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Review article

Dual or multi-targeting inhibitors: The next generation anticancer agents

Nulgumnalli Manjunathaiah Raghavendra [a, *], Divya Pingili [b, c], Sundeep Kadasi [d], Akhila Mettu [e], S.V.U.M. Prasad [c]

[a] Center for Technological Development in Health, National Institute of Science and Technology on Innovation on Neglected Diseases, Fiocruz, Rio de Janeiro, Brazil
[b] Sri Venkateshwara College of Pharmacy, Osmania University, Hyderabad, India
[c] Department of Pharmacy, Jawaharlal Nehru Technological University, Kakinada, India
[d] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Osmania University, Hyderabad, India
[e] Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Osmania University, Hyderabad, India

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ABSTRACT

Dual-targeting/Multi-targeting of oncoproteins by a single drug molecule represents an efficient, logical and alternative approach to drug combinations. An increasing interest in this approach is indicated by a steady upsurge in the number of articles on targeting dual/multi proteins published in the last 5 years. Combining different inhibitors that destiny specific single target is the standard treatment for cancer. A new generation of dual or multi-targeting drugs is emerging, where a single chemical entity can act on multiple molecular targets. Dual/Multi-targeting agents are beneficial for solving limited efficiencies, poor safety and resistant profiles of an individual target. Designing dual/multi-target inhibitors with predefined biological profiles present a challenge. The latest advances in bioinformatic tools and the availability of detailed structural information of target proteins have shown a way of discovering multi-targeting molecules. This neoteric artifice that amalgamates the molecular docking of small molecules with protein-based common pharmacophore to design multi-targeting inhibitors is gaining great importance in anticancer drug discovery. Current review focus on the discoveries of dual targeting agents in cancer therapy using rational, computational, proteomic, bioinformatics and polypharmacological approach that enables the discovery and rational design of effective and safe multi-target anticancer agents.

Contents

* Corresponding author. Center for Technological Development in Health (CDTS), Fundação Oswaldo Cruz (Fiocruz), Av. Brasil 4036, Prédio da Expansão, 8° Andar, Sala 814, Manguinhos, 21040-361 Rio de Janeiro, RJ, Brazil.
E-mail address: nmraghav@cdts.fiocruz.br (N.M. Raghavendra).

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1. Introduction

Cancer disease is characterized by the multiple molecular lesions and functional redundancy of many signaling pathways affected by abnormal mutations [1,2]. Efficient targeting of tumor pathways needs the detailed understanding of molecular alterations that lead to the formation and maintenance of malignant phenotype of cancer cells. Uncovering the complex signaling pathways modulated by all the oncoproteins would aid in the discovery and development of more effective and less toxic anticancer treatments [3–5].

Anticancer drug discovery has been strongly focused on the development of drugs intended to act against a specific target with high potency and selectivity. Clinical experience including the discoveries of drug resistance in cancer chemotherapy has disclosed that single targeting might not always produce the desired biological effect, even if the target is inactivated or inhibited [6–8]. The reason is the development of resistance either by self-modification of the target through mutation or by the adoption of new pathways by a cancer cell, for the growth and multiplication. The approach of identifying and targeting a single oncoprotein has not produced a successful treatment and may not be sufficient to achieve durable remission in patients [9]. Therefore, modulation of the biological network is recognized to be beneficial.

Currently, there are two contrasting strategies to design the multi-targeting therapeutics. Combination drug therapy is the first strategy by creating an additive or synergistic effect of multiple drugs acting on separate targets. There are many successful treatments with the combination therapies, for example, preclinical evidence of increased apoptosis and delayed resistance to serine/threonine-protein kinase B-Raf [10,11] has led the FDA to approve the combination of dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor) for the treatment of metastatic melanoma with BRAF mutations [12,13]. Combination therapy with both RAF inhibitor (vemurafenib) and MEK inhibitor (cobimetinib) has been found to be promising in phase III clinical trials against BRAF mutated melanoma [14]. Another example of successful combined therapy is the use of palbociclib and letrozole in the treatment of advanced breast cancer [15]. Inhibition of multiple pathways by the combination of different drugs (topotecan, cyclophosphamide, doxorubicin, and vincristine) was successfully reported for the treatment of small-cell lung cancer [16]. One of the most common regimens, known as “AC”, combines adriamycin and cyclophosphamide; sometimes docetaxel, is also included, and the regime is then known as “AC-T” is practiced worldwide for the treatment of breast cancer [17].

The second strategy is to design and develop multiple-targeting drugs to effectively block the multiple oncogenic pathways synergistically [8,18]. The approach of multi-targeting therapeutics involves discovering a single agent that can act on two or more targets simultaneously. For example, US Food and drug administration (FDA) has approved lenvima (lenvatinib) as a receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1, VEGFR2 and VEGFR3 [19]. Cabozantinib, marketed under the trade name cabometyx was approved by FDA as a small molecule dual-targeting inhibitor of the tyrosine kinases c-Met and VEGFR2; and has been shown to reduce tumor growth, metastasis, and angiogenesis [20].

2. Dual targeting ligands

2.1. Inhibitors of BRAF and MEK

BRAF somatic mutation, particularly $BRAF^{V600E}$ is a common oncogenic mutation among several tumors, and it drives the tumorogenesis through constitutive activation of downstream mitogen-activated protein kinase (MAPK) signaling [21]. Selective BRAF inhibitors such as vemurafenib (zelboraf) and dabrafenib (tafinlar) as single agents were approved by the FDA for the treatment of BRAF-mutated unresectable or metastatic melanoma [22,23]. But selective and single targeted BRAF inhibition acquired resistance by reactivation of the MAPK pathway and/or increased Phosphoinositide 3-kinases (PI3K)/serine-threonine kinase (AKT) signal transduction cascade [24,25]. MEK is a member of the MAPK signaling cascade that is activated in melanoma [26]. When MEK is inhibited, cell proliferation is blocked and apoptosis is induced. Several MEK inhibitors including trametinib were found to be effective in the treatment of advanced melanoma [26–28] until the discovery of amplification of BRAF as a mechanism of acquired MEK inhibitor resistance [29]. Inhibition of BRAF has been shown to reverse resistance to the MEK inhibitor AZD6244 in colorectal