Role of AXL activation on adaptive resistance to KRAS-G12C inhibitors in KRAS-G12C-mutated non-small cell lung cancer

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Background
KRAS is the most frequent targetable oncogene in non-small cell lung cancer (NSCLC). Recently, novel KRAS inhibitor have been clinically developed for treatment of KRAS G12C-mutated NSCLC patients. However, it is difficult to achieve complete remission of tumor. Therefore, the optimal combined therapeutic intervention with KRAS G12C inhibitors has a potentially crucial role in the clinical outcomes of patients. In this study, we focused on the mechanisms underlying adaptive resistance to KRAS G12C inhibitors and therapeutic strategies required to overcome them.

Methods
We used KRAS G12C-mutated NSCLC cell lines to evaluate the adaptive response to KRAS G12C inhibitors in vitro and in vivo. We also investigated the correlation between AXL expression in pre-treated tumors and clinical outcomes with sotorasib for KRAS G12C-mutated NSCLC patients.

Results
We reveal that AXL signaling was caused to the adaptive resistance to KRAS G12C inhibitors in KRAS-G12C mutated NSCLC, activation of which was induced by GAS6 production via transcriptional coactivator YAP. AXL inhibition reduced the viability of AXL-overexpressing KRAS G12C-mutated lung cancer cells by enhancing KRAS G12C inhibition-induced apoptosis. In xenograft models of AXL-overexpressing KRAS G12C-mutated lung cancer treated with KRAS G12C inhibitors, initial combination therapy with AXL inhibitor markedly regressed tumors and delayed tumor regrowth compared with KRAS G12C inhibitor alone or the combination after acquired resistance to KRAS G12C inhibitor. AXL was highly expressed in clinical specimens of KRAS G12C-mutated lung cancers and its high expression was associated with a low response rate to sotorasib.

Conclusions
These results indicated pivotal roles for AXL activation and its inhibition in the intrinsic resistance to KRAS G12C inhibitor.

Legal entity responsible for the study
The authors.

Funding
Has not received any funding.

Disclosure