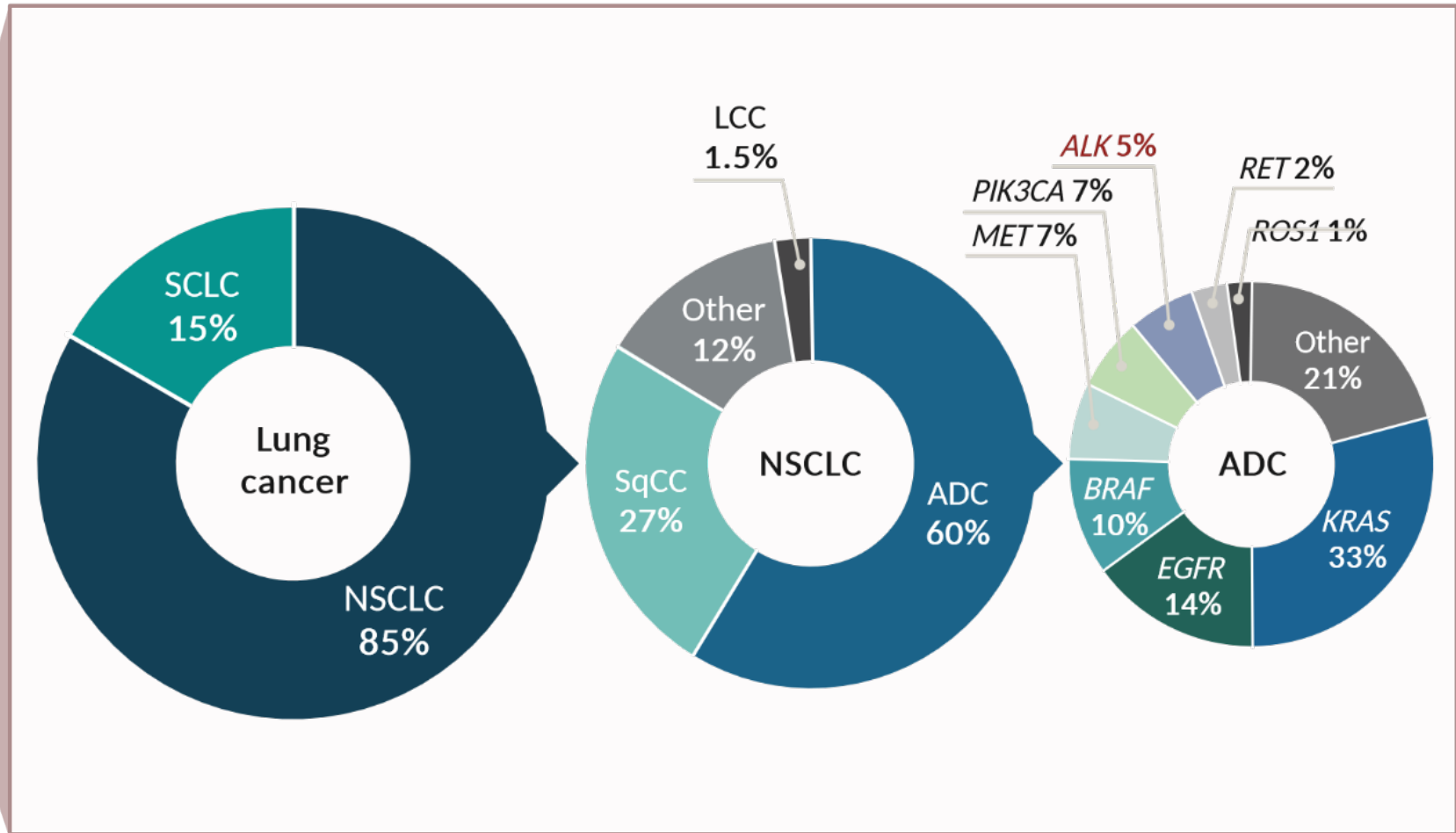
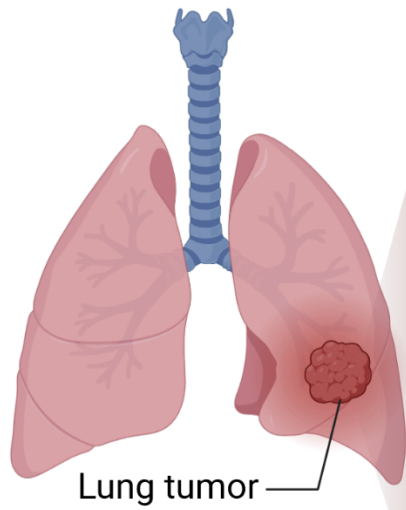


Cancer-associated fibroblast-induced lipid metabolic reprogramming promotes drug resistance in ALK-driven lung adenocarcinomas

Ann-Kathrin Daum, PhD
Div. of Cancer Genome Research
German Cancer Research Center (DKFZ)

