mutated *CALR* transfected cells. They also enhanced the inhibitory effect of ruxolitinib. Azithromycin and clarithromycin, which inhibit autophagy, did not suppress these cells but did enhance the inhibitory effect of ruxolitinib. Further, ER stress inducers, such as tunicamycin and thapsigargin, strongly suppressed the growth of these cells.

These results suggest that inducing ER stress contributes to the anti-PMF effect by JAK inhibitors in *CALR*-mutated cells.

4-3.

Canonical TGF-β signaling upregulates sensitivity to tyrosine kinase inhibition in EGFR-mutated lung adenocarcinoma

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【Background】 By contrast with the numerous genetic mechanisms of acquired resistance to epidermal growth factor receptor（EGFR）tyrosine kinase inhibitors（TKI）in EGFR-mutated lung adenocarcinoma, the few mechanisms of primary resistance have been reported. Transforming growth factor（TGF）-β is the pivotal cytokine to regulate the progression and metastasis of cancers. Canonical TGF-β signaling pathway is mediated through TGF-β-specific receptor-regulated SMADs（R-SMADs）: SMAD2 and SMAD3 and the common SMAD : SMAD4. However, whether and how TGF-β regulates primary EGFR-TKI resistance in lung adenocarcinoma are yet to be determined.

【Objective】 We sought to determine whether and how SMADs regulate primary EGFR-TKI resistance in EGFR-mutated lung adenocarcinoma.

【Methods】 We examined immunohistochemistry of the EGFR-mutated lung adenocarcinoma specimens obtained from EGFR-TKI sensitive and resistant patients to evaluate the expression and phosphorylation status of SMADs. We examined lung adenocarcinoma cell lines : HCC827 harboring EGFRE746_A750del, NCI-H1975 harboring EGFRT790M and mouse Ex3LL-luc cells for the mechanistic investigation.

【Results】 We found that C-terminal phosphorylation of SMAD2 and SMAD3 along with the expression of SMAD4 were significantly downregulated in the lung adenocarcinoma from the patients who presented primary resistance to gefitinib or osimertinib, which were significant in the lung adenocarcinoma from the sensitive patients. RNA-seq of the lung cancer cell lines in which SMADs were overexpressed or knocked-down has identified the target genes of canonical TGF-β signaling for induction of EGFR-TKI sensitivity.

【Conclusion】 Downregulation of C-terminal phosphorylation of R-SMADs and SMAD4 in the treatment-naïve tumor biopsies could be biomarkers to predict primary resistance to EGFR-TKI in EGFR-mutated lung adenocarcinoma.

4-4.

HDAC 阻害剤の抗骨髄腫作用に関する研究

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