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Targeting PI3K/AKT/mTOR Pathway and Mutant EGFR to Overcome Resistance to Tyrosine Kinase Inhibitors in Mutant EGFR-Mediated Lung Cancer

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ABSTRACT

Lung cancer is the leading cause of cancer-related deaths in the United States and worldwide. Targeted therapy of mutant Epidermal Growth Factor Receptor (EGFR)-mediated lung cancer with tyrosine kinase inhibitors (TKIs) has greatly improved clinical outcome. However, lung tumors inevitably develop resistance to TKI drugs within a year. Identified resistant mechanisms include: acquisition of a secondary mutation in EGFR (T790M) or mutations in PI3KCA, amplification of MET tyrosine kinase receptor, overexpression of MET ligand Hepatocyte Growth Factor (HGF), or transformation to small cell lung cancer. Many of these resistant mechanisms involve the reactivation of the phosphatidylinositol 3-kinase (PI3K) /AKT/ mammalian target of rapamycin (mTOR) pathway in tumor cells. Studies have shown that inhibition of the PI3K/AKT/mTOR pathway suppressed the growth of EGFR mutant TKI-resistant lung cancer cell lines; furthermore, a combination of PI3K/AKT/mTOR inhibitor and an EGFR TKI enhanced turmor regression in xenograft models. The data reviewed in this literature suggests that a combinatory therapy of PI3K/AKT/mTOR inhibitors with EGFR TKIs provides a promising way to overcome EGFR TKI resistance.

Keywords: *EGFR mutant, Lung cancer, TKI resistance, PI3K/AKT/mTOR pathway, mTOR inhibitor, Tumor regression*

Introduction

Treatment for lung cancer has been a big challenge in the United States, and the five-year survival rate of lung cancer is only about 17% [1]. Lung adenocarcinoma is the major histopathological subtype of lung cancer and is implicated in about 40% of lung cancer patients. Recent research advances in the identification of driver events, such as Epidermal Growth Factor Receptor (EGFR) mutations, in lung adenocarcinoma have greatly promoted precision medicine. EGFR activating mutations are found in 10-15% of lung adenocarcinomas [2-4]. These mutations lead to constitutive activation of the EGFR receptor [5,6] and are sufficient to induce lung tumors in mice [7,8]. Tumors bearing activating EGFR mutations are sensitive to treatment with reversible EGFR tyrosine kinase inhibitors (TKIs) with a response rate of about 70%, which is more effective compared to a 40% response rate with chemotherapy [9,10]. However, patients who initially respond to TKI treatment inevitably develop resistance on average within about a year. Currently, the resistance to EGFR TKIs remains a major problem for lung cancer patients. Various strategies are in development to circumvent EGFR TKI-resistance including a combinatory treatment with PI3K/AKT/mTOR inhibitors and EGFR TKIs. This review will discuss the role of PI3K/AKT/mTOR pathway in EGFR TKI-resistant lung cancers, and focuses on the recent research advances made in combined blockade of the PI3K/AKT/mTOR pathway and mutant EGFR.

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EGFR TKI Resistant Mechanisms Involve Reactivation of The PI3K/AKT/mTOR pathway

Activating mutations of EGFR, either deletions in exon 19 or a point mutation L858R in exon 21, constitutively activate EGFR downstream signaling including the mitogen-activated protein (MAP) kinase pathway and the PI3K/AKT/mTOR pathway (Fig. 1). Upon activation, receptor tyrosine kinases

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(RTKs), including EGFR, activate PI3 kinase, which converts phosphatidylinositol-3,4-bisphophate (PI(3,4)P2) to phosphatidylinositol-3,4,5-triphosphate (PI(3,4,5)P3). PIP3 then recruits PDK-1 (phosphoinositide-dependent kinase 1) and AKT to cell membrane, and leads to activation of AKT by PI3K and PDK1. AKT then dissociates from plasma membrane, and activates a variety of downstream targets in the cytoplasm and nucleus to regulate cell growth, proliferation, and survival. One important AKT downstream mediator is mTOR, which phosphorylates eIF4E binding proteins (4E-BPs) and S6 kinases and regulates protein synthesis (Fig. 1).

