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Commentary

Modulation of cell sensitivity to antitumor agents by targeting survival pathways

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ABSTRACT

The advent of drugs targeting tumor-associated prosurvival alterations of cancer cells has changed the interest of antitumor drug development from cytotoxic drugs to target-specific agents. Although single-agent therapy with molecularly targeted agents has shown limited success in tumor growth control, a promising strategy is represented by the development of rational combinations of target-specific agents and conventional antitumor drugs. Activation of survival/antiapoptotic pathways is a common feature of cancer cells that converge in the development of cellular resistance to cytotoxic agents. The survival pathways implicated in cellular response to drug treatment are primarily PI3K/Akt and Ras/MAPK, which also mediate the signalling activated by growth factors and play a role in the regulation of critical processes including cell proliferation, metabolism, apoptosis and angiogenesis. Inhibitors of PI3K, Akt and mTOR have been shown to sensitize selected tumor cells to cytotoxic drugs through multiple downstream effects. Moreover, the MAPK pathway, also implicated in the regulation of gene expression in response to stress stimuli, can interfere with the chemotherapy-induced proapoptotic signals. Targeting Hsp90, which acts as a molecular chaperone for survival factors including Akt, may have the potential advantage to simultaneously block multiple oncogenic pathways. Overall, the available evidence supports the interest of rationally designed approaches to enhance the efficacy of conventional antitumor treatments through the inhibition of survival pathways and the notion that the concomitant targeting of multiple pathways may be a successful strategy to deal with tumor heterogeneity and to overcome drug resistance of tumor cells.

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1. Introduction

The limited success of antitumor therapy with conventional agents reflects the presence or development of resistance of tumor cells. Most of the conventional antitumor drugs target fundamental cellular processes involving DNA functions or cell division. A variety of novel agents, able to interfere with specific oncogenic processes or with relevant cellular targets, have been developed in the hope to identify treatment strategies characterized by improved efficacy and reduced toxic side effects. However, the single-agent therapy with molecularly targeted agents (small molecule or biological) has shown a limited efficacy, because the alterations of the most common diseases are very complex and, in general, solid tumors exhibit a large heterogeneity. Therefore, drug resistance is a common problem involving both cytotoxic and targeted agents [1,2].

A well-established principle of cancer therapy to overcome tumor resistance is the combination of non-cross-resistant drugs characterized by different mechanisms of action and non-overlapping profiles of toxicity. The knowledge of molecular alterations and features of tumors and the identification of mechanisms of tumor resistance provide the opportunity to test novel rationally designed drug combinations. With the emergence of novel targeted agents with well-defined mechanisms of action, new effective drug combinations could be explored on the basis of tumor type-specific alterations which may be relevant in determining the resistant phenotype. Tumor-specific drug resistance has been ascribed to mutational events (intrinsic or drug-induced), to karyotypic changes or to epigenetic alterations. Cellular response to cytotoxic agents may involve the activation of defence systems and the modulation of signalling pathways implicated in the control of tumor growth or progression. The prosurvival cell response is of particular relevance at subtoxic concentrations, because it may result in survival of resistant cells. Thus, the combination of drugs targeting survival pathways

Abbreviations: AMPK, AMP-dependent protein kinase; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinases; GRP78, glucose-regulated protein 78; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; SAPK/JNK, stress-activated protein kinase/c-Jun N-terminal kinases; RTK, receptor tyrosine kinase; UPR, unfolded protein response; VEGF, vascular endothelial growth factor.

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appears to be promising for tumor therapy in an attempt to reduce cell ability to survive under stress conditions induced by hypoxia or chemotherapy. However, suppression of a single pathway may be inadequate to provide a general impact in antitumor therapy efficacy, because multiple features or alterations of tumor cells contribute to the sensitivity of targeted agents. This article focuses specifically on the available evidence supporting the interest of combination therapy that interferes with survival signals, as a promising strategy to optimize the application and rational incorporation of novel target-specific agents into a variety of therapeutic approaches.

2. PI3K–Akt–mTOR pathway

The deregulation of oncogenic signalling pathways provides survival advantages and can influence the sensitivity of tumor cells to antitumor agents. The aberrant signalling activated by over-expressed or mutant growth factor receptors is mainly mediated by the PI3K–Akt–mTOR and the Ras–MAPK networks. The PI3K–Akt–mTOR pathway plays a key role in regulating critical cellular functions including cell growth and metabolism [3,4]. The pathway is activated in several human cancers and inappropriate activation can result from aberrant activation of RTKs or from specific mutations of components of the pathway itself. Although three classes of PI3Ks are known, class IA appears the most critical in regulation of tumor cell growth and proliferation [3]. These enzymes are lipid kinases which phosphorylate the 3′ OH of phoshoinositols in response to growth factors and cytokines. PI3Ks are heterodimers composed of regulatory subunits (p85, involved in the interaction with RTKs) and catalytic subunits (p110) releasing PIP_3, a phospholipid acting as a potent second messenger able to recruit Akt, the critical mediator of the signalling cascade [4]. The cellular availability of PIP_3 is reduced by the phosphatase activity of the tumor suppressor gene PTEN [5]. Since the activation and signalling of the P13K pathway can occur at multiple levels (e.g., mutated or overexpressed RTKs and Akt), the PI3K signalling cascade has been referred to as a "super-highway" [6]. Akt has been implicated in the regulation of the transcriptional activity of the antiapoptotic NF-κB, by inducing activation of IκK and subsequent phosphorylation and degradation of IκB [7]. Relevant to this point is the implication of NF-κB in prosurvival response following treatment with cytotoxic agents (e.g., cisplatin) [8]. Indeed, NF-κB is recognized to be a mediator of drug resistance by inhibiting drug-induced apoptosis.

