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PERSPECTIVES

Autophagy facilitates the EGFR-TKI acquired resistance of non-small-cell lung cancer cells

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Lung cancer is the leading cause of cancer-related mortality worldwide, with approximately 1.6 million new cases and 1.4 million deaths each year.[1] Non-small-cell lung cancer (NSCLC) accounts for nearly 85% of all cases of lung cancer. Once diagnosed, the 5-year survival rate of NSCLC patients hardly reaches 15% despite many different treatments including surgery, radiotherapy, and chemotherapy being widely used.[1] However, the therapeutic effect of chemotherapy is still not satisfactory in patients with advanced NSCLC and the response rate is only 20–35% with a median survival of 10–12 months.

Epidermal growth factor receptor (EGFR) is overexpressed in many solid tumors including NSCLC, and the overexpression of EGFR can affect the pathogenesis of cancer, such as cell proliferation, invasion, and metastasis. Activated EGFR can recruit a number of downstream signaling molecules such as phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) and Ras-Raf-MAPK-ERK kinase (MEK).[2] Thus, EGFR has been the focus of molecular-targeted therapies. Drugs that inhibit the tyrosine kinase activity of EGFR, such as the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib, have been developed for the treatment of NSCLC. Although both EGFR-TKIs show good anticancer effects in NSCLC patients, the efficacy of EGFR-TKIs remains limited mainly because of acquired resistance in clinics.[3] Therefore, it is very important to investigate the underlying mechanisms to influence the sensitivity of EGFR-TKIs.

Macroautophagy, hereafter referred to as autophagy, is an evolutionarily conserved catabolic process involving the degradation of cytoplasmic constituents, and the recycling of long-lived or aggregated proteins. In many tumor cells, autophagy can be upregulated during disadvantaged conditions, such as chemoradiotherapy or in a nutrient-deficient environment, and promote tumor cell survival, thus autophagy may be regarded as a potential mechanism of drug resistance. For example, inhibition of autophagy can enhance the effects of apoptosis induced by cisplatin in esophageal cancer cells.[4]

The PI3K-Akt-mTOR pathway, as one of the downstream signaling pathway of EGFR, is one of the two main molecular regulation mechanisms of autophagy, which suggests a potential link between EGFR-targeted therapy and induction of autophagy. Another TKI named imatinib can promote cytoprotective autophagy in many cell lines such as chronic myeloid leukemia stem cells.[5] Therefore, we propose the hypothesis that autophagy may be a potential factor influencing the acquired resistance of lung cancer cells to EGFR-TKIs.

Although autophagy can be induced in many different cancer cell lines including lung cancer cells, the exact role of autophagy in tumor cell death or survival is still unclear. Autophagy can be activated to promote cell survival in

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various forms of cellular stress through the lysosomal-mediated degradation of cellular proteins and organelles, and can act as a cellular survival mechanism. Thus, it could serve as a potent oncogenic mechanism to promote tumor cell survival.

In fact, many studies have indicated that induction of autophagy can enhance tumor resistance to different anticancer therapies in different tumor cell lines. Chemotherapy-induced high mobility group box 1 (HMGB1) expression in osteosarcoma cells can promote autophagy, which could inhibit apoptosis and increase drug resistance.[6] In esophageal cancer cells, autophagy can promote the survival of drug-resistant cancer cells following treatment with chemotherapeutics.[7] In addition, inhibition of autophagy can enhance the growth inhibition and apoptotic effect of cisplatin in lung acquired resistant cells (A549/DDP).[8] Therefore, these results have indicated that autophagy may play an important role in the drug resistance of tumor cells to anticancer therapeutics.

Furthermore, other studies have proven that autophagy can protect tumor cells against the effect of EGFR-TKIs. In lung cancer cells, autophagy can be activated by EGFR-TKIs through inhibition of the PI3K/Akt/mTOR signaling pathway, and inhibition of autophagy can augment the growth inhibitory effect of EGFR-TKIs.[9] Other findings also suggest that inhibition of autophagy can induce a marked increase in the death-inducing activity of EGFR-TKIs (erlotinib) in glioblastoma cells.[10] Thus, combining conventional chemotherapy with therapeutic strategies that aim to inhibit autophagy in patients, that is novel targeted therapy with EGFR-TKIs, and it may represent a promising approach with higher efficacy for NSCLC patients.

Previous studies have indicated that inhibition of autophagy can enhance the efficacy of EGFR-TKIs in many different cancer cells including NSCLC cells.[9,10] Therefore, we propose the hypothesis that autophagy may facilitate the acquired EGFR-TKI resistance of lung cancer cells, which might be one of the mechanisms for tumor recurrence and metastasis.

In recent years, the role of autophagy in the chemoradiotherapy resistance of cancer cells has been explored extensively. Although the function of autophagy in the EGFR-TKI acquired resistance is still uncertain and more studies are needed to investigate the possible resistant mechanism, at least it offers us a new alternative strategy for overcoming acquired resistance to EGFR-TKIs.

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