The mTOR Pathway and Molecularly Targeted Therapy for Lung Cancer

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Abstract

New drug technology aims to target the changes in cancer cells that help them grow. New current and upcoming drugs differ from standard chemotherapy as they can overcome the secondary resistance by cancer cells, but they may also harbor life-threatening side effects. Secondary resistance by cancer cells to anticancer therapy is one of the major challenges that face oncologists. It is a complex situation in which multiple signaling pathways may be activated. The new pathologic classification of lung cancer affects clinical practice and opens new avenues for research, and new molecularly targeted strategies are being evaluated based on the new classification. The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway is one of most commonly deregulated pathways in cancer. Targeted therapy as inhibitors of mammalian target of rapamycin (mTOR) opens the door for a new hope of longer survival rates for lung cancer patients including both small and non-small cell lung cancer.

Keywords: Lung cancer; Non-small cell lung cancer; Targeted therapy; mTOR signaling pathway; Resistance; Inhibitors

Introduction

Cancer treatment using targeted therapy has made a leading progress in increasing survival rates and extending interval to disease progression. However, most current therapies may be hindered by the development of progressive resistance by cancer cells. Researchers have tried targeted therapy to overcome this resistance, but some of these drugs have major side effects. For example, Bevacizumab (Avastin®), a humanized VEGF monoclonal antibody can cause severe bleeding which limits its use [11]. Other drugs that target the epidermal growth factor receptor (EGFR) are added to standard chemotherapy as first line for treating non-small-cell lung cancer (NSCLC). However, not all patients respond to this therapy and some acquire resistance in less than a year. Resistance is a complex phenomenon, which involves the activation of multiple signaling pathways. Phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) is one of the commonly deregulated pathways in cancer [19]. Activation of this pathway leads to resistance to anticancer therapies, including tyrosine kinase inhibitors, radiation and cytotoxics [33]. It is activated by the binding of extracellular growth factors (EGFR, HER2, insulin-like growth factor receptor, vascular endothelial growth factor receptor, platelet derived growth factor receptor) to transmembrane receptor tyrosine kinases. Targeting agents against the PI3K/AKT/mTOR pathway are under trial for the treatment of lung cancer and advanced solid tumors. The inhibition of this pathway leads to rash, hyperglycemia (through insulin resistance) and transaminase elevations. Each agent of the inhibitors differ from standard chemotherapy as they can overcome the secondary resistance by cancer cells, but they may also harbor life-threatening side effects. Secondary resistance by cancer cells to anticancer therapy is one of the major challenges that face oncologists. It is a complex situation in which multiple signaling pathways may be activated. The new pathologic classification of lung cancer affects clinical practice and opens new avenues for research, and new molecularly targeted strategies are being evaluated based on the new classification. The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway is one of the most commonly deregulated pathways in cancer. Targeted therapy as inhibitors of mammalian target of rapamycin (mTOR) opens the door for a new hope of longer survival rates for lung cancer patients including both small and non-small cell lung cancer.

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Lung Cancer Classification and Therapeutic Modalities

Lung cancer is a common disease and is the leading cause of cancer-related mortality in most of the industrialized countries [10]. NSCLC accounts for approximately 85% of lung cancer cases. Therapeutic decisions in non-small cell lung cancer have been based mainly on disease stage, the patient’s performance status and co-morbidities, and rarely on histological or molecular profiling until recently. In 2011, the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and European Respiratory Society (ERS) introduced a new adenocarcinoma classification for lung cancer to provide uniform terminology and diagnostic criteria [37]. Importantly, the new classification involved experts representing IASLC, ATS, and ERS with oncologists/pulmonologists, surgical and clinical pathologists, radiologists, molecular biologists, and thoracic surgeons. The 1999/2004 WHO classification of adenocarcinoma seemed to cause a lot of confusion among clinicians especially the term bronchioloalveolar carcinoma (BAC) which is now replaced by new subcategories including adenocarcinoma in-situ and minimally invasive adenocarcinoma. Invasive adenocarcinoma is further divided into five subtypes according to the predominant histological pattern. Focus has also been given to small biopsies and cytology in advanced cases to distinguish squamous cell carcinoma from adenocarcinoma by appropriate immunohistochemical markers [34].

