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Drug Resistance Updates 10 (2007) 81–100
DRUG RESISTANCE Updates
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Overcoming resistance to molecularly targeted anticancer therapies: Rational drug combinations based on EGFR and MAPK inhibition for solid tumours and haematologic malignancies

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Received 14 February 2007; received in revised form 22 March 2007; accepted 22 March 2007

Abstract

Accumulating evidence suggests that cancer can be envisioned as a "signaling disease", in which alterations in the cellular genome affect the expression and/or function of oncogenes and tumour suppressor genes. This ultimately disrupts the physiologic transmission of biochemical signals that normally regulate cell growth, differentiation and programmed cell death (apoptosis). From a clinical standpoint, signal transduction inhibition as a therapeutic strategy for human malignancies has recently achieved remarkable success. However, as additional drugs move forward into the clinical arena, intrinsic and acquired resistance to "targeted" agents becomes an issue for their clinical utility. One way to overcome resistance to targeted agents is to identify genetic and epigenetic aberrations underlying sensitivity/resistance, thus enabling the selection of patients that will most likely benefit from a specific therapy. Since resistance often ensues as a result of the concomitant activation of multiple, often overlapping, signaling pathways, another possibility is to interfere with multiple, cross-talking pathways involved in growth and survival control in a rational, mechanism-based, fashion. These concepts may be usefully applied, among others, to agents that target two major signal transduction pathways: the one initiated by epidermal growth factor receptor (EGFR) signaling and the one converging on mitogen-activated protein kinase (MAPK) activation. Here, we review the molecular mechanisms of sensitivity/resistance to EGFR inhibitors, as well as the rationale for combining them with other targeted agents, in an attempt to overcome resistance. In the second part of the paper, we review MAPK-targeted agents, focusing on their therapeutic potential in haematologic malignancies, and examine the prospects for combinations of MAPK inhibitors with cytotoxic agents or other signal transduction-targeted agents to obtain synergistic anti-tumour effects.

Keywords: Targeted therapy; Drug resistance; Combination therapy; Molecular markers; EGFR; IGFR1; MAPK; MEK inhibitors; AML

1. Introduction

The term "targeted therapy" refers to a new generation of cancer drugs designed to interfere with a specific molecular target, typically a protein, believed to have a critical role in tumour growth or progression (Scaltriti and Baselga, 2006; Baselga and Arteaga, 2005). The clinical success of the small-molecule tyrosine kinase inhibitor (TKI) imatinib mesylate (Gleevec®) in chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours (GIST) has established a paradigm for the treatment of tumours whose growth is critically dependent on specific kinase targets. Indeed, CML

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doi:10.1016/j.drup.2007.03.003

is driven by the mutant kinase fusion protein BCR-ABL, which contains a constitutively activated ABL kinase, while GIST are caused by activating point mutations in the c-KIT or platelet-derived growth factor receptor (PDGFR) kinases. Imatinib effectively blocks the activity of all three kinases and produces dramatic clinical responses in all three clinical situations in a manner that correlates precisely with the presence of these mutations in the tumour (Sawyers, 2003). Encouraging clinical studies have opened the approval path to other targeted agents: the epidermal growth factor receptor (EGFR) inhibitor erlotinib in non small cell lung cancer (NSCLC) (Shepherd et al., 2005); the multi-kinase inhibitors sunitinib (Sutent®) in advanced renal cell cancer (Motzer et al., 2007); and the dual EGFR-HER2 TK inhibitor lapatinib (Tykerb®) in HER2-positive, Trastuzumab-resistant, advanced breast cancer (Geyer et al., 2006).

However, other compounds that specifically target protein kinases have been much less successful in the clinic, especially when combined with classical cytotoxic agents (Becker, 2004). These setbacks reflect a variety of factors, including a rush to get compounds into the clinic, a lack of validated biomarkers, insufficient characterization of patient populations appropriate for treatment, and oversight of pharmacodynamic and scheduling issues. One important point to keep in mind is that a single genetic alteration necessary and sufficient to drive the array of phenotypic hallmarks of malignancy is the exception rather than the rule in human tumours; their malignant behaviour is usually driven by the accumulation of several genetic and epigenetic aberrations (Fojo, in press). Emerging evidence indeed indicates that clinically successful new therapeutic strategies will most likely rely on the selection of patients whose tumours harbour genetic aberrations that render them "addicted" to the constitutive activation of a certain pathway (and therefore exquisitely sensitive to the inhibition of that pathway), as well as on the mechanism-based manipulation of multiple, cross-talking pathways involved in growth and survival control (Broxterman and Georgopapadakou, 2005; Blum and Kloog, 2005).