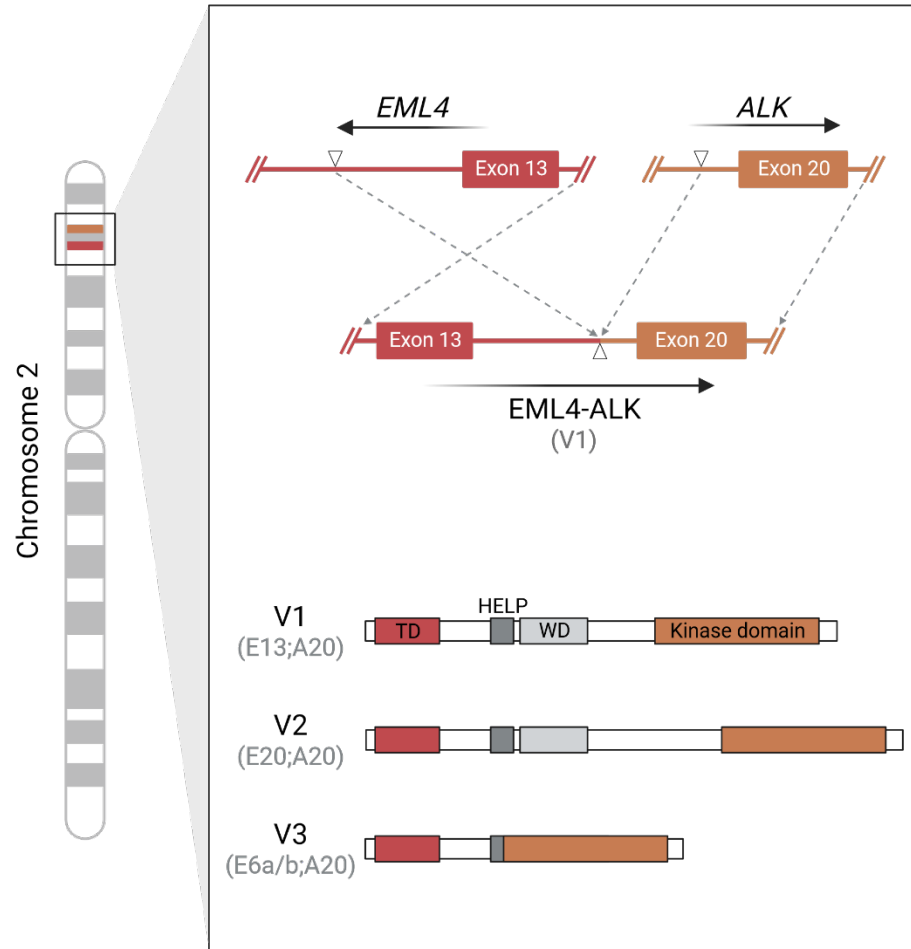
23th November 2023
Session 2

Lung cancer subtypes



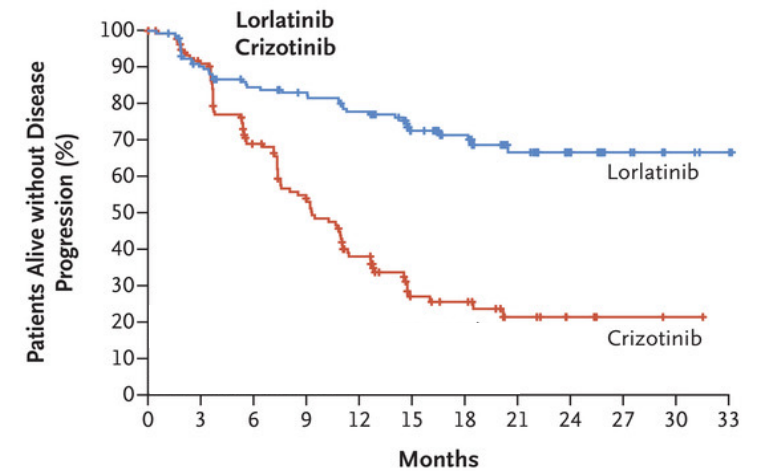
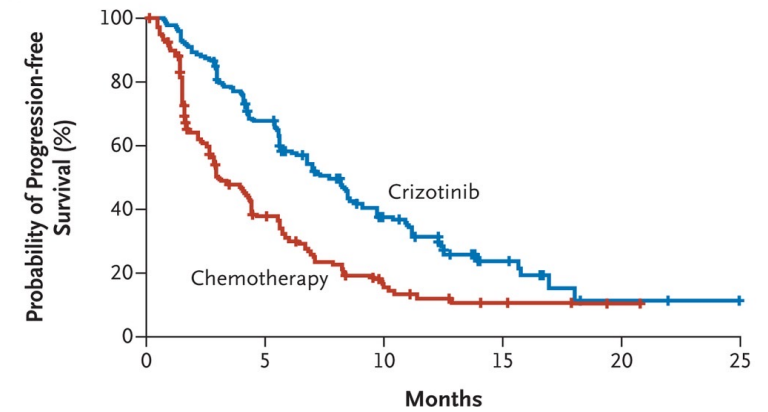
EML4-ALK gene fusions in lung adenocarcinoma

