Lipophilic bisphosphonates plus rapamycin: a deadly combination for *KRAS*-mutated lung adenocarcinoma

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Lung cancer has remained the No. 1 cause of cancer mortality in the world, responsible for more than a million deaths annually (1). Lung adenocarcinoma is one of the three major subtypes of non-small cell lung cancer (NSCLC), the most common type of lung cancer. About half of the lung adenocarcinomas harbor driver mutations that may serve as therapeutic targets. For instance, most of the lung adenocarcinomas with *EGFR* mutations can be treated with *EGFR* tyrosine kinase inhibitors, such as gefitinib and erlotinib (2). The ALK inhibitor crizotinib has also been proven to improve the progression free survival (PFS) and overall survival (OS) of lung adenocarcinoma patients with *ALK* rearrangements (3).

The *KRAS* gene (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) encodes for a small GTPase that is essential for embryogenesis (4). Oncogenic *KRAS* mutations that lead to its constitutive activation have been discovered for about two decades. Overall, about 10-30% of lung adenocarcinoma patients harbor *KRAS* mutations, and the incidence of mutation may be higher in smokers and Caucasian patients (5-7). As *KRAS*-mutated lung adenocarcinomas have poor prognosis, preclinical and clinical studies have been focusing on various strategies that target either KRAS (e.g., the farnesyltransferase inhibitor antroquinonol) (8) or its downstream signaling pathways (e.g., the MEK1/2 inhibitor selumetinib) (9). However, despite some exciting effect reported in preclinical studies and early phase trials, clinical efforts to cure *KRAS*-mutated lung adenocarcinomas have been unsuccessful. In addition, *KRAS* mutations in lung adenocarcinomas are known to associate with resistance to targeted therapy, for instance the resistance to EGFR inhibitors (5,6). Thus, there is a critical need for developing novel therapeutics for *KRAS*-mutated lung adenocarcinomas.

In a recent study published in last November issue of *Science Translational Medicine*, Xia *et al*. presented promising and exciting evidence that the combined use of lipophilic bisphosphonates and rapamycin may effectively treat *KRAS*-mutated lung adenocarcinomas (10). Bisphosphonates, such as alendronate and risedronate, can bind to bone mineral and inhibit farnesyldiphosphate synthase. They have been used to treat osteoporosis, Paget's disease of bone, and bone metastasis (en.wikipedia.org). Xia *et al*. reported that lipophilic bisphosphonates inhibited both farnesyl and geranylgeranyldiphosphate synthases, blocked the prenylation of KRAS, induced the degradation of KRAS, enhanced ER stress, and initiated autophagy, which was unsuccessful but eventually led to the accumulation of p62 and p62-dependent NF-κB activation, resulting in enhanced cell growth and reduced anti-tumor efficacy of lipophilic bisphosphonates *in vivo* (10). Intriguingly, co-treatment with rapamycin, an autophagy activator and mTOR inhibitor, dramatically sensitized *KRAS*-mutated lung adenocarcinoma cells to lipophilic bisphosphonates treatment *in vivo* by facilitating the lipophilic bisphosphonates-induced autophagy and by preventing the p62-dependent NF-κB activation and cell proliferation (10).

These results undoubtedly warrant future studies

testing the efficacy of a combined therapy using lipophilic bisphosphonates and rapamycin in treating *KRAS*-mutated lung adenocarcinomas. On the other hand, they also raised a number of interesting questions that are critical for both understanding better the action mechanisms of the drugs and identifying patients who may benefit from such a combined therapy. For instance, what is the role of autophagy in *KRAS*-mutated lung adenocarcinomas? It is known that autophagy has a context-dependent role in carcinogenesis. It may act as a surveillance program to prevent malignant transformation and tumorigenesis, but can also be utilized as a survival mechanism to drive tumor growth (11). Autophagy may also play differential roles in different types of cancer cells. In lung and pancreatic cancer cells, autophagy was thought to promote metabolite turnover to drive tumor growth (11). In genetically engineered mouse model of *KRAS*-mutated lung adenocarcinomas, autophagy was essential for the metabolism and growth of tumor cells, and inhibition of autophagy (by *ATG7* deletion) led to the regression of adenoma and adenocarcinoma to benign oncocytic neoplasms or oncocytomas (12). This seemingly contrasts to the findings by Xia *et al*. that lipophilic bisphosphonates and rapamycin promoted autophagy to inhibit *KRAS*-mutated lung adenocarcinoma growth (10). However, it should be noted that rapamycin has an additional role as a growth inhibitor by inhibiting mTOR, a critical component of KRAS-dependent cell survival and growth signaling pathways, making the combined use of rapamycin and lipophilic bisphosphonates as a promising strategy to treat *KRAS*-mutated lung adenocarcinomas. As autophagy may have distinct effect in the cancer initiation and malignant progression (11), future studies should also determine whether early *vs*. advanced stage lung adenocarcinomas differentially respond to this combination therapy. In this case, mouse models of human lung adenocarcinomas may be especially useful as that lung tumors at different stages develop in these models with relatively well-defined pathological processes (13). Another interesting question is whether this combination therapy is only specifically effective for *KRAS*-mutated lung adenocarcinomas? Given that other GTPases were also targeted by lipophilic bisphosphonates (10), and bisphosphonates were effective to treat *EGFR*-mutated lung tumors (14), it would be interesting to determine if this combination therapy has broader applications and is useful for treating lung adenocarcinoma patients with other gene mutations. This would be helpful for identifying patients that likely will respond to the treatment.

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Footnote

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