Mounting evidence indicates that many TKI-resistant mechanisms in EGFR mutant lung cancer involve reactivation of the PI3K/AKT/mTOR pathway (Fig. 1). First, mutant EGFR activates the PI3K/AKT/mTOR pathway by forming a homo-dimer or hetero-dimer with ERBB3. EGFR with acquired resistant mutation T790M, which is found in about 50% of resistance cases, causes sustained activation of ERBB3 and AKT in the presence of reversible EGFR tyrosine kinase inhibitors, gefitinib or erlotinib [11]. Second, the PI3K/AKT/mTOR pathway can be activated by receptor tyrosine kinases such as MET or Insulin-like growth factor 1 receptor (IGFIR). MET amplification has been reported in 5-22% of TKI-resistant tumors with EGFR mutation [12-14]. In a subset of EGFR TKI-resistant lung cancer with MET amplification, MET constitutively activates the PI3K/AKT/mTOR pathway in the presence of gefinitib by transactivating ERBB3 [15]. Third, amplification of MET ligand HGF also leads to sustained activation of AKT without involving EGFR or ERBB3 [16].

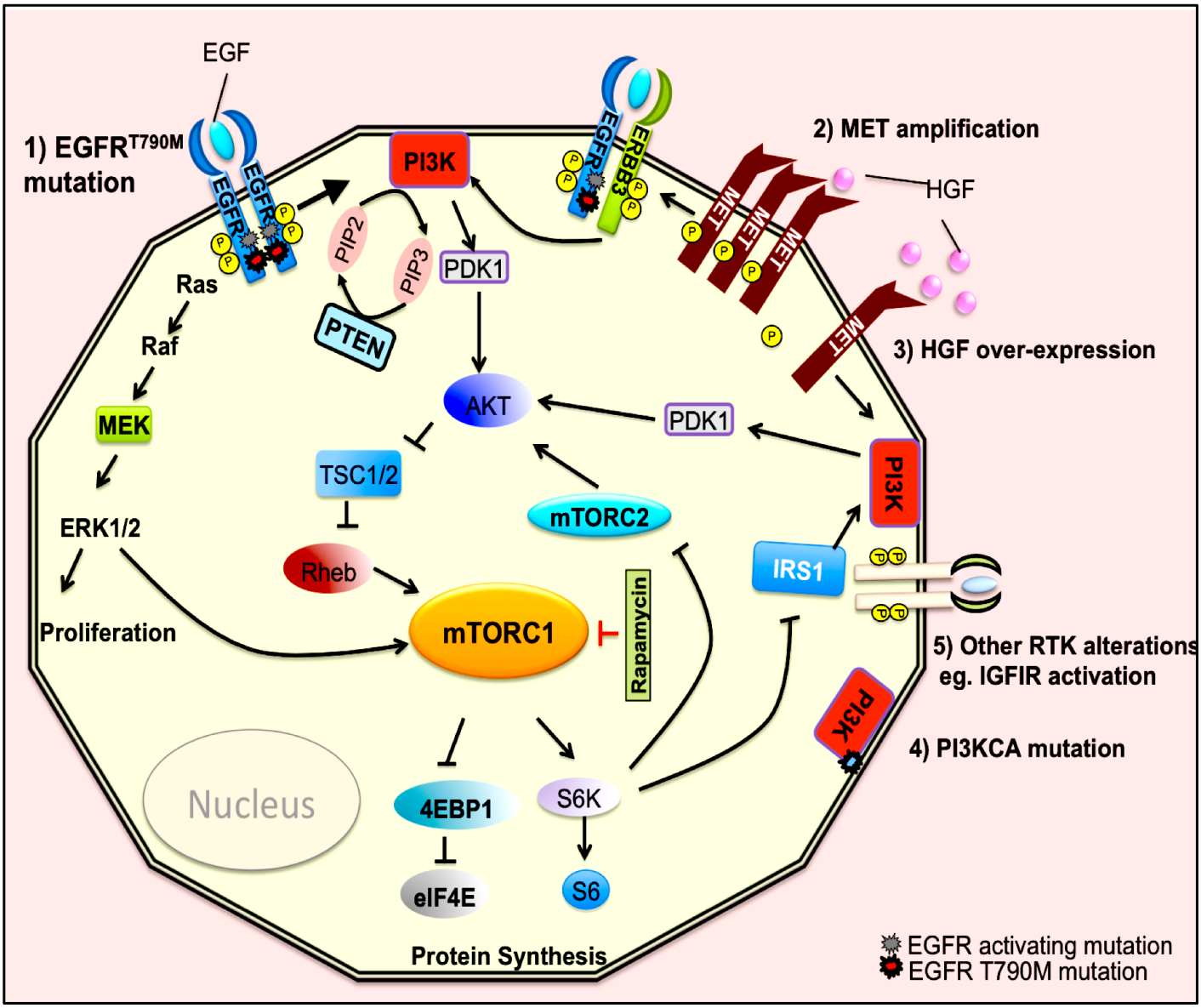

Figure 1: Different EGFR TKI-resistant mechanisms involve reactivation of the PI3K/AKT/mTOR pathway: EGFR TKI resistant mechanisms include: 1) acquisition of a second mutation T790M on mutant EGFR, 2) amplification of MET, 3) over-expression of HGF, 4) PI3KCA mutation, and 5) other RTK alterations (eg. IGFIR) lead to reactivation of the PI3K/Akt pathway in the presence of EGFR reversible tyrosine kinase inhibitors. Notably, mutant EGFR do not need the presence of EGF to be activated. Inhibition of mTORC1 by rapamycin and its analogs leads to feedback activation of AKT through mTORC2 and IRS1.

