Targeting mTOR Signaling for Lung Cancer Therapy

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The mammalian target of rapamycin (mTOR), a 289 kD serine/threonine kinase, belongs to the phosphatidylinositol kinase-related kinase family. It plays a central role in regulating cell growth, proliferation, and survival, in part by regulation of translation initiation.1–3 In response to mitogen or nutrient stimulation, mTOR regulates translation initiation, primarily through two distinct pathways: ribosomal p70 S6 kinase (p70S6K) and eukaryotic translation initiation factor 4E (eIF4E) binding proteins (4E-BPs). Activated p70S6K by mTOR further phosphorylates the 40S ribosomal protein S6, leading to enhancement of the translation of mRNAs. In addition, mTOR also directly phosphorylates 4E-BP1, which triggers additional phosphorylation events that cause phosphorylated 4E-BP1 to dissociate from eIF4E, thereby increasing the cap-dependent translation of mRNAs, such as cyclin D1 and c-Myc (Fig. 1).1–3 Therefore, phospho-p70S6K (or phospho-S6) and phospho-4E-BP1 are common read-outs of the mTOR signaling.

The PI-3 kinase (PI3K)/Akt signaling represents a major cell survival pathway. Its activation has long been associated with malignant transformation and apoptotic resistance.4 It is generally thought that mTOR functions downstream of the PI3K/Akt pathway and is phosphorylated (or activated) in response to stimuli that activate the PI3K/Akt pathway (Fig. 1).1,3 In addition to positive regulation of the mTOR axis by PI3K/Akt, recent evidence has linked LKB1, a serine/threonine kinase with tumor suppression activity, to the negative regulation of the mTOR axis.5 It has been proposed that, in response to cellular energy stress, AMP-activated protein kinase (AMPK) is activated through LKB1-mediated phosphorylation and then phosphorylates TSC2 (or tuberin) to enhance TSC2 function. TSC2 subsequently inhibits mTOR function via TSC2’s GAP activity toward the Rheb small GTPase (Fig. 1).5 Under normal conditions, LKB1/AMPK activation overrides the mitogenic signal from Akt and tightly controls mTOR signaling. However, in the absence of LKB1, AMPK cannot be activated, nor can mTOR be inactivated, in response to cellular energy stress.4,7

PI3K/Akt is one of the best characterized pathways downstream of the Ras oncogene.8 Because of mutation and overexpression of growth factors and/or their receptors, the Ras signaling pathway is frequently activated in human non-small cell lung cancer (NSCLC).9–11 As a result, the PI3/Akt pathway is also frequently activated in human NSCLC, as demonstrated in several studies.12–16 Although somatic LKB1 mutations are rare in most sporadic tumor types,17,18 there is a high frequency of LKB1 mutations in human NSCLC, particularly adenocarcinomas. It has been reported that LKB1 gene alterations were present in 54% of lung adenocarcinoma cell lines and in approximately 30% of primary lung adenocarcinomas.19,20 Thus, it seems that LKB1 inactivation is a critical event in the development of sporadic lung adenocarcinomas.

Because of the constitutive activation of PI3K/Akt signaling and frequent mutations or inactivation of the LKB1 gene, it is likely that the mTOR axis is dysregulated and activated in human NSCLC, particularly adenocarcinomas. Indeed, a recent report by Balsara et al.14 indicates that phosphorylation or activation of mTOR was detected in 74% of NSCLC, which was significantly associated with activation of Akt. Therefore, the mTOR signaling axis represents a highly promising therapeutic target for lung cancer therapy. Rapamycin and its derivatives CCI-779 and RAD001 are novel anticancer drugs developed to modulate mTOR activation.1,3 Our studies have shown that rapamycin is effective in inhibiting the growth of human NSCLC cells.21 In animal models, rapamycin effectively inhibited the growth of a NSCLC tumor22 and alveolar epithelial neoplasia induced by oncogenic K-Ras.23

Several recent studies have shown that an mTOR inhibitor such as RAD001 sensitizes cancer cells to chemother-apy,24,25 radiation,26 or overcomes chemoresistance27 in several types of cancer cells, including lung cancer cells. Our unpublished data also show that the combination of rapamycin and docetaxel is synergistic in inhibiting the growth of lung cancer cells. Therefore, we postulate that mTOR inhibitors, like other signal transduction inhibitors, could be more efficacious if used in combination with other agents or therapies, such as chemotherapy or other targeted agents in lung cancer treatment, as long as these combinations are based on sound preclinical and clinical drug development principles. Our recent data clearly show that mTOR inhibition by rapamycin triggers rapid and sustained activation of PI3K/Akt survival pathway, in human lung and other types of cancer.
cells. Thus, one rational approach for mTOR-targeted lung cancer therapy is to use an mTOR inhibitor in combination with a drug that blocks PI3K/Akt activation such as a PI3K inhibitor, as we demonstrated in our study.

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