「肺がんの分子標的薬耐性を克服する治療の開発／Circumvention of Target Drug Resistance for Lung Cancer」

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Lung cancer is the leading cause of malignancy related death worldwide. Recently, several driver oncogenes, such as mutations in *EGFR* and rearrangements of *ALK, ROS-1*, and *BRAF*, in lung adenocarcinoma. Dramatic response has been achieved with targeted drugs in lung cancer expressing corresponding targets. However, cancer cells acquire resistance to these drugs and cause recurrence. On the other hand, minor population of patients show intrinsic resistance or insufficient response to targeted drugs even their tumors have driver gene alteration. Both acquired resistance and intrinsic resistance are critical problem of the management of lung cancer with driver oncogenes. Known major mechanisms for resistance to targeted drugs include gatekeeper mutations in the target gene, activation of bypass survival signal via receptors other than the target receptors, and epithelial to mesenchymal transition (EMT).

The third generation EGFR-tyrosine kinase inhibitor (TKI), osimertinib, has marked efficacy in patients with *EGFR*-mutated lung cancer. However, some patients show intrinsic resistance and an insufficient response to osimertinib. This study showed that osimertinib stimulated AXL by inhibiting a negative feedback loop. Activated AXL was associated with EGFR and HER3 in maintaining cell survival and inducing the emergence of cells tolerant to osimertinib. AXL inhibition reduced the viability of EGFR-mutated lung cancer cells overexpressing AXL that were exposed to osimertinib. The addition of an AXL inhibitor during either the initial or tolerant phases reduced tumor size and delayed tumor re-growth compared to osimertinib alone. AXL was highly expressed in clinical specimens of EGFR-mutated lung cancers and its high expression was associated with a low response rate to EGFR-TKI. These results indicated pivotal roles for AXL and its inhibition in the intrinsic resistance to osimertinib and the emergence of osimertinib-tolerant cells.