The histological classification of IASLC/ATS/ERS has important correlation with molecular changes because most adenocarcinoma subtypes show EGFR, Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations and rearrangement of anaplastic lymphoma kinase (ALK) [35]. Those molecular changes have significant correlation in predicting patient prognosis and the requirement of adjuvant chemotherapy [36,42]. Recently, experts from IASLC, College of American Pathologists (CAP), and Association for Molecular Pathology (AMP) recommended that EGFR and ALK molecular testing should be used to select patients for EGFR- or ALK-targeted TKI therapy, respectively [18].
NSCLCs are not sensitive to chemotherapy [28] or radiation, so surgery is the treatment of choice if diagnosed at an early stage, often with cisplatin as adjuvant chemotherapy. Other treatment choices are chemotherapy, radiation therapy and molecularly targeted therapy. Advanced cases of NSCLC have a median survival time of 10-12 months with conventional chemotherapy as some patients with particular mutations in the EGFR gene may respond to EGFR tyrosine kinase inhibitors such as gefitinib [16]. About 7% of NSCLC have EML4-ALK translocations; clinical trials need to prove the benefit from ALK inhibitors in those patients [17]. Other trials including the mammalian target of rapamycin (mTOR) already demonstrated great promise and has been found to be activated in a substantial number of other lung cancer cases [2].

Patients with NSCLC, in particular, adenocarcinoma or mixed adenosquamous carcinoma, overexpress EGFR in 40-60% of patients who have never smoked [18]. FDA has approved EGFR-targeted therapies such as erlotinib or gefitinib for patients with EGFR-positive tumors. However, not all patients respond to this therapy and others acquire resistance in less than 12 months [15]. Clinical resistance to EGFR inhibitors in NSCLC is due to reactivation of PI3K/AKT/mTOR pathway through genetic alterations [32].

The PI3K/AKT/mTOR signaling pathway:

Ongoing research into the molecular basis and signaling pathways of lung cancer has yielded insights into many pathways that are deregulated during the process of carcinogenesis. One such pathway that has recently commanded a great deal of attention is the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway, which was first described in the 1990s and is a downstream target of EGFR. It is activated early in lung carcinogenesis and plays a role in cell growth, cell proliferation, angiogenesis and protein synthesis [27].

The PI3K/AKT/mTOR signaling cascade has been described in details elsewhere [2,6,22]. Briefly, activated growth factor receptors trigger activation of the PI3K/AKT pathways and the Ras/MEK/Erk pathway. Activated AKT leads to increased mTOR activity through signaling by means of the tuberous sclerosis complex (TSC1/2). Importantly, mTOR then phosphorylates S6K1 and 4E-BP1, resulting in increased gene transcription, cell growth, and cell proliferation. Activation of the pathway is frequently implicated in resistance to anticancer therapies. This can be shown by comparing the parental gefitinib-sensitive cell line and adenocarcinoma cell lines that are resistant to EGFR TKI gefitinib. The naturally resistant NSCLC cell lines are associated with increased AKT phosphorylation, reduced PTEN protein expression and loss of the EGFR gene [9]. NSCLC cell lines with acquired resistance to the EGFR-specific antibody cetuximab show AKT hyperactivation due to PTEN protein loss, but was not revoked by cetuximab [14]. Increased PI3K/AKT/mTOR signaling pathway can lead to drug resistance as it extends cell survival and modulates the expression of multidrug resistance-1 (a transmembrane drug transporter). Based on this, potential inhibitors for the PI3K/AKT/mTOR are used in preclinical models to restore sensitivity to cetuximab in resistant HCC827-CR NSCLC cells [13]. Each agent of this pathway can be studied separately.

BKM-120 (Novartis) is a specific inhibitor of class I PI3K. It has proapoptotic effects in PI3K-mutated breast cancer cell lines. The effect of BKM-120 combined with chemotherapy is being tested in colorectal carcinoma, glioblastoma and NSCLC. BKM-120 combined with carboplatin and pemetrexed are given as Phase1 clinical trial in advanced NSCLC, which show nonsquamous histology. Phase 1 includes BKM-120 combined with erlotinib given to EGFR-mutated lung adenocarcinoma patients who were previously sensitive to EGFR Tyrosine Kinase Inhibitors (TKI).

Another oral PI3K inhibitor GDC-0941(Genentech) is under clinical trial Phase1b for treatment of NSCLC given in combination with bevacizumab. Phase 1 will test first line treatment of metastatic NSCLC with GDC-0941 associated with carboplatin and paclitaxel depending on lung cancer histology (squamous or nonsquamous) [20].

