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Mini-review

Overcoming ABC transporter-mediated multidrug resistance: The dual role of tyrosine kinase inhibitors as multitargeting agents

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ABSTRACT

Resistance to conventional and target specific antitumor drugs still remains one of the major cause of treatment failure and patience death. This condition often involves ATP-binding cassette (ABC) transporters that, by pumping the drugs outside from cancer cells, attenuate the potency of chemotherapeutics and negatively impact on the fate of anticancer therapy. In recent years, several tyrosine kinase inhibitors (TKIs) (e.g., imatinib, nilotinib, dasatinib, ponatinib, gefitinib, erlotinib, lapatinib, vandetanib, sunitinib, sorafenib) have been reported to interact with ABC transporters (e.g., ABCB1, ABCC1, ABCG2, ABCC10). This finding disclosed a very complex scenario in which TKIs may behave as substrates or inhibitors depending on the expression of specific pumps, drug concentration, affinity for transporters and types of co-administered agents. In this context, in-depth investigation on TKI chemosensitizing functions might provide a strong rationale for combining TKIs and conventional therapeutics in specific malignancies. The reposition of TKIs as antagonists of ABC transporters opens a new way towards anticancer therapy and clinical strategies aimed at counteracting drug resistance. This review will focus on some paradigmatic examples of the complex and not yet fully elucidated interaction between clinical available TKIs (e.g. BCR-ABL, EGFR, VEGFR inhibitors) with the main ABC transporters implicated in multidrug resistance.

1. Introduction

The aim of the anticancer chemotherapy is the eradication of tumors and metastatic malignant cells. After the administration, chemotherapeutic agents encounter many obstacles and barriers (absorption through lipophilic membranes, distribution to the body, cells and tissues via blood stream), that importantly impact on the delivery of the drug (pharmacokinetics) [1–3]. Pharmacological effects and body's response are the result of therapeutic drug concentrations achieved at the target site (pharmacodynamics). Conventional anticancer drugs work at maximum tolerated doses and this feature governs the clinical management of patients suffering from cancer in medical practice. The narrow therapeutic index, the lack of tumor selectivity associated with important toxic side effects (including thrombocytopenia, neutropenia and anemia), as well as drug resistance that attenuates antitumor potency often require the suspension of the treatment [4,5]. Although not completely elucidated, drug resistance to antitumor agents depends on several mechanisms, including the administration of inadequate doses or scheduling of the drug, altered pharmacokinetics, or limited penetration of the drug into the tumor. The emergence of drug resistant tumors is importantly associated with tumor heterogeneity [6]. This finding implies that, on exposure to anticancer drugs, cancer cells insensitive to the

Abbreviations: ABC, ATP binding cassette; ADME-tox, absorption, distribution, metabolism, excretion, toxicity; AKT, v-akt murine thymoma viral oncogene homolog; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATP, adenosine 5′-triphosphate; BCR-ABL, breakpoint cluster region-Abelson; CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HER, human EGFR-related; LRP, low density lipoprotein receptor-related protein; MDR, multi-drug resistance; NBDs, nucleotide-binding domains; NSCLC, non small cell lung cancer; OCT1, organic cation transporter 1; OCTN1, organic cation/carnitine transporter 1; OATP1A2, organic anion-transporting polypeptides 1A2; PI3K, phosphoinositide-3-kinase; RCC, renal cell carcinoma; RET, rearranged during transfection; RTK, receptor tyrosine kinases; TK, tyrosine kinase; TKI, tyrosine kinase inhibitors; TMs, transmembrane domains; VEGFR, vascular endothelial growth factor receptor; VHL, Von Hippel Lindau.

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treatment proliferate and repopulate a tumor mass resistant to chemotherapy (intrinsic drug resistance) [7]. Moreover, cancer cells develop drug resistance after exposure to chemotherapeutics by learning how to counteract chemotherapy-mediated cell death (acquired drug resistance). In both cases, the selective pressure exerted by the drug is responsible for the development of drug resistant tumors. Generally, cancer drug resistance is divided in three major types on the base of different aspects [8]: i) kinetic, involving tumors possessing slow growth rate. Since conventional antitumor drugs usually impair DNA replication and cellular division, tumor cells showing low mitotic index are unavailable targets and often insensitive to chemotherapy, ii) pharmacological, implicating tumors located in anatomic sites protected by peculiar physiologic defense systems (e.g., blood brain, blood testis and ovarian-blood folliculate barrier) which limit drug accumulation [8,9], and iii) biochemical, involving several cellular mechanisms including [10,11]: a) mutations of the target; b) oncogene and oncosuppressor gene expression variation; c) activation/improvement of alternative/compensatory cellular pathways inactivating/counteracting the drug action; d) improved DNA damage repair pathways; e) increased protein expression of drug efflux pumps (ATP Binding Cassette—ABC- transporters), implicated in multidrug resistance (MDR) phenotype. In order to counteract drug resistance, several strategies have been considered over the years [12], including the discovery of novel small molecules/targeted agents and the rational design of drug combination consisting of antitumor compounds with different mechanisms of action [12–15]. A still intensive field of research is the development of new agents through the chemical modification of clinically established drugs or the discovery of naturally derived compounds using high-throughput screening and system biology approaches [16,17].