Fourth, PI3KCA mutation, p110αE545K, has been reported in about 5% of acquired resistance cases [12]. The oncogenic mutation of PI3KCA causes prolonged phosphorylation of AKT and reduced apoptosis of cancer cells in the presence of gefitinib [11]. Based on the observations that many TKI-resistant mechanisms relate to reactivation of the PI3K/AKT/mTOR pathway, it is likely that the combined treatment with PI3K/AKT/mTOR inhibitors and EGFR TKIs might overcome resistance in EGFR mutant TKI-resistant lung cancer.

Feedback Activation of AKT Limits Single Agent Use of mTOR Inhibitors

mTOR inhibitors rapamycin and its derivatives are the most extensively studied inhibitors of the PI3K/AKT/mTOR pathway. These inhibitors form a complex with FKBP12 to inhibit mTOR complex 1 (mTORC1) activity and cause G1 cell cycle arrest [17]. mTORC1 downstream targets p70 S6 kinase (S6K) was shown inhibited by rapamycin in several lung cancer cell lines [18]. However, S6K negatively regulates both Insulin Receptor Substrate 1 (IRS-1) and mTORC2 which both activate AKT, and rapamycin cannot block the activity of mTORC2; therefore, blockade of mTORC1 eventually activates AKT by feedback activation of IRS-1 and mTORC2 [18]. Feedback activation of AKT greatly attenuates the anti-proliferation effect of rapamycin in lung cancer cells [17] (Fig. 1).

