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APE1 promotes EGFR-TKI acquired resistance in non-small cell lung cancer through regulating epithelial to mesenchymal transition

Xiao Yang and Mengxia Li
Daping Hospital, China

While EGFR-tyrosine kinase inhibitors (TKIs) significantly improve the survival and quality of life in advanced non-small cell lung cancer (NSCLC) patients carrying EGFR mutations, its acquired resistance limits the clinical benefit thus becoming a big concern of oncologists' community. The current study reported that human apurinic/apyrimidinic endonuclease 1 (APE1) plays pivotal roles in EGFR-TKI resistance and the expression of APE1 in the biopsy tissue pretreatment could be a predictive marker for the survival of EGFR-TKI treatment. This implies a possible predicting strategy for EGFR-TKI responses by detecting tissue, or monitoring serum APE1 levels. More importantly, the APE1 redox inhibitor, E3330, turned back on cellular response to EGFR-TKIs in established resistant cell lines further suggests a promising therapeutic combination of APE1 inhibitor and EGFR-TKIs with hope of continuous clinical benefit. To link APE1 to the responses to EGFR-TKIs in NSCLC, the protein level of APE1 were analyzed in cancerous tissue of NSCLC patients receiving EGFR-TKIs treatment. The correlation between APE1 expression and progression-free survival (PFS), overall survival (OS) or response rate were analyzed. The impact on EGFR-TKI responses by APE1 was measured by exogenously manipulation of APE1 in EGFR-TKI sensitive and resistant cell lines. Further mechanistic studies were performed to explore the regulatory roles of APE1 in important EGFR-TKI resistance related process, epithelial-to-mesenchymal transition (EMT) by detection of E-cadherin and vimentin markers. The current study revealed a significant role of APE1 in EGFR-TKI resistance via a novel regulatory effect on EMT in NSCLC. It suggested the potential of APE1 inhibitors in combination of EGFR-TKIs for continuous clinical benefit in NSCLC patients carrying EGFR mutations.

2548183003@qq.com

Promises and challenges of molecular imaging for detection and image-guided therapy of pancreatic cancer

Lily Yang
Emory University School of Medicine, USA

Development of novel targeted imaging agents holds great promise for early detection of pancreatic cancer. The ability of noninvasive imaging of biomarker expression in pancreatic cancers further offers a means for the application of precision oncology using targeted cancer therapy. We have developed receptor targeted and multi-imaging modality nanoparticles that are targeted to cell surface receptors highly expressed in pancreatic cancer and active tumor stromal cells, such as urokinase plasminogen activator receptor (uPAR) and IGF-1R. This magnetic iron oxide nanoparticle platform coupled with near infrared (NIR) dye labeled targeting ligands has been demonstrated to be excellent NIR optical, MRI, photoacoustic, spectroscopic, and fluorescence tomography contrasts in human pancreatic tumor cell line derived or pancreatic cancer patient tissue (PDX) derived xenograft models in nude mice. Targeted delivery of the nanoparticles has also been demonstrated in a K-ras transgenic mouse pancreatic cancer model. Efficient accumulation of the nanoparticles in the early tumor lesions could be detected by NIR optical and MR imaging. We found that the majority of the receptor targeted nanoparticles in tumor tissues were localized in tumor stroma due to the presence of an intensive stromal barrier that limited nanoparticle delivery into tumor cells, which prevented accurately detection of the level of biomarker expression and efficient drug delivery in tumor cells. Therefore, tumor stromal barrier presents a major challenge for the application of targeted imaging nanoparticles to determine the level of biomarker expression in cancer cells for designing a biomarker targeted therapy.

lyang02@emory.edu