Moreover, the therapeutic inactivation of an essential protein creates selective pressures for tumour cells to evolve mechanisms of resistance, in a manner similar to the extensively studied emergence of resistance in microorganisms after exposure to antimicrobial agents (Bardelli et al., 2003; Samuels et al., 2004).

In this review, we will focus on the molecular mechanisms of sensitivity/resistance to agents targeted at EGFR and mitogen-activated protein kinase (MAPK), with particular emphasis on EGFR/MAPK inhibition-based combination strategies, designed to achieve synergistic anti-tumour activity and to overcome resistance to the single agent.

2. Mechanisms of resistance to EGFR tyrosine kinase inhibitors

Resistance to targeted agents may occur by mechanisms similar to cytotoxic agent resistance (Broxterman et al., 2003) such as inactivating metabolism, poor absorption, reduced drug availability or defective immune system-mediated functions. An example is the acquired resistance to imatinib as a result of increased plasma activity of α1-acid glycoprotein,

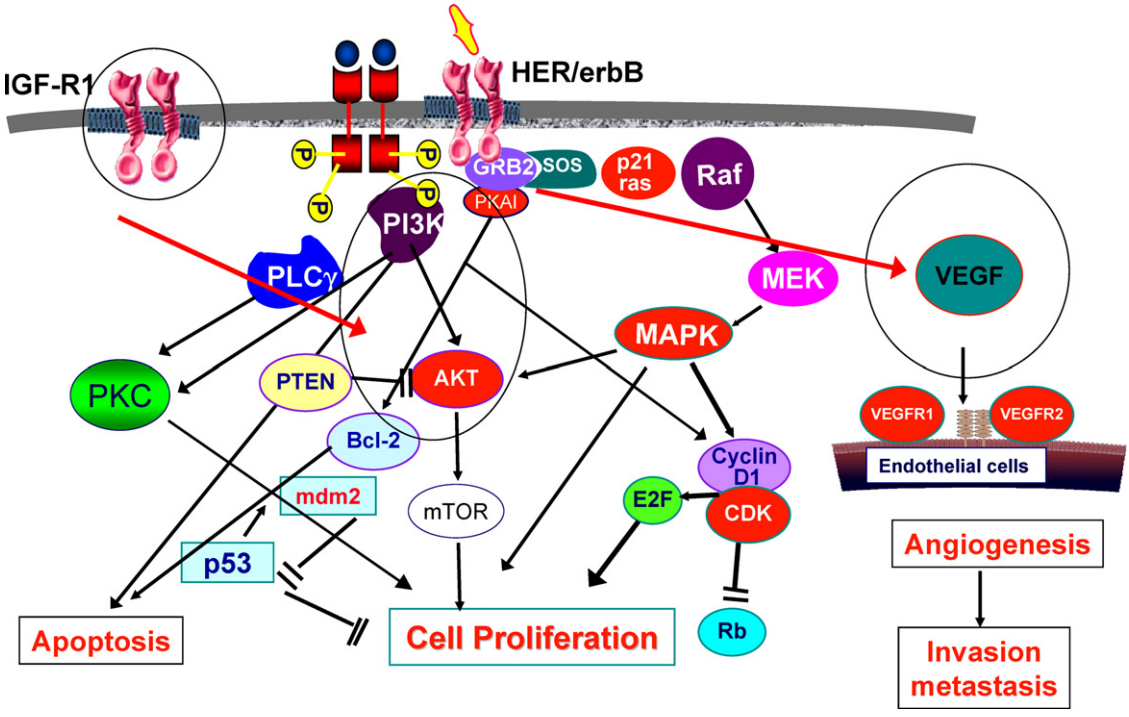

Fig. 1. IGFI-R, PI3K/Akt and VEGF are "escape pathways" responsible of the resistance to EGFR-targeted therapies.