenesis process [5]. Moreover, the faulty expressed PTK is correlated with invasive tumors and tumor-antitumor

drug resistance [6]. Consequently, the PTK has become as a hot area of drug research and development to target anti-tumor drugs. In this study, the authors aim to highlight the advances of TKIs and focus on some challenges of such therapies.

Types of kinase inhibitors

The types of TKIs can be sorted as follows:

First type

This type involves the ATP-competitors that resembles the purine ring of the adenine group of the ATP molecule. These TKIs bind to the active enzymatic site and manipulate the conformational pose of the enzyme [7, 8].

Second type

Unlike the first type, this type acts through targeting the kinase enzyme at its inactive configuration. Hence, the TKIs of the second type interact with the active site in its inactive form [9].

Third type

This type of TKIs binds allosterically (i.e. outside the catalytic region of the enzyme) to PTK. Some researchers have further subdivided these allosteric inhibitors into A and B subtypes depending on the site at which these inhibitors would bind [10].

Fourth type

This type is also known as substrate-directed inhibitors. This kind is characterized by the reversible binding with the PTK outside the active site. This in turn leads to higher selectivity pattern as they do not affect by the existence of ATP as they do not compete with this substrate [11].

ABSTRACT

Protein tyrosine kinase (PTK) is considered as one of the main signaling catalysts during the transduction of cell signal. The role of PTK is to transfer the ATP-γ-phosphate to the tyrosine moiety in the targeted protein. This, in turn, resulted in many cellular processes, including; phosphorylation, controlling cell growth, regulation of the cell differentiation, apoptosis and many other cellular processes. Accordingly, any faulty expression of PTK however, resulted in faulty cell multiplication. Nowadays, various PTKs are utilized as targets for the treatment of cancer.

The mechanism by which the tyrosine kinase inhibitors (TKIs) act as antitumor can be simplified as the TKIs prevent the ATP from reaching its binding site by competitory mechanism. This in turn will inhibit the phosphorylation of tyrosine kinase leading to suppress the tumor cell proliferation. TKIs have gained a great attention by researchers leading to discover many successful therapies, nevertheless, there are always challenges to be tackled.

In this work, the authors summarize the mechanism of TKIs, highlighted the successes and drawbacks of TKIs for anticancer therapies.

Keywords: Antitumor, Tyrosine kinase inhibitors, Protein tyrosine kinase.

Fifth type

This kind of TKIs is also known as covalent kinase inhibitors. As illustrated from the name, these inhibitors form an irreversible covalent binding with PTK active site [12,13].

CHALLENGES AND LIMITATIONS

One of the most challenges facing the TKIs is the development of kinase acquired drug-resistance via kinase mutations [14]. Acquired resistance is build-up after a while of successful treatment. While the other kind of drug resistance is so called de novo resistance which refers to initial failure of getting response since the first treatment [15, 16]. Changes in the lipophilic pocket of the binding site. This will affect primarily both first type and second type of kinase inhibitors [17]. It has been recorded as one-fifth of the cases of the acquired TKI resistance are also include the amplification of the MET (MET proto-oncogene, receptor tyrosine kinase) gene [18]. These mutations are considered important because tiny or no kinase activity alteration while it significantly confer the resistance to the applied kinase inhibitor drug molecules [19].

Another challenge is that of the obvious off-target multiple toxicities associated with TKIs. The toxicities of myocardium, thyroid gland, and the skin manifestations are exemplified in literatures to reveal this concept [20, 21]. For instance, there is a case report of "Diffuse Hypopigmentation Followed by Hyperpigmentation in an African American Woman with Hemangiopericytoma Treated with Dasatinib" [22]. This led to start thinking with other alternatives reported to be safe [23]. Nevertheless, clinical resistance to TKIs still the main challenge to be considered when designing kinase inhibitor drugs.

FUTURE DEVELOPMENTS

Therapeutic responses of patients receiving TKIs after clinical evaluation, showed a very variable effects from patient to another. Utmost all the new TKIs are developed utilizing the computer-aided drug design (CADD) rather than relying on the traditional screening and SAR studies [24-28]. Tackling the off-target activities of TKIs is pointed out and considered of such importance. This would reduce the undesired side effects and make the TKIs more tolerable to the targeted patients [29].

According to the above-mentioned strategies, the coming era of kinase-targeted anticancer drugs shows a very promising features that can be established to assist the advances in TKIs figure out the treatment obstacles.

CONCLUSIONS

The authors conclude that the drug design approach of TKIs is significantly progressed. For instance, around 33% of all targeted proteins in researches in pharmaceuticals are related to kinases. Basically, TKIs are considered a very significant, modern, and promising discipline of tumor-fighting strategy with an evidence based clinical beneficial effects.

SOURCE OF SUPPORT

Nil.

CONFLICT OF INTEREST

None.

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