EML4-ALK rearrangements



Targeted treatment of mutant ALK

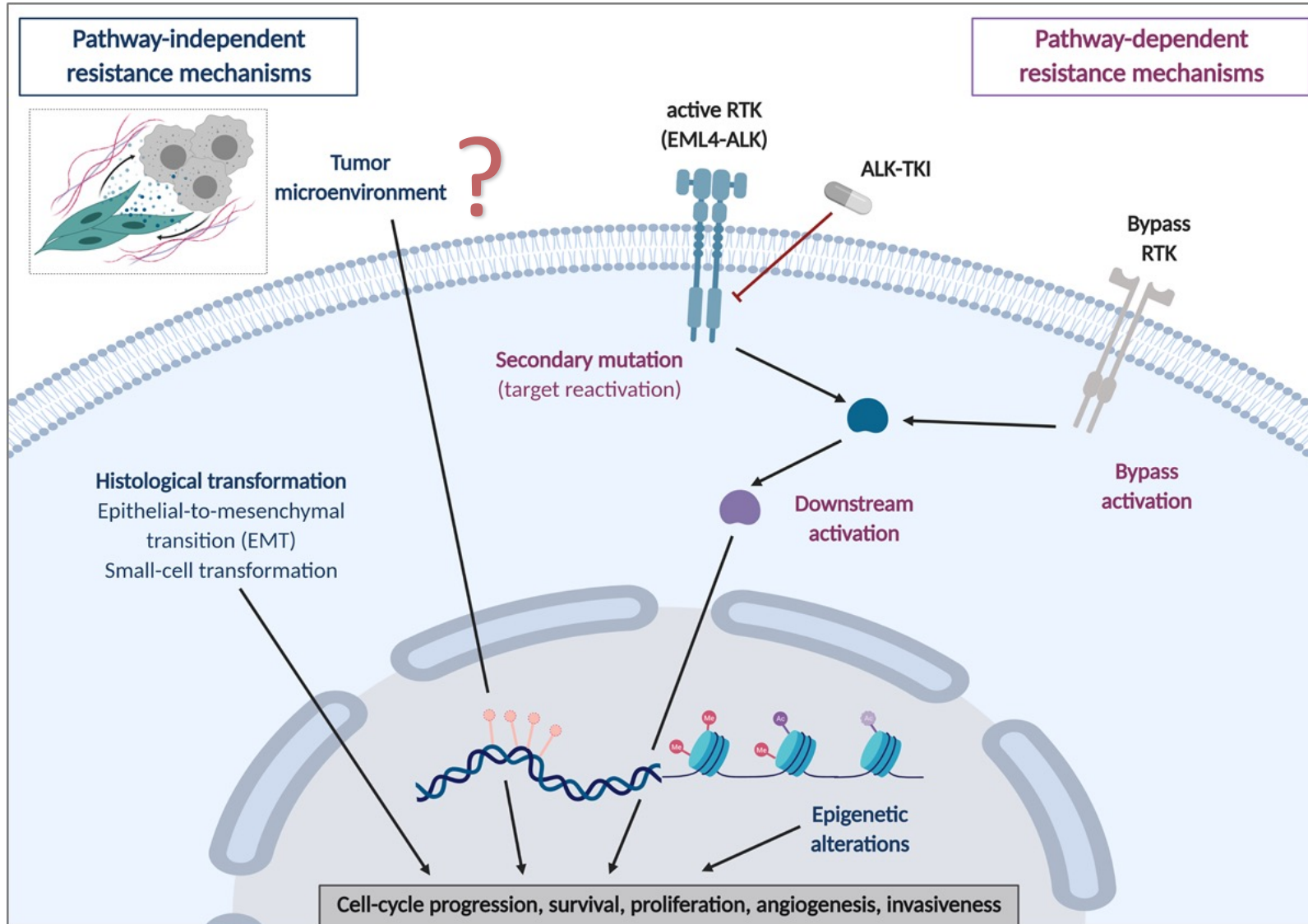
Progression-free Survival



AT Shaw et al. N Engl J Med 2013

AT Shaw et al. N Engl J Med 2020

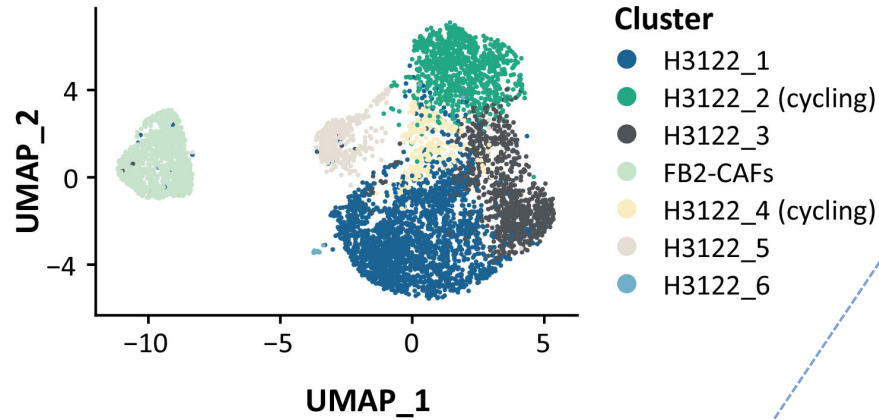
Resistance mechanisms in ALK+ lung adenocarcinomas



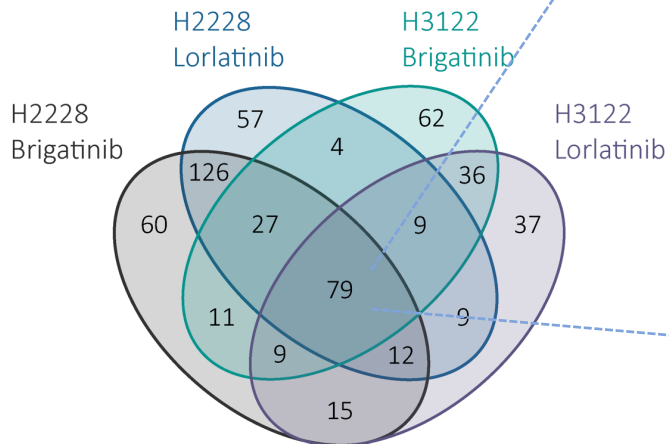
Adapted from Hu X et al., Trends Genet. 2016

CAF-induced transcriptional changes on single-cell level

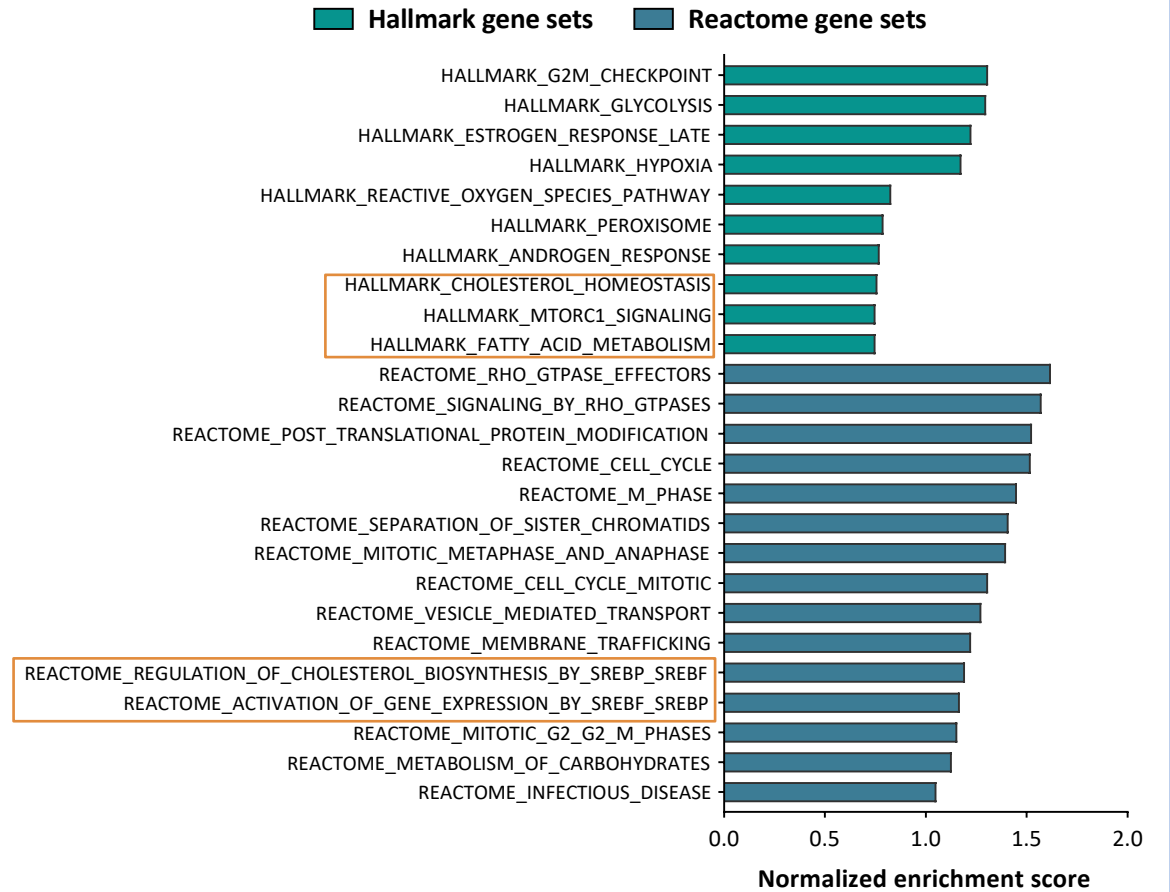
Droplet-based scRNA-seq



Overlap of upregulated genes in TKI-treated co- vs. mono-cultures

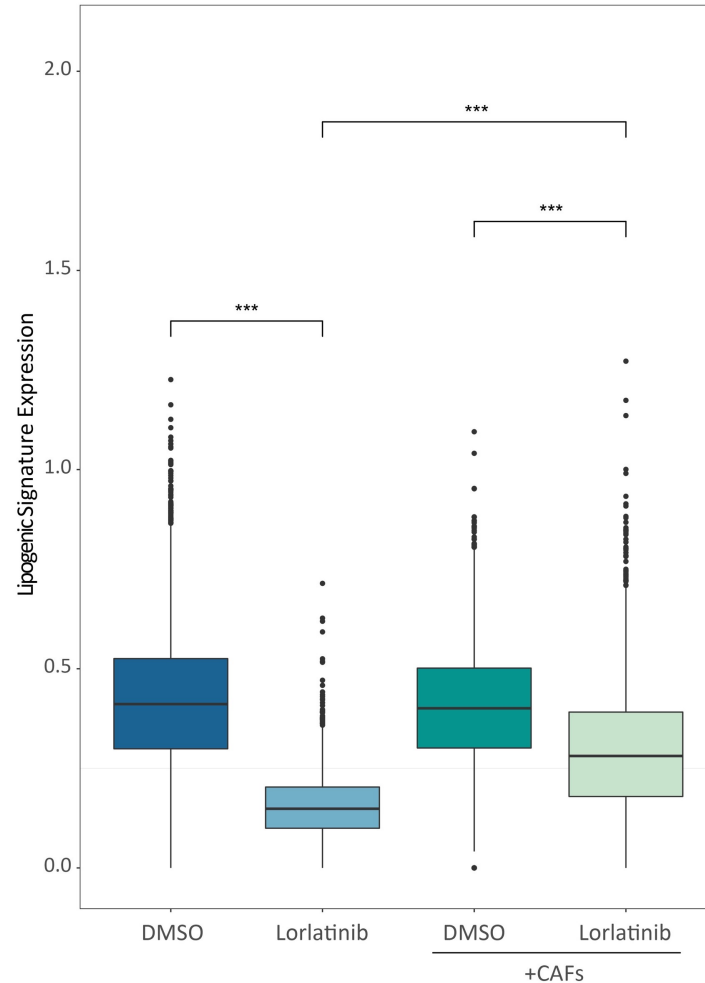
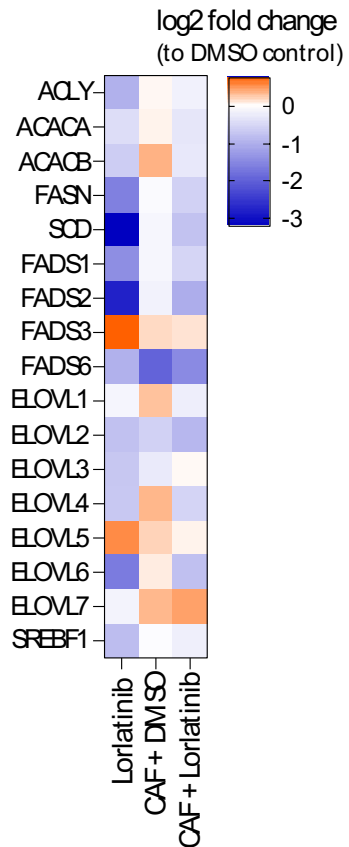


Gene set enrichment analysis

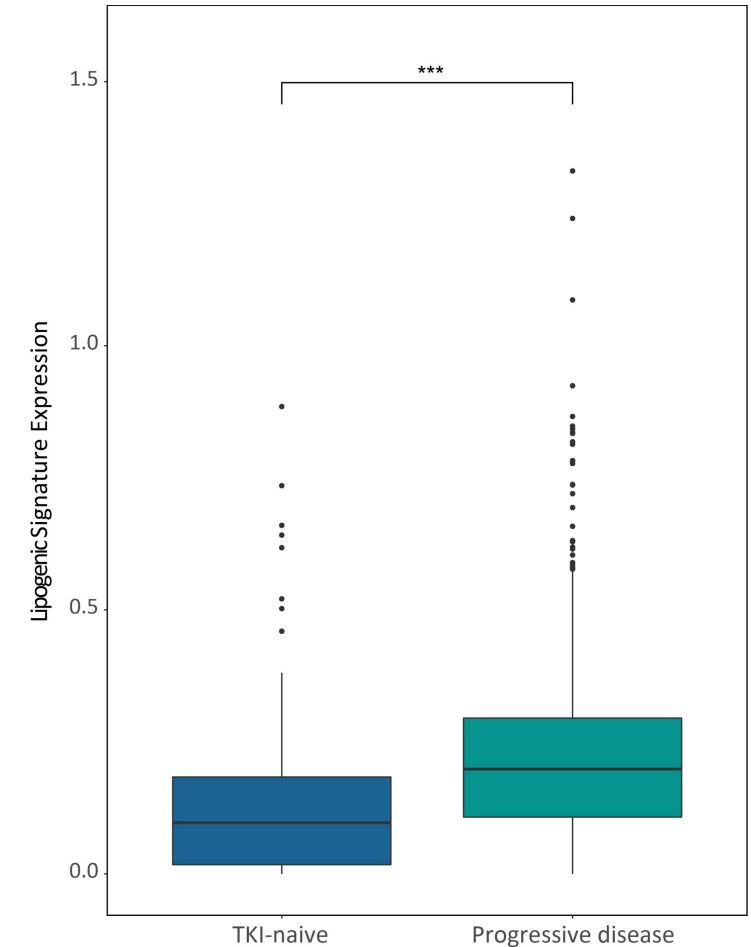


A lipogenic gene signature is differentially expressed in a TKI- and CAF-dependent manner

Expression changes of lipogenic genes in ALK+ lung mono- and co-culture models

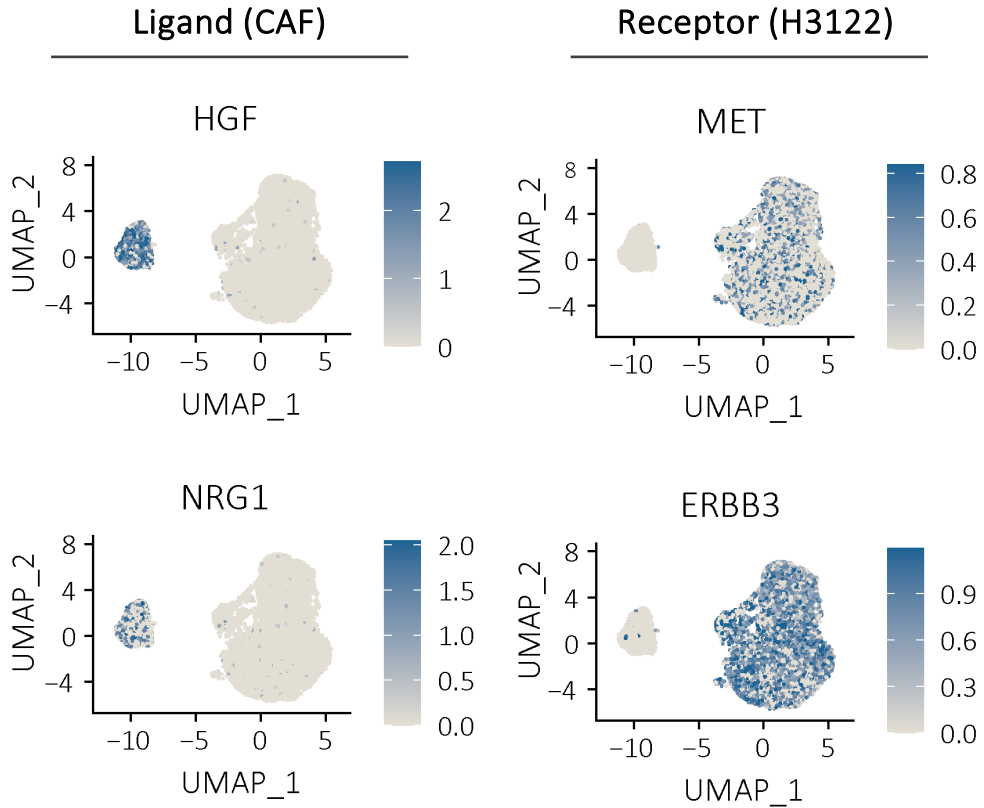


Expression changes of lipogenic genes in ALK+ patient samples

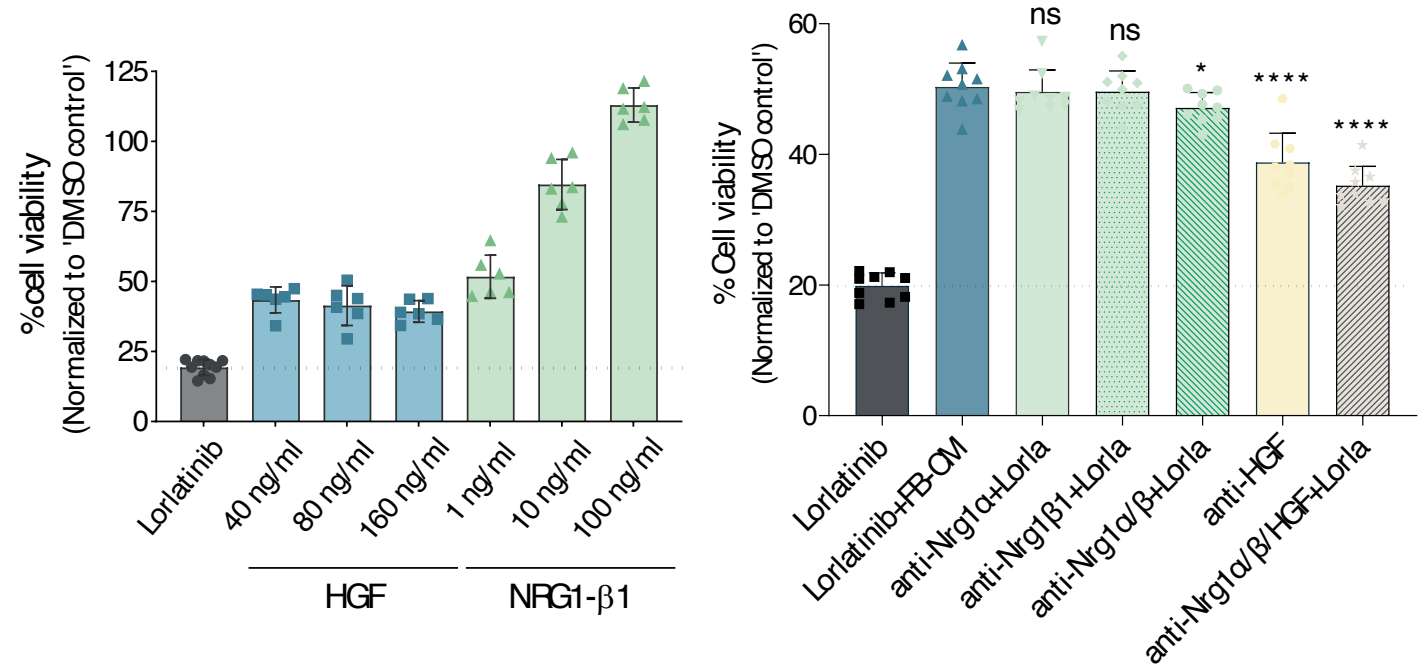


In silico-predicted ligand-receptor pairs show potential routes of cell-cell communication

Ligand-receptor interaction analysis

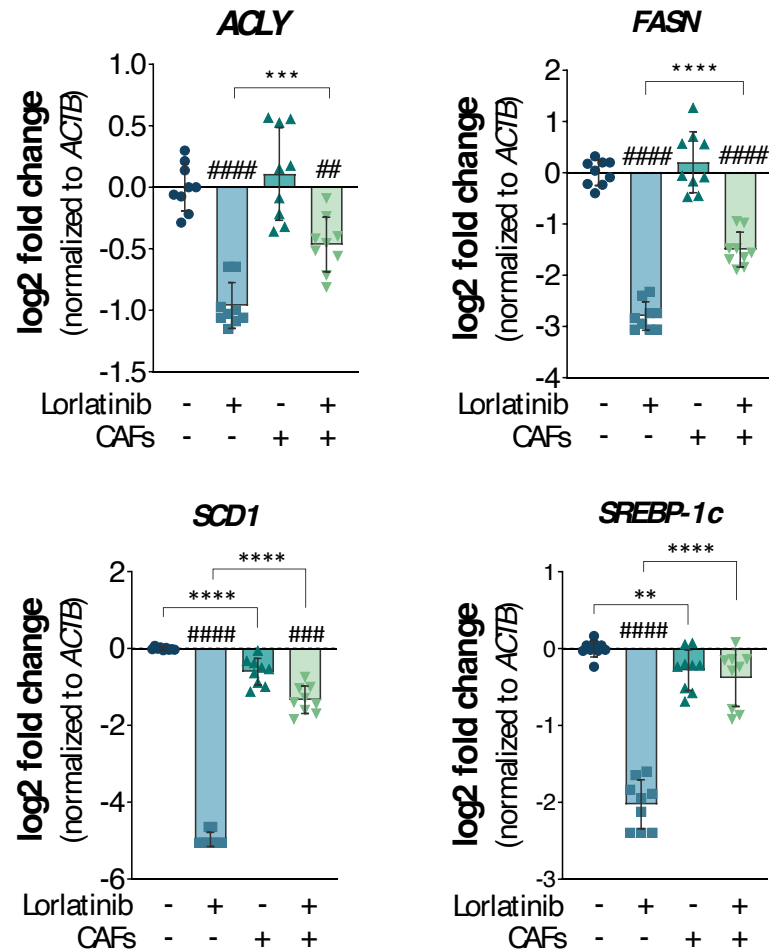


Validation of CAF-derived ligands

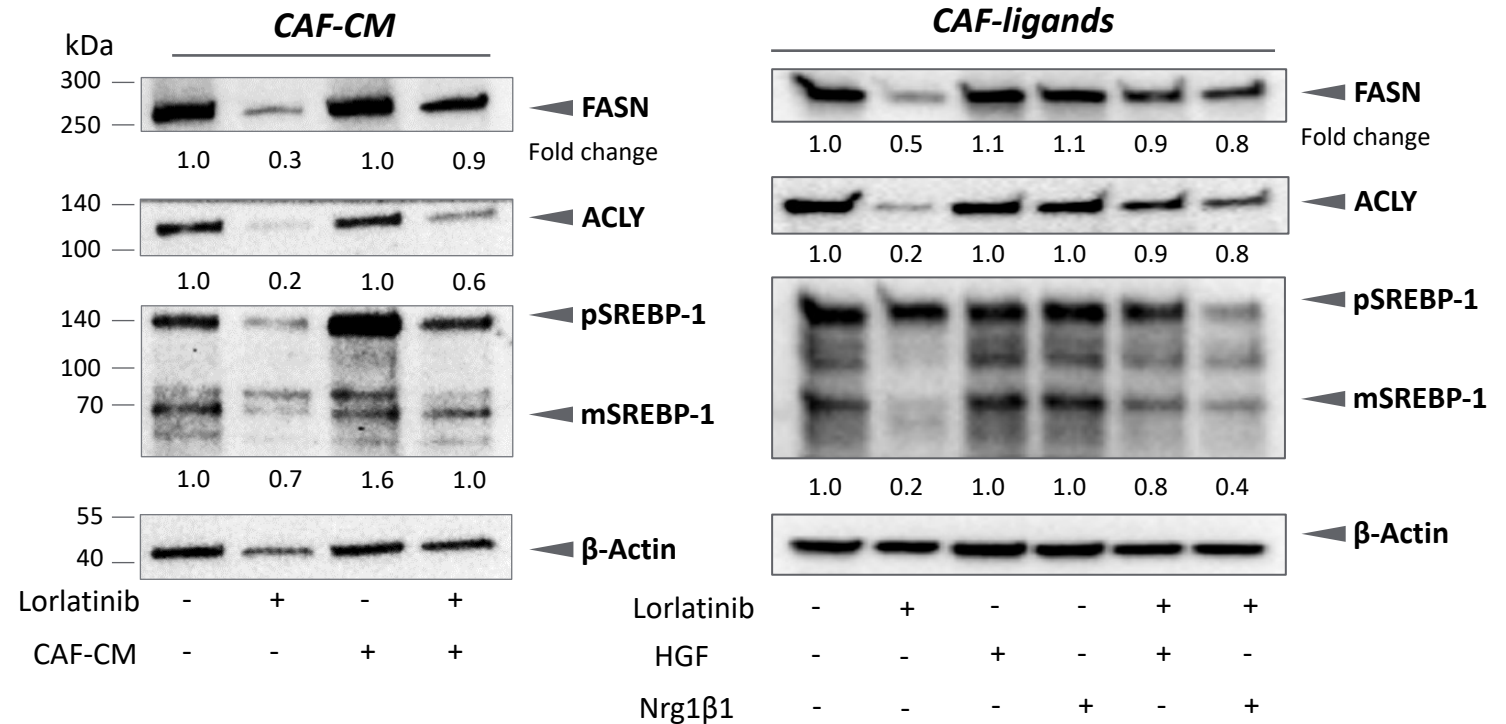


CAFs rescue ALKi-induced interference with lipid metabolism

Expression changes of lipogenic genes

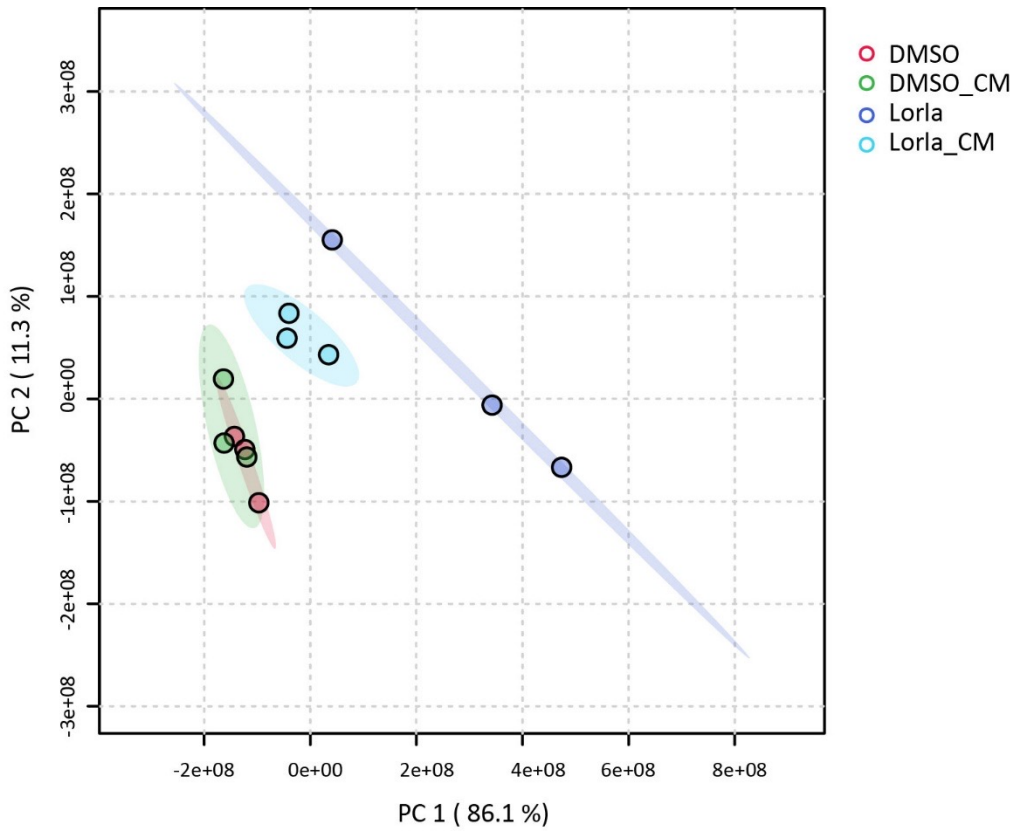


Protein expression of lipid metabolism-related targets

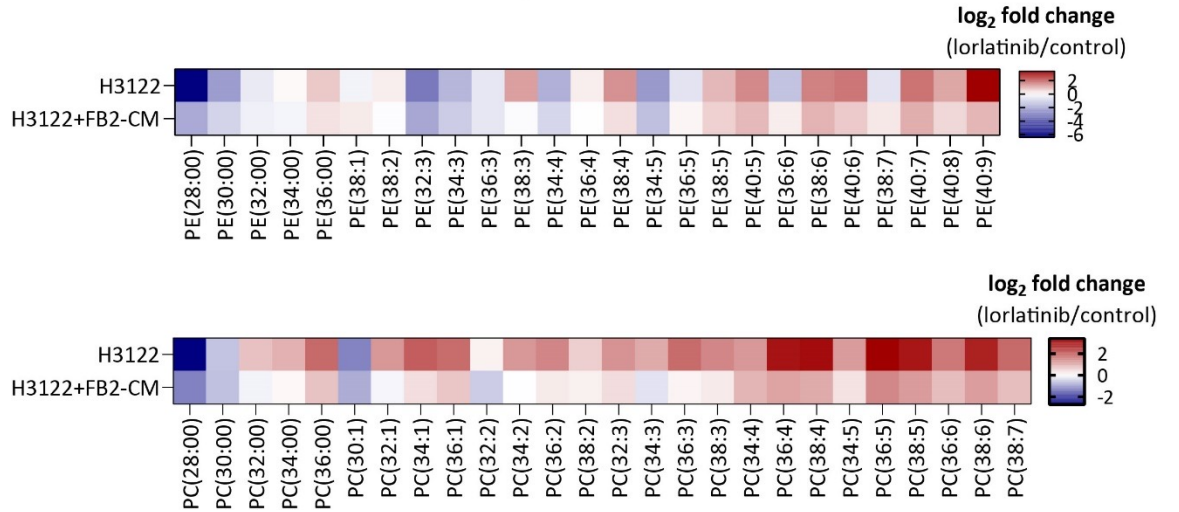


CAFs rescue ALKi-induced interference with lipid metabolism

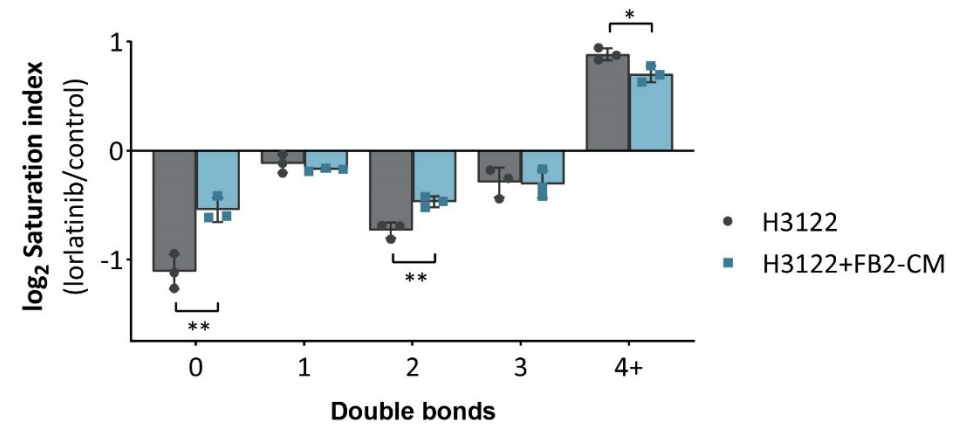
PCA of mass spectrometry-based signal intensities



Phospholipid abundances

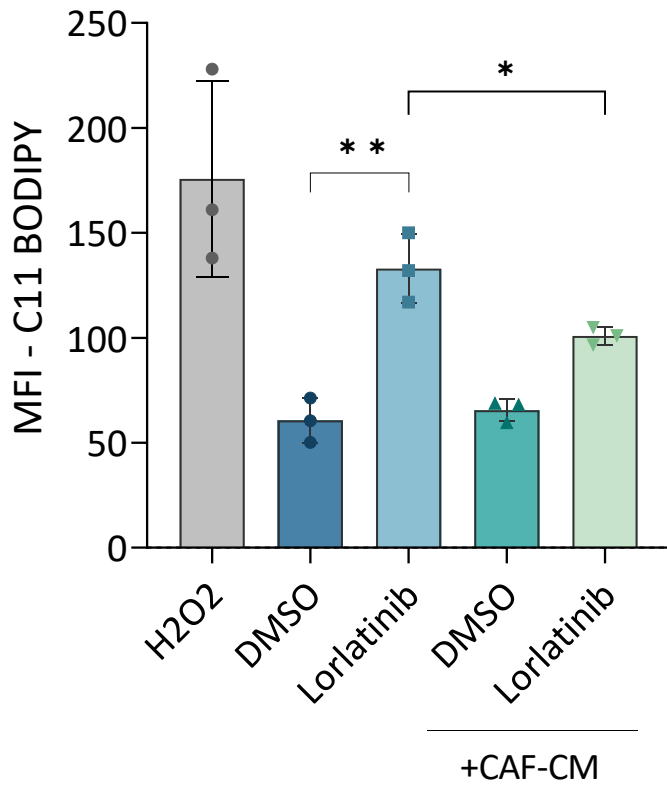


Saturation level of phospholipid species

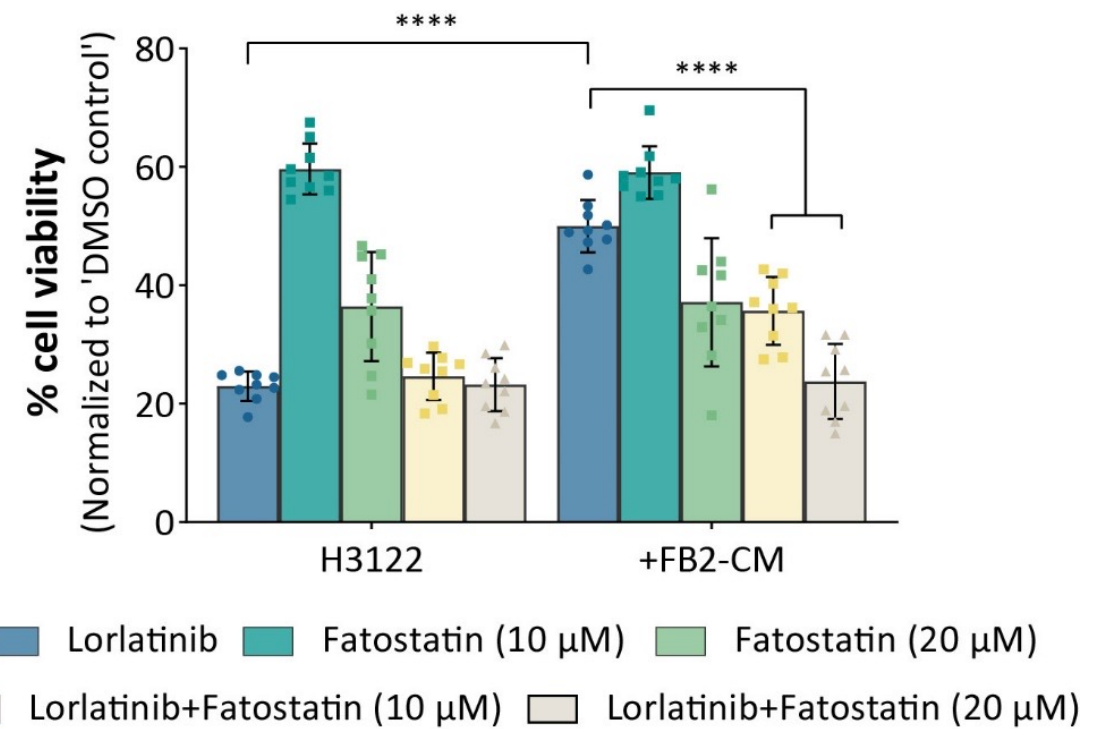


CAFs rescue ALKi-induced interference with lipid metabolism

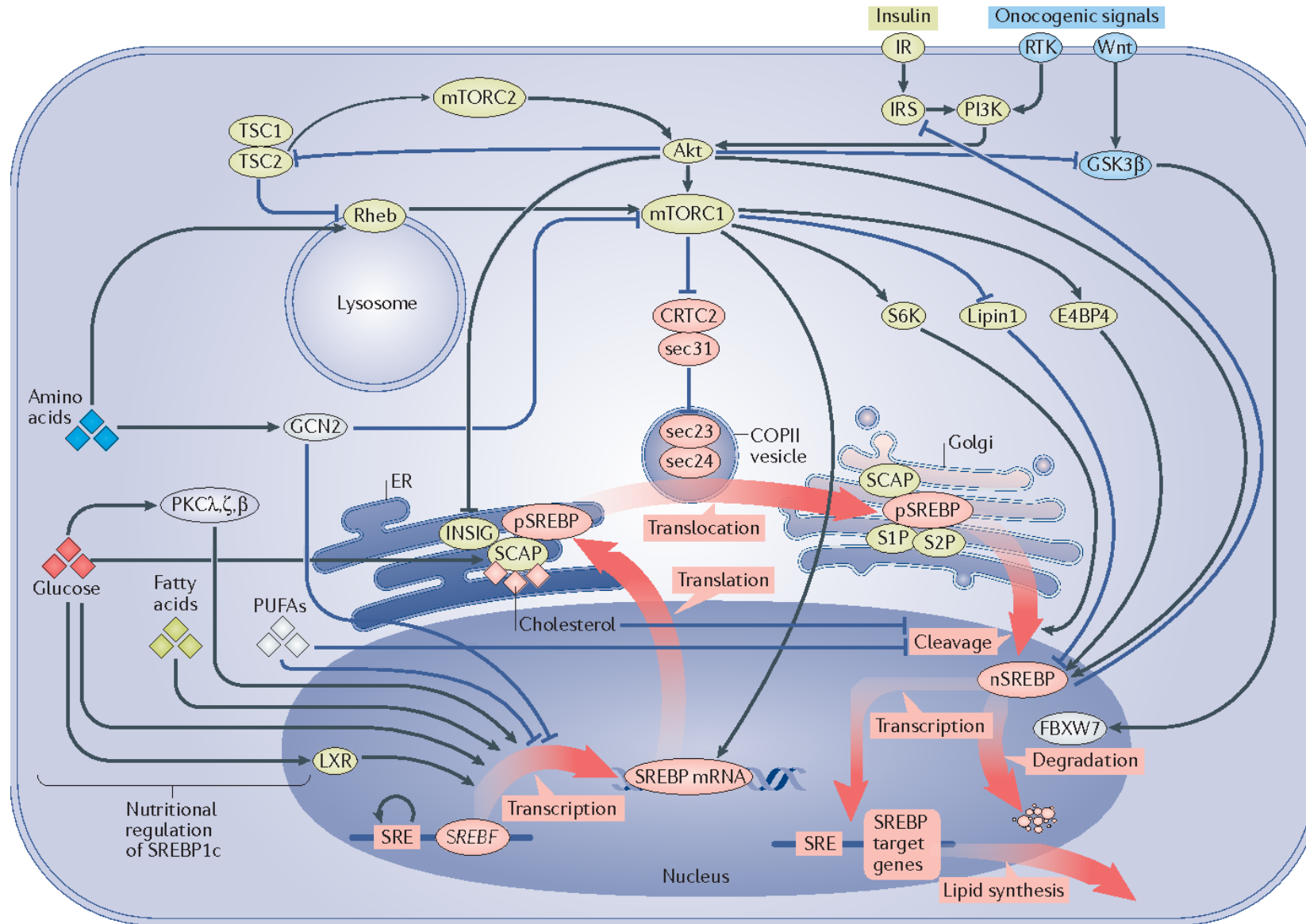
Lipid peroxidation



SREBP1 inhibition

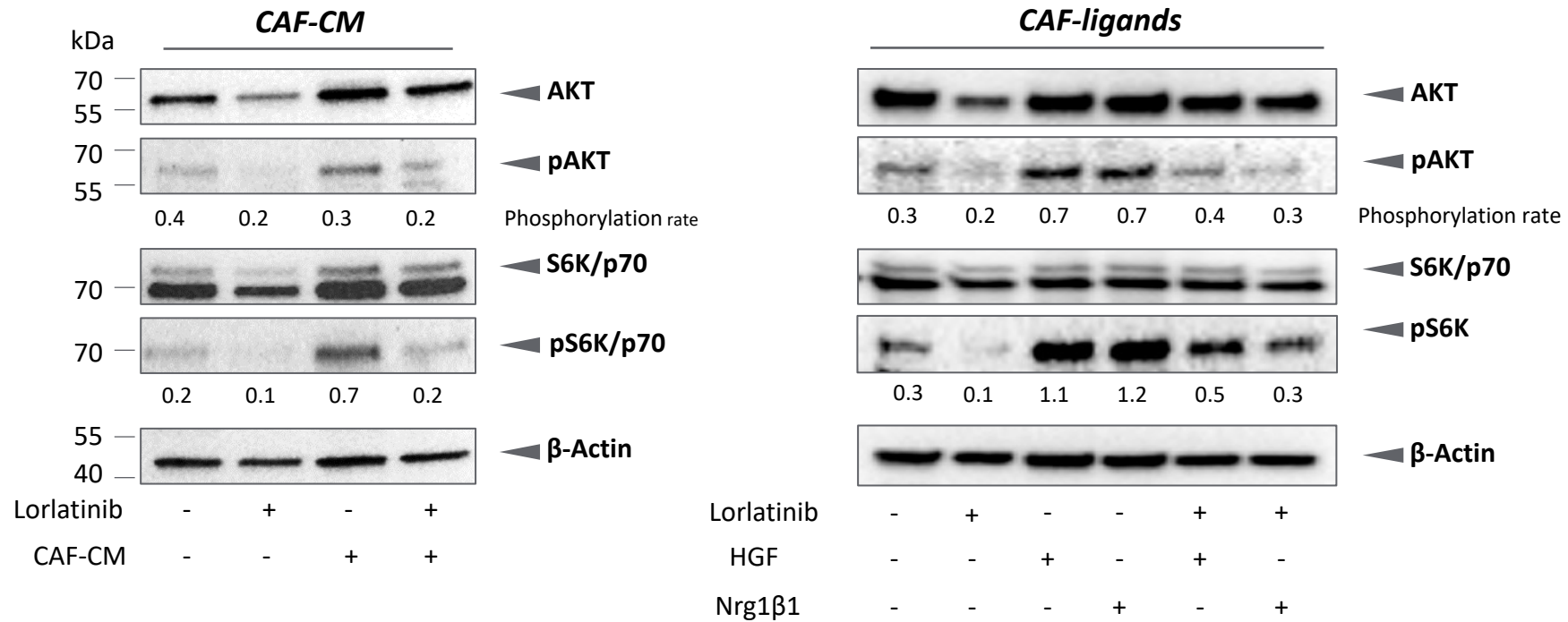


Snapshot: signaling to SREBPs