The potent oral PI3K inhibitor PX-866 is still under trial for the treatment of metastatic NSCLC. It is characterized by its covalent binding to the major forms of PI3K causing an irreversible inhibition [31].

AKT inhibitors are still under trial as Phase I combination therapy study is complete and phase II is underway for the treatment of metastatic NSCLC ([BATTLE] 2 trial) [41].

mTOR inhibitors

In the 1970s, a bacterial strain, Streptomyces hygroscopicus, was found to produce an antifungal metabolite named "rapamycin", which was subsequently found to exhibit immunosuppressive effects and to suppress cell proliferation [39]. The target protein of rapamycin, designated TOR (target of rapamycin) has a corresponding mammalian TOR (mTOR), which is a 289KD protein with serine/kinase activity that regulates cell growth, protein and lipid synthesis, mitochondrial metabolism and cell cycle [4]. Impairment of this protein would favor the evolution of many types of cancer including lung cancer. mTOR functions as mTORC1 and mTORC2 complexes. mTORC1 regulates cell size through protein transcription while mTORC2 controls cell shape through actin cytoskeleton reorganization [1].

mTORC1 has two major substrates 56K1and 4E-BP1 which initiate eIF4E upon phosphorylation. Eukaryotic translation initiation factor 4E, is a protein encoded by the eIF4E gene and functions in directing ribosomes to the cap structure of mRNAs [12,25]. Several studies linked the mTOR role in lung carcinogenesis to its coupling with the oncogenic eIF4E, [21] which shows significantly higher levels in atypical adenomatous hyperplasia and adenocarcinoma of the human lung [30]. The link between mTOR and lung cancer is supported by studies including inhibitors of mTOR pathway as PTEN and LKB1 which act as tumor suppressors and also undergo mutation in lung cancer [8]. Another inhibitor of mTOR rapamycin analogue CCI-779 reverses alveolar epithelial neoplasia induced by oncogenic KRAS, resulting in a reduction in size and number of alveolar epithelial cells [40].

Conde et al. [3] studied the relation between EGFR alterations and activation of mTOR and reported evidence for mTOR signaling in EGFR-mutant tumors [3]. Data also suggest the dual inhibition of EGFR and mTOR pathways in small cell lung cancer [29]. Other trials state that inhibitors of PI3K/AKT pathway are effective in treatment of NSCLC, but couldn’t induce apoptosis in NSCLC cases with resistance to EGFR-TKIs [5]. mTOR signaling pathway plays a major role in the metastatic spread of lung cancer and the mTOR inhibitor rapamycin antagonizes the activation of hypoxia inducible factor-1α (HIF-1α) and consequently up-regulates CXCR4 expression [38].
mTOR inhibitors include everolimus, temsirolimus, and ridaforolimus. The FDA has approved everolimus and temsirolimus to treat renal cell carcinoma and astrocytoma respectively. Clinical trials are ongoing to test ridaforolimus antitumor activity both in cell lines and in xenograft tumor models. Ridaforolimus has shown promising clinical data in treating sarcoma and hematological malignancy, but its effect in lung cancer is still under trial. Everolimus shows limited activity in NSCLC whether used alone or in combination with other chemotherapeutic agents [23]. Temsirolimus has shown minimal effect when used as monotherapy for NSCLC and clinical trials are ongoing for its use in combination with other chemotherapy as neratinib and pemetrexed [26]. Ridaforolimus shows promising results in cases of NSCLC with KRAS mutation [22].

Future lung cancer therapy and recommendations

Lung cancers can show resistance to TKI therapy, even in the presence of an activating mutation in EGFR. Recent studies have uncovered many different molecular mechanisms underlying the primary and secondary resistance to TKI therapy [24]. Biomarkers are used to identify patients who would benefit from the specified targeted treatments and also to avoid the development of unnecessary toxicity. mTOR inhibitors are monitored by the measurements by Western blotting or immunohistochemistry of S6K and 4E-BP1 phosphorylation. The data for lung cancer biomarkers is limited and need more investigations.

mTOR has a complex function and is tumor specific which necessitates the use of different classes of biomarkers to accurately predict responses to mTOR inhibitors. The mTOR inhibitors might only benefit patients with specific molecular alterations, therefore, predictive biomarkers are essential for future clinical trials to select the proper patients and adjust the dosage together with other targeted molecular therapy. Researchers in laboratory medicine and pathology play a vital role in identifying and validating new parameters or biomarkers for cancer treatment and early detection, as well as surgical and clinical pathologists are often involved in the direction of multicentric clinical trials.

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