Due to the feedback regulation of the PI3K/AKT/mTOR pathway by mTOR inhibitors, a combined treatment of an mTOR inhibitor with a PI3K or AKT inhibitor might be necessary to fully inhibit the PI3K pathway. Alternatively, inhibitors that target both mTORC1 and mTORC2 might overcome the feedback regulation of the PI3K/AKT/mTOR pathway and enhance drug efficacy. A variety of novel inhibitors against multiple mediators of the PI3K/AKT/mTOR pathway have been investigated, including pan-PI3K inhibitors [19] and dual PI3K/mTOR inhibitors [20] (Fig. 3). It has been shown that combined use of rapamycin with LY294002, an inhibitor of both mTOR kinase and phosphatidylinositol 3-kinase (PI3K), in lung cancer cells greatly enhanced the inhibition effect of rapamycin on growth and colony formation [18]. A different study showed that using rapamycin with a dual inhibitor of PI3K and mTOR (NVP-BEZ235) synergistically inhibited the growth of both EGFR mutant and EGFR wild type non-small cell lung cancer [21].

In TKI-resistant EGFR mutant lung cancer cells, both the PI3K/AKT/mTOR pathway and the MAPK pathway are highly activated, and mTOR can be activated by the MAPK pathway [22] (Fig. 1). Therefore, PI3K/AKT/mTOR pathway inhibiton alone is not enough to achieve maximum inhibition; hence, EGFR TKIs, which inhibit both the PI3K/AKT/mTOR pathway and the MAPK pathway, are essential to inhibit of lung cancer cell growth. A combination of PI3K/mTOR pathway inhibitors with EGFR TKIs is thus necessary to treat the TKIs-resistant lung cancer.

Inhibitors of PI3K Signaling Pathway in Combination With EGFR TKI Reverse Lung Tumor Progression

Because the PI3K/AKT/mTOR pathway is highly activated in many EGFR mutant TKI-resistant lung cancer, strategies that inhibit the PI3K/AKT/mTOR pathway have been investigated in combination with EGFR TKIs. Some of these inhibitors have been shown to work cooperatively with EGFR TKIs to regress the growth of TKI-resistant lung cancer cells.

A. **mTOR inhibitors:** To monitor the erlotinib resistant mechanisms of mutant EGFR-mediated lung cancer, mouse models have been built to express mutant EGFR with both activating mutation L858R and the gatekeeper resistant mutation T790M [23]. In these TKI-resistant mouse models, an irreversible EGFR TKI (HKI-272) has been tested alone or in combination with mTOR inhibitor rapamycin [23,24]. HKI-272 inhibited the activity of both EGFR and ERBB2. ERBB2 is a member of the EGFR family and is frequently activated in mutant EGFR-mediated lung tumor. Although rapamycin alone did not result in tumor regression, and HKI-272 alone led to regression of peripheral murine lung tumors, a combination of HKI-272 and rapamycin led to extensive regression of both peripheral and bronchial tumors induced by resistant EGFR mutants. However, although erlotinib synergized with rapamycin in inhibiting the growth of some EGFR wild type lung cancer cell lines, there was no synergism observed in EGFR mutant TKI-resistant lung can cells [23, 25]. These studies suggest that combination of mTOR inhibitors with the second generation irreversible EGFR tyrosine kinase inhibitors provide a better way to treat EGFR mutant TKI-resistant lung cancer with T790M mutation.

B. AKT kinase-interacting protein 1 (AKI1) targeting: Adaptor scaffold protein AKI1 is another ideal target in blocking the PI3K/AKT pathway. In EGFR wild type cells, AKI1 recruits both PDK1 and AKT to phosphorylateded EGFR, which in turn leads to activation of the AKT-mediated signaling [26] (Fig. 2). In EGFR mutant lung cancer cells, AKI1 is broadly expressed [26], and mutant EGFR is constitutive active [5,6]. Thus, AKI1 constitutively activates the AKT/mTOR pathway in these cancer cells even in the absence of EGFR ligands [26] (Fig. 2). Data showed that knockdown of AKI1 by siRNA decreased the phosphorylation level of AKT and S6, promoted cell apoptosis, and significantly inhibited the growth of TKI-resistant EGFR mutant lung cancer cells [26]. Concurrent treatment with AKI1 siRNA and EGFR irreversible TKIs, such as HKI-272, afatinib(BIBW2992) or WZ4002, potentiated the growth inhibition effect of those TKIs in lung cancer cells [26].

C. PI3K inhibitors: Increased level of HGF confers EGFR TKI resistance by activating downstream the MEK/ERK pathway and the PI3K/AKT pathway (Fig. 1). Although mTOR inhibitors reduced the cell viability of EGFR mutant lung cancer cells in the presence of HGF, and reduced the tumor

growth of HGF-mediated TKI-resistant xenograft; mTOR inhibition did not sensitizing EGFR mutant lung cancer cells to erlotinib in HGF-mediated resistance [27]. On the contrary, a short time exposure of class I PI3K inhibitor PI-103 with gefitinib treatment produced a prolonged inhibition of AKT phosphorylation, promoted cell apoptosis, and led to tumor regression in HGF-mediated TKI-resistant xenograft model [28].

D. Dual inhibitors of PI3K/mTOR: H1650 is a lung adenocarcinoma cell line expressing mutant EGFR (exon 19 deletion) with PTEN loss and EGFR TKI resistance [32]. Using a dual inhibitor of PI3K and mTOR (NVP-BEZ235) with erlotinib synergistically decreased cell viability of H1650 [21].

E. Inhibitors of other factors in the PI3K/AKT/mTOR pathway: Glycolysis inhibitor 2DG (2-deoxy-d-glucose) enhanced afatinib sensitivity in T790M-mediated TKI-resistant lung cancer cell lines by phosphorlating AMP-activated protein kinase (AMPK) and inhibiting mTOR [33]. In addition, MET inhibitor bufalin blocked the activation of the PI3K/AKT/mTOR pathway and sensitized HGF-mediated TKI-resistant cells to gefitinib by decreasing the protein levels of c-Met [29-31].

Clinical Trials Using PI3K/AKT/mTOR Pathway Inhibitors and EGFR TKIs For Treatment of EGFR Mutant Lung Cancer

Observations from *in vitro* and *in vivo* experiments that PI3K/AKT/mTOR inhibitors work cooperatively with EGFR TKIs to overcome resistance have led to several clinical trials [34, 35]. Most ongoing clinical trials use the combination of PI3K/AKT/mTOR inhibitors with the first generation reversible EGFR inhibitor erlotinib or gefitinib. These combinatory inhibitors being tested include(Fig. 3): *1) Pan-PI3K inhibitor:* XL147 with erlotinib (Phase I, Trial# NCT00692640); *2) dual PI3K/mTORC1/2 inhibitor*: XL765 + erlotinib (phase I, NCT00777699); *3) pan-AKT inhibitor*: MK-2206 + gefinitinib (phase I, NCT01147211) or MK-2206 + erlotinib or AZD6244 (MEK inhibitor, phase II, trial # NCT01248247) and MK-2206 + erlotinib (phase II, trial # NCT01294306). Because the second-generation irreversible EGFR TKIs are more potent than the first generation reversible TKIs in inhibition of mutant EGFR activity, using irreversible EGFR inhibitors more likely achieves a better response in EGFR mutant TKI-resistant lung cancer than using the first generation of TKIs especially in those T790M-mediated resistance cases. Recently, a second-generation EGFR TKI afatinib (Boehringer Ingelheim Pharmaceuticals, Inc.) has been approved as a first line therapy for lung cancer patients with EGFR mutations [36]. An ongoing clinical trial (Phase Ib, NCT00993499) using afatinib plus mTOR inhibitor Sirolimus (Rapamune, Boehringer Ingelheim Pharmaceuticals) to treat patients with relapsed EGFR mutant lung adenocarcinoma shows more promise than erlotinib or gefitinib treatment.

Discussion and Conclusions

The PI3K/AKT/mTOR pathway is highly activated in resistance to chemotherapy and EGFR-targeted therapy of lung cancer. Although many antagonists of the PI3K/AKT/mTOR pathway have been developed, a combined treatment with multiple inhibitors or dual inhibitors is more efficicent in inhibition of the PI3K/AKT/mTOR pathway due to feedback regulation. Advances have been made in both research and

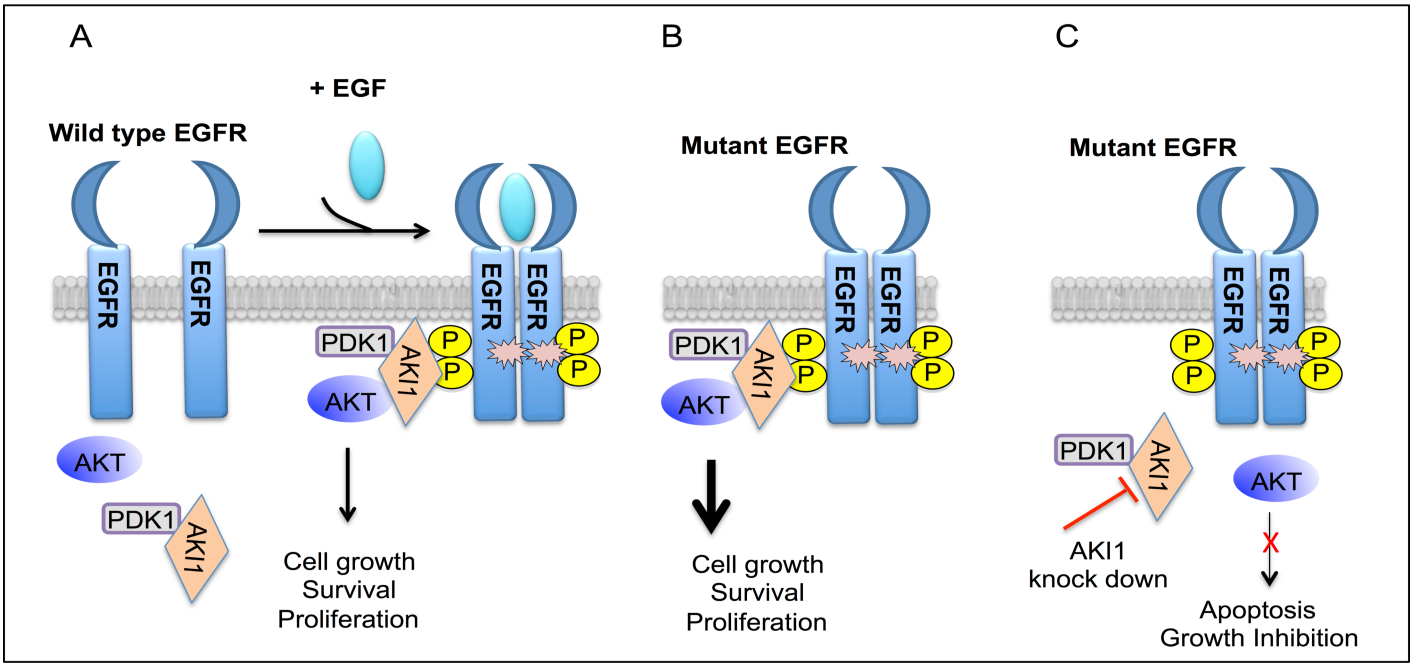

Figure 2: AKI1 associates PDK1 and AKT with activated EGFR: A) In the absence of EGF, AKI1 does not bind AKT and EGFR. After addition of EGF, EGFR is activated and associated with AKT and PDK1 via AKI1. B) Mutant EGFR is highly active even in the absence of EGF. Mutant EGFR, both activating and resistant conferring, is constitutively associated with AKT and PDK1 via AKI1. C) AKI1 knockdown dissociates AKT and PDK1 from EGFR and leads to inhibition of AKT activity. This figure was adapted from Yamada [26].

clinical use of PI3K/AKT/mTOR inhibitors in EGFR mutant lung cancer treatment. Convincing data show that inhibition of both the PI3K/AKT/mTOR pathway and mutant EGFR is a promising way to overcome drug resistance. Some EGFR mutant TKI-resistant cancer cells do not respond to erlotinib due to acquisition of a secondary mutation T790M in EGFR, which decreases the ATP binding affinity to first generation TKIs. In these cases, due to the high potency of second-generation irreversible TKIs in the ability to inhibit mutant EGFR, irreversible TKIs are more promising to regress tumor growth. Therefore, a combination of PI3K/AKT/mTOR inhibitors with an irreversible TKI is superior to that of using a reversible inhibitor to treat TKI drug resistant lung cancer.

There are also other rational combination drug therapies in development to overcome EGFR TKI resistance in EGFR-mutant lung cancer. First example is combined therapy of EGFR tyrosine kinase inhibitor and MET kinase inhibitor. Treatment with the combination of MET inhibitors and EGFR TKIs may overcome the resistance mediated by MET amplification or overexpression of MET ligand HGF. A combined therapy of dual AXL/c-MET inhibitor (CEP-40783) and erlotinib has significantly enhanceded tumor regression in erlotinib-resistant Champions TumorGraft™ models [37]. Currently, the efficacy of combination therapy of using EGFR and MET inhibitor is being tested by phase I clinical trial (NCT01121575). Another example is blocking both ERBB3 and EGFR to overcome TKI resistance. ERBB3 has shown involved in MET-mediated TKI resistance. Co-administration of ERBB3 antibody MM121 with EGFR antibody cetuximab led to the regression of EGFR TKI resistant tumors expressing T790M in mouse models [38], which has spurred an ongoing

