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Review article

Exploiting polypharmacology for improving therapeutic outcome of kinase inhibitors (KIs): An update of recent medicinal chemistry efforts

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ABSTRACT

Polypharmacology has been increasingly advocated for the therapeutic intervention in complex pathological conditions, exemplified by cancer. Although kinase inhibitors (KIs) have revolutionized the treatment for certain types of malignancies, some major medical needs remain unmet due to the relentless advance of drug resistance and insufficient efficacy of mono-target KIs. Hence, "multiple targets, multi-dimensional activities" represents an emerging paradigm for innovative anti-cancer drug discovery. Over recent years, considerable leaps have been made in pursuit of kinase-centric polypharmacological anti-cancer therapeutics, providing avenues to tackling the limitation of mono-target KIs. In the review, we summarize the clinically important mechanisms inducing KI resistance and depict a landscape of recent medicinal chemistry efforts on exploring kinase-centric polypharmacological anti-cancer agents that targeting multiple cancer-related processes. In parallel, some inevitable challenges are emphasized for the sake of more accurate and efficient drug discovery in the field.

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1. Introduction

Considering the flaws of radiation and conventional cytotoxic agents, the emergence of target-based therapy represents a remarkable breakthrough during the efforts of scientific community to conquer human malignancies [1]. In today's therapeutic armory, small-molecule kinase inhibitors (KIs) have ranked as the predominant category of target-based anti-cancer agents [2,3]. The massive pharmaceutical investment in KIs has been aroused by some stunning strides in unraveling the molecular mechanism of oncogenic process since the beginning of this century [4]. Among these, identification of the intimate role of kinases in tumor genesis and progression is of particular importance.

The mutant kinases along with their mutant regulators, as oncogenes, frequently facilitate tumor cell survival, proliferation, differentiation and metastasis *via* dysregulating the growth-related signaling pathways [5–8]. Thus, pharmacological modulation of kinase function can endow a therapeutically desirable intervention in the oncogenic signaling process. Another stimulus to the enthusiasm in KI development stems from the druggable profile of kinases as drug targets [1,9]. Specifically overexpressed in targeted tissues, they provide an opportunity for efficient intervention while lowering toxicity. Alternatively, their ATP binding sites are commonly well-characterized, thereby accessible for small-molecule mimics to occupy them. Pioneering KIs, exemplified by imatinib, have revolutionized the therapy and provided a long-term of control for malignancies that exhibiting strict cell survival dependency on the targeted oncogenic kinases, embracing chronic myeloid leukemia (CML) and gastrointestinal stromal tumors [10–13]. However, numerous factors can compromise the response to KIs and an urgent demand for enhanced therapeutic efficacy exists in treating highly mortal cancers [14]. In particular, tumors tend to evade treatment mono-targeting a single kinase or solely ablating a single signaling cascade [15–18]. Owing to their clinical importance, the resistance to KIs has become a major complication affecting numerous cancers, kinases and drugs [19–24].

To tackle the obstacle, multi-targeted remedy [25,26] has been progressed in respect of the complicate pathology associated with malignancies, such as the frequent alteration of cancer cells and the redundancy of survival-related pathways. Two distinct strategies are involved in the multi-targeted therapy, the first being drug cocktail [27–30] and the second being exploiting polypharmacology to concomitantly modulate multiple oncogenic drivers with a single chemical entity [2,31]. Although synergetic effect has been fulfilled in a myriad of preclinical or clinical studies, drug cocktail suffers from some pharmacokinetic (PK) and pharmacodynamic shortcomings [31–33]. By virtue of the merits over drug cocktail, the exploit of polypharmacology is presently rapidly evolving and considerable efforts have been undertaken in the field to improve the response to KIs. Nonetheless, some issues remain to be addressed, including the challenges of identifying desirable target combinations and rationally designing polypharmacological agents. Hence, in this review, we provide an up-to-date account of the achievements in pursuit of multi-functional anti-cancer therapeutics for improving therapeutic efficacy of KIs and critically point out the underlying challenges in the field. The polypharmacological agents enumerated herein are mainly those interfering with distinct cancer-driving processes. Besides, various clinically important mechanisms upon which KI-resistance advances will be overviewed to direct the future development of less resistance-prone drugs.

2. Clinically important mechanisms inducing KI resistance

2.1. Extrinsic resistance

PK profiles, tumor microenvironment and gene polymorphisms constitute the target-cell extrinsic factors leading to KI-resistance. Principal PK factors impacting on cellular potency comprise drug capture in the extracellular space, delivery, absorption, tissue penetration, metabolic consumption, clearance as well as excretion [34]. Microenvironment-related resistance can be observed in gefitinib-treated EGFR-mutant non-small cell lung cancer (NSCLC), where the stromal cell paracrine HGF secretion resulted in the decreased therapeutic efficacy [35]. In addition, gene polymorphisms, as the most representative pharmacogenomic factor, also account for the discrepancy in drug efficacy and toxicity among patients [1,36], thereby necessitating the individually optimized dosing regimen.

2.2. Intrinsic resistance

The intrinsic resistance developed by tumors following mono-inhibition of a single kinase has posed a remarkable challenge to the clinical progress of KIs. Some of intrinsic resistance mechanisms are relevant to targeted kinase itself. Among them, the missense point mutation [37–40] leads to steric hindrance or conformational alteration, thereby preventing KI-binding and lowering its affinity. Besides, target gene amplification/overexpression and abnormal epigenetic activation can render tumors insusceptible to KIs as well [39,41]. Both of them are implicated in imatinib-resistance in CML patients. Beyond these, drug resistance can be acquired relying on mechanisms not involved with the targeted kinases. On one hand, owing to the critical biological role of some kinases, KI treatment can boost the function of a second surrogate kinase [42]. On the other hand, downstream effectors are among the components that may undergo mutation to adapt to a targeted therapy [43–45]. The last but not the least, the expression of multiple oncogenic kinases in various tumors, along with the molecular reciprocity among signaling cascades gives rise to redundancy in survival pathways, consequently making mono-therapy insufficient to trigger apoptosis [33,46–48].

3. Recent achievements in exploiting multi-functional therapeutics for improving the treatment outcome of kinase inhibitors

Attributed to tumors' multi-faceted capability of escaping from mono-therapy, rectification of oncoproteins at multiple levels or blockage of multiple oncogenic pathways represents a standard approach to harness the resistance to KIs. Despite increasing drug cocktails under clinical trials, multi-targeted inhibition with a single agent, termed as polypharmacology, can provide substantial therapeutic advantages, such as favorable patient compliance,