The improvement of favorable pharmacokinetic and pharmacodynamic effects is the purpose of the rational drug combination studies. The development of chemotherapeutic cocktails composed of two or more drugs affecting diverse cellular pathways allows to reduce i) drug dosages while maintaining antitumor potency, ii) side effects, and iii) drug resistance [12,18,19]. Although the understanding of the cellular pathways targeted by the chemotherapeutics is critical for the prediction of a favorable drug combination, the drug association does not always produce synergistic effect. Cellular compensatory actions, intricate pathways crosstalk and redundancy are often responsible for antagonistic response. In recent years, drug combination studies have been also supported by the availability of proteomic and gene expression profiles. These tools provide a broader view of the pathways involved in drug action in a specific population of patients [20]. However, despite the enormous progress achieved in this field, the positive result is not guaranteed since genetic variations, environmental factors, host properties, drug scheduling and heterogeneity of tumor cells importantly impact on patient's response. In addition, combination regimens suffer from drawbacks depending on pharmacokinetic behavior of each drug, the difficulty to administrate the optimal doses for the required time exposure, unpredictable drug interactions and enhancement of adverse effects. Based on these findings, chemotherapeutics that hit multiple cellular pathways implicated in cell survival and defense, or the development of bifunctional agents that simultaneously inhibit more targets represent an intriguing area of research for anticancer chemotherapy that recapitulates the combined regimens [21,4,5]. The rationale of this approach is based on the expected synergistic interaction of two or more pharmacologically active components that could be favored by optimal pharmacodynamic conditions. In this context, the tyrosine kinase (TK) inhibitors (TKIs), which are active against various targets/receptors, have been hypothesized to enhance the potency of the compounds by convergent effects on related pathways [22,23]. However, the initial enthusiasm in the discovery and development of drug targeting TKs has been dampened by the temporary clinical benefits observed in TK-addicted cancers [24,25]. In fact, although the deregulated activity of some TKs has been causally linked to specific malignancies [26], the clinical experience has evidenced that the presence of a driver genetic lesion does not predict *a priori* positive response to TKI treatment [25,27]. Moreover, after initial response, patients often invariably develop resistance, a phenomenon not restricted to conventional chemotherapeutics but actually extended to TKIs. The emergence of acquired drug resistance, leading to disease relapse, is due to a multitude of often unpredictable events that highlight the robustness and plasticity of cancer [25,28–32]. In this context, the elucidation of the mechanisms underlying the occurrence of drug resistance remains a great challenge to be faced for improving the therapeutic efficacy of TKIs, both as single agents and particularly in combination regimens. Interestingly, small molecules TKIs have been found to have the capability to interact with ABC transporters, which are best known for their contributions to chemoresistance through the efflux from cancer cells of many conventional antitumor drugs (e.g., taxanes, anthracyclines, camptothecins, platinum compounds, Vinca alkaloids, epipodophyllotoxins etc; Fig. 1) [33–35].

In this review, we will focus on some paradigmatic examples of interaction between clinical available TKIs (e.g., BCR-ABL, EGFR and VEGFR inhibitors) with the main ABC transporters implicated in MDR.

2. Overview on receptor tyrosine kinases and ATP-binding cassette transporters as targets for anticancer chemotherapy

2.1. Tyrosine kinases as therapeutic targets

The deregulation of several protein kinases, mostly tyrosine kinases (TKs), has been intimately implicated in human cancer development and progression [36–39]. The approximately 518 kinases encoded by the human genome shared a unique catalytic core deputed to transfer the γ-phosphate of adenosine (5′)-triphosphate (ATP) to the hydroxyl group of serine, threonine and tyrosine residues in protein substrates. They represent crucial nodes in the complex signaling networks orchestrating a wide range of essential cellular and biological processes such as proliferation, survival, cell cycle progression, differentiation, migration as well as intercellular communications, morphogenesis and metabolism [36,37,39,40]. Historically, many TKs have been referred as protoncogenes by virtue of the role taken as a consequence of functional/structural alterations in several human malignancies. Among the 90 identified genes encoding TKs, 58 are receptor type (RTK) and 32 are non receptor TKs [36]. Specifically, RTKs share a basic common molecular structure with an extracellular ligand-binding domain, a single transmembrane helix and an intracellular region containing a conserved TK catalytic core [39]. The canonical model of RTK activation involves, upon ligand binding, conformational changes of the receptor, formation of homo- and hetero-oligomers resulting in autophosphorylation of the TK domains and finally enzymatic activation [39,41]. RTK activities are seriously deregulated in cancers, mostly as a consequence of receptor structural alterations/mutations and overactivation due to increased receptor or ligand expression [42]. Also chromosomal aberrations, in particular translocations, may produce fusion proteins endowed with constitutive TK activity [43].

Decades of studies on TK expression patterns and functional deregulation have allowed some disease associations with a clear genotype-phenotype relationship in specific tumors [44]. Moreover, elucidation of mechanisms responsible for TK aberrant