# Origin of resistance to lung-cancer drug discovered

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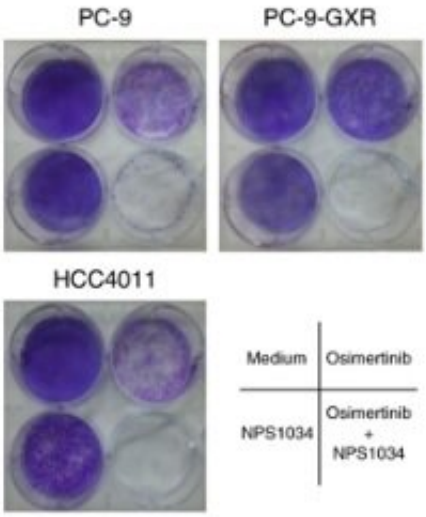


Treatment with osimertinib alone, AXL inhibitor NPS1034 alone, and osimertinib and NPS1034 combined. Credit: Kanazawa University

Researchers at Kanazawa University report in *Nature Communications* that AXL, a protein belonging to the class of receptor tyrosine kinases, causes some lung cancer patients to have an intrinsic resistance to the drug osimertinib. The combined application of osimertinib and an AXL inhibitor is shown to limit intrinsic resistance to the drug.

For treating cancer, drugs based on molecules known as tyrosine kinase inhibitors are sometimes used. One such tyrosine kinase inhibitor, called osimertinib, has been used to treat EGFR-mutated lung cancer with a certain degree of efficacy. (EGFR refers to epidermal growth factor receptor, a protein that plays an important role in signaling from the extracellular environment to a cell.) However, in some patients, intrinsic resistance and inadequate response to osimertinib has been observed. Seiji Yano from Kanazawa University and colleagues have now discovered that AXL causes the resistance to osimertinib and the emergence of osimertinib-tolerant cells.

The researchers first showed that in vitro, osimertinib activated AXL in EGFR-mutated lung cancer cells. Then they demonstrated an inverse correlation between AXL and susceptibility to tyrosine kinase inhibitors; AXL expression correlated with a poor response to treatment with osimertinib and with early tumor relapse.

Yano and colleagues checked whether drug-tolerant cells (cells with significantly reduced sensitivity to drugs) exhibited higher levels of AXL. Indeed, tolerant cells were found to display a higher expression of AXL compared to parental cells. Application of an AXL inhibitor called NPS1034 led to a decrease in survival of the drug-tolerant cells.

The scientists then investigated the effect of the AXL inhibitor combined with osimertinib in a mouse model. Treatment with only NPS1034 had no effect on the tumors. Treament with only osimertinib initially led to tumor regression, but tumor regrowth was observed within 7 weeks. Simultaneous treatment with NSP1034 and osimertinib led to tumor regression within a week, and the size of the tumors stabilized for 10 weeks. No adverse effects such as weight loss were observed during treatment.

The findings of Yano and colleagues provide important insights into the molecular mechanisms causing the tolerance to osimertinib in EGFR-mutated lung cancer cells, and particularly into the role of AXL—and the effect of inhibiting its activity. The scientists write, "These results suggest that treatment during the initial phase with a combination of osimertinib and an AXL inhibitor may prevent the development of intrinsic resistance to osimertinib and the emergence of drug-tolerant cells in EGFT-mutated lung cancer overexpressing AXL."

**More information:** Hirokazu Taniguchi et al, AXL confers intrinsic resistance to osimertinib and advances the emergence of tolerant cells, *Nature Communications* (2019). DOI: 10.1038/s41467-018-08074-0

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