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Editorial

Targeted therapy: tailoring cancer treatment

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Abstract

Targeted therapies include small-molecule inhibitors and monoclonal antibodies, have made treatment more tumor-specific and less toxic, and have opened new possibilities for tailoring cancer treatment. Nevertheless, there remain several challenges to targeted therapies, including molecular identification, drug resistance, and exploring reliable biomarkers. Here, we present several selected signaling pathways and molecular targets involved in human cancers including Aurora kinases, PI3K/mTOR signaling, FOXO-FOXM1 axis, and MDM2/MDM4-p53 interaction. Understanding the molecular mechanisms for tumorigenesis and development of drug resistance will provide new insights into drug discovery and design of therapeutic strategies for targeted therapies.

Key words Targeted therapy, Aurora kinases, PI3K/mTOR signaling, FOXO-FOXM1 axis, MDM2/MDM4-p53 interaction

In the past three decades, survival rate has been improved significantly in a number of cancer types owing to advances in active prevention and early diagnosis. However, we still face tremendous challenges in cancer treatment: non-specific, non-selective, and toxic. Newly emerging targeted cancer therapies give us a promising perspective in tailoring cancer treatment based on individual patient genetic/proteomic profiles. Targeted cancer therapies work by interfering with specific molecules and signal pathways necessary for tumor growth and progression. Current targeted cancer agents are broadly classified as either monoclonal antibodies or small molecules, including kinase inhibitors, angiogenesis inhibitors, proteasome inhibitors, and molecular receptor blockers.

Our lab is exploring the molecular mechanisms that are involved in initiation and progression of human cancers, and investigating the approaches for targeted therapies. Mitotic Aurora kinases play a key role in maintaining accurate chromosome segregation. Besides its role in interrupting normal mitotic event, we found dysregulation of mitotic kinase Aurora-A–enhanced cell survival[1] as well as promoted migration and invasion of tumor cells[2-4], providing a promising molecular target for anticancer treatment.

For tailoring cancer treatment, an important thing is to have good biomarkers that not only predict disease prognosis but also subdivide patients for treatment selection. For example, recent work from our lab showed that small molecule VX-680 preferentially induced death in leukemic cells of Aurora^{high} or Aurora^{low}Flt3^{mutant} expression profiles, suggesting that Aurora-targeted cancer therapy would be best used for a subgroup of patients with certain biomarker expressions[5]. Through a retrospective study of 1,303 patients, we demonstrated that pretreatment serologic antienzyme rate (AER) of Epstein-Barr virus (EBV) DNase-specific neutralizing antibody might serve as an independent prognostic factor for complimenting TNM staging in nasopharyngeal carcinoma[6]. Furthermore, our study suggested that in patients with early-stage disease (stages I and II) but with a high AER level, radiotherapy alone might not be sufficient, chemotherapy plus radiation would be more beneficial; for patients with advanced disease (stages III and IV) and a high AER level, the current chemotherapy regimen (cisplatin plus either 5-fluorouracil or paclitaxel) plus radiation seem not enough, more intensive therapy may be used. Thus, an ideal biomarker segregates patients for more accurate risk definition and selective therapy.

Drug resistance is a major reason for the failure of

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targeted therapies, limiting clinical efficacy. A significant amount of research effort should be devoted to elucidate the underlying molecular mechanism of resistance. Accumulated evidence points to the rationale for combination of molecule-targeted therapies to delay or overcome the acquired treatment resistance. A good example is that combined treatment with proto-oncogene B-Raf (BRAF) inhibitor dabrafenib and mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor trametinib delays the development of treatment resistance in patients with BRAF-positive metastatic malignant melanoma[7]. Consistently, our recent study found that targeting Aurora kinases by VX-680 induced apoptosis, as well as autophagy, which contributed the resistance of breast cancer cells to VX-680. Repression of autophagy significantly enhanced VX-680–induced apoptosis in breast cancer cells, suggesting a novel strategy for overcoming the resistance in clinical applications[8].

In the current issue, we presented 3 reviews focusing on molecular targets in cancer progression and drug resistance, providing potential strategies for cancer treatment. The forkhead transcription factors FOXO and FOXM1 play pivotal roles in a wide range of biological processes, including cell cycle progression, cell differentiation, apoptosis, angiogenesis, senescence, tissue homeostasis, and DNA damage repair. Gomes *et al*.[9] summarized the role of FOXO-FOXM1 axis in tumorigenesis and drug resistance. On the other hand, the phosphatidylinositide 3-kinase (PI3K)-AKT pathway is frequently dysregulated in human cancers, and small-molecule inhibitors of PI3K-mTOR signaling are being rapidly evaluated in preclinical models and in clinical studies. Tan *et al*.[10] gave an overview of the molecular mechanisms of tumor resistance to PI3K-mTOR–targeted cancer therapy. Regulation of p53 tumor suppressing activity by its degradation partners, MDM2 and MDM4, contributes to maintenance of genetic stability, cell cycle progression, and cell survival. In another report, Xiong[11] described the mouse models of *Mdm2* and *Mdm4*, which are two key negative regulators of tumor suppressor *p53*. Loss of function of p53 contributes to the development of most human cancers. The mouse models of *Mdm2* and *Mdm4* suggest potential implications in preclinical and clinical studies.

Although faced with challenges, targeted therapy represents an exciting new approach to cancer treatment. Understanding the molecular mechanisms of cancer causation and progression, as well as tumor resistance, improvements of disease models and diagnostic tools (e.g., genomic sequencing technologies) will lead to greater development of targeted therapies. Thus, we wish that, eventually, treatments may be individualized based on the unique set of molecular targets produced by the tumor.

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