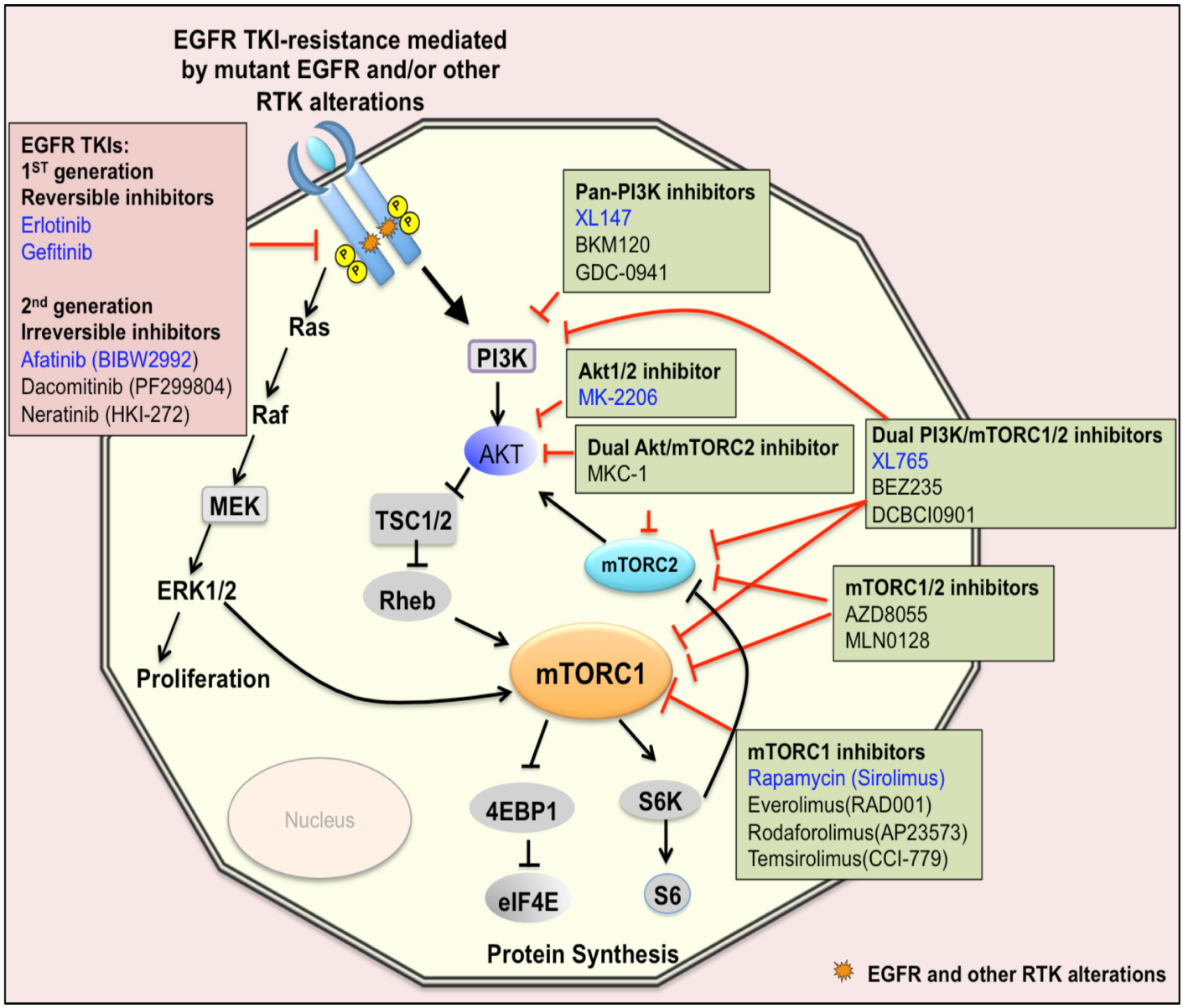

Figure 3: Inhibitors have been developed to target mutant EGFR and the PI3K/Akt/mTOR pathway in treatment of lung adenocarcinoma. Inhibitors of the PI3K/Akt/mTOR pathway that are undergoing investigation for treatment of lung adenocarcinoma are listed. Inhibitors of the PI3K/Akt/mTOR pathway or mutant EGFR that are used in current clinical trials to overcome EGFR TKI resistance are shown in blue.

phase I clinical trial of using MM-121 and cetuximab (NCT01451632) in advanced non-small cell lung cancers. Simultanesouly, a phase I/2 clinical trial using MM-121 with erlotinib as a standard therapy is ongoing (NCT00994123). While using specific inhibitors/antibodies against MET or ERBB3 provides benefits to a subset of patients, targeting both the PI3K/AKT/mTOR pathway mediators and mutant EGFR is likely to be a promising therapeutic strategy for a broad range of lung cancer patients. Furthermore, due to the heterogeneity of lung cancer, more than one resistant mechanism may exist in the same patient; thus, targeting the common PI3K/AKT/mTOR pathway downstream from several resistant mechanisms likely provides a superior way to overcome EGFR TKI resistance.

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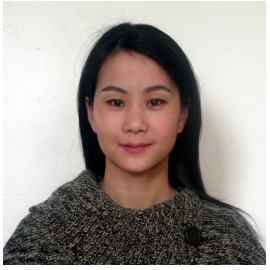

Dr. Song is a postdoctoral fellow at Yale University School of Medicine. She got her Ph.D. at Iowa State University, where she received training in genetics, molecular biology, and biochemistry. During her postdoc, her research is focused on cancer biology, signal transduction, and mouse modeling of human lung cancer. Currently, Dr. Song is studying the role of ERBB2 and ERBB3 in mutant EGFR-mediated lung tumorigenesis and drug resistance. Dr. Song is a grant recipient of the Uniting Against Lung Cancer 2012 Legacy Program. She received the 2013 *Leslie H. Warner Postdoctoral Fellowship for Cancer Research* from Yale Cancer center.