In addition, Akt activates mTOR, which is the major effector of the signalling cascade. mTOR has been implicated in the regulation of critical cellular processes, including mRNA translation and metabolism. mTOR is known to form two complexes, i.e., mTORC1, which is activated by growth factors and nutrients, and mTORC2, which phosphorylates Akt, thereby contributing, through a feedback mechanism, to the continuous activation of the PI3K–Akt–mTOR axis [9]. The participation of the PI3K pathway in a large number of cellular processes influencing cell growth, survival and resistance to chemo- and radiotherapy have stimulated considerable efforts to identify inhibitors as potential therapeutic agents. Although the clinical experience with PI3K inhibitors is still limited, a number of compounds with variable degree of specificity have been developed [10]. The family of small molecules proposed as novel drugs is quite large and include also dual inhibitors, i.e., compounds capable of simultaneously inhibiting PI3K p110α and mTOR [11]. The complexity of the malignant phenotype, the presence of multiple redundant pathways/networks and the crosstalks between pathways suggest that the use of PI3K inhibitors will be better exploited in combination with other agents. On the basis of the primary function of PI3K enzymes as mediator of signalling activated by growth factor receptors, it is conceivable that the modulation of this pathway critically affects the efficacy of growth factor receptor antagonists/inhibitors. An effective combination of the PI3K inhibitor GDC-0941 with HER2-directed agents (trastuzumab and pertuzumab) has been recently reported in the treatment of breast carcinoma models [12]. The efficacy of the combination is related to the concomitant suppression of the PI3K–Akt and MAPK pathways. In addition, PI3K inhibitors have been shown to modulate cell sensitivity to cytotoxic agents (e.g., taxanes and platinum compounds). LY294002, a competitive inhibitor of the ATP-binding pocket of PI3Ks, has been combined with conventional cytotoxic agents in several *in vitro* and *in vivo* studies. The LY294002/cisplatin combination was effective in pancreatic cancer cells in which the inhibitor increased the apoptotic response through decreasing Akt-mediated BAD phosphorylation [13]. The non-small cell lung cancer A549/CDDP cells, resistant to cisplatin and exhibiting an increased Akt1 expression, were also more sensitive to the same combination than the parental counterparts as a result of decreased phospho-Akt levels [14]. Triciribine is a potent and selective inhibitor of the kinase activity of all three Akt family members, without off-target effects on upstream activators [15]. In an ovarian carcinoma cell line resistant to cisplatin (SKOV3/DDP), triciribine enhanced cisplatin cytoxicity and apoptosis induction, thus providing a target-specific way to overcome acquired resistance [16].

Given the role of Akt in regulation of mTOR, its inhibition is expected to have critical influence on multiple downstream events. Unfortunately, only a limited number of Akt inhibitors have been developed [3]. In contrast, mTOR inhibitors are now clinically available. In addition to rapamycin derivatives, which inhibit mTOR when complexed in mTORC1, novel ATP-competitive mTOR inhibitors targeting the kinase domain are expected to interfere with the activity of both mTORC1 and mTORC2 [17]. The water-soluble ester of rapamycin CCI-779 (Temsirolimus) has been used to restore cisplatin sensitivity in two lung cancer cell lines endowed with high levels of phospho-mTOR, phospho-Akt and other growth-related proteins, such as human telomerase reverse transcriptase and cyclin D3 [18]. These data confirmed the previous observations indicating the ability of rapamycin to restore cisplatin sensitivity in platinum-resistant non-small cell lung cancer cells [14]. Combined with cisplatin, RAD001 (Everolimus) induced a striking suppression of hepatocellular carcinoma growth both *in vitro* and *in vivo*, accompanied with a significant increase in the number of apoptotic cells [19,20]. The inhibition of mTOR was found effective in sensitizing cancer cells to other clinically relevant cytotoxic drugs [21,22].

Overall, these observations are consistent with the prosurvival role of PI3K–Akt pathway, which, through the activation of downstream effectors, may lead to drug resistance. The stress induced by cytotoxic agents, including cisplatin, may induce the modulation of different survival pathways, including the PI3K–Akt–mTOR axis [23,24]. A number of mutations or alterations in several tumor cells may cooperate to allow cell survival. The presence of redundant pathways may represent a resistance mechanism for specific inhibitors. In cells exhibiting activation of multiple pathways, the concomitant blockade of complementary pathways or the inhibition of specific steps of multicomponent pathways is expected to enhance antitumor effects. For example, resistance to the HER2 inhibitor, lapatinib, as a consequence of PTEN mutation or activating mutations in PIK3CA, could be reversed by dual mTOR/PI3K inhibitors [25,26]. Similarly, breast cancer models, exhibiting resistance to trastuzumab, appear to be sensitive to mTOR inhibitors [27]. Dual inhibitors of the PI3K–Akt–mTOR pathway represent a promising class of agents able to overcome the feedback loops and to effectively inhibit the deregulated pathway [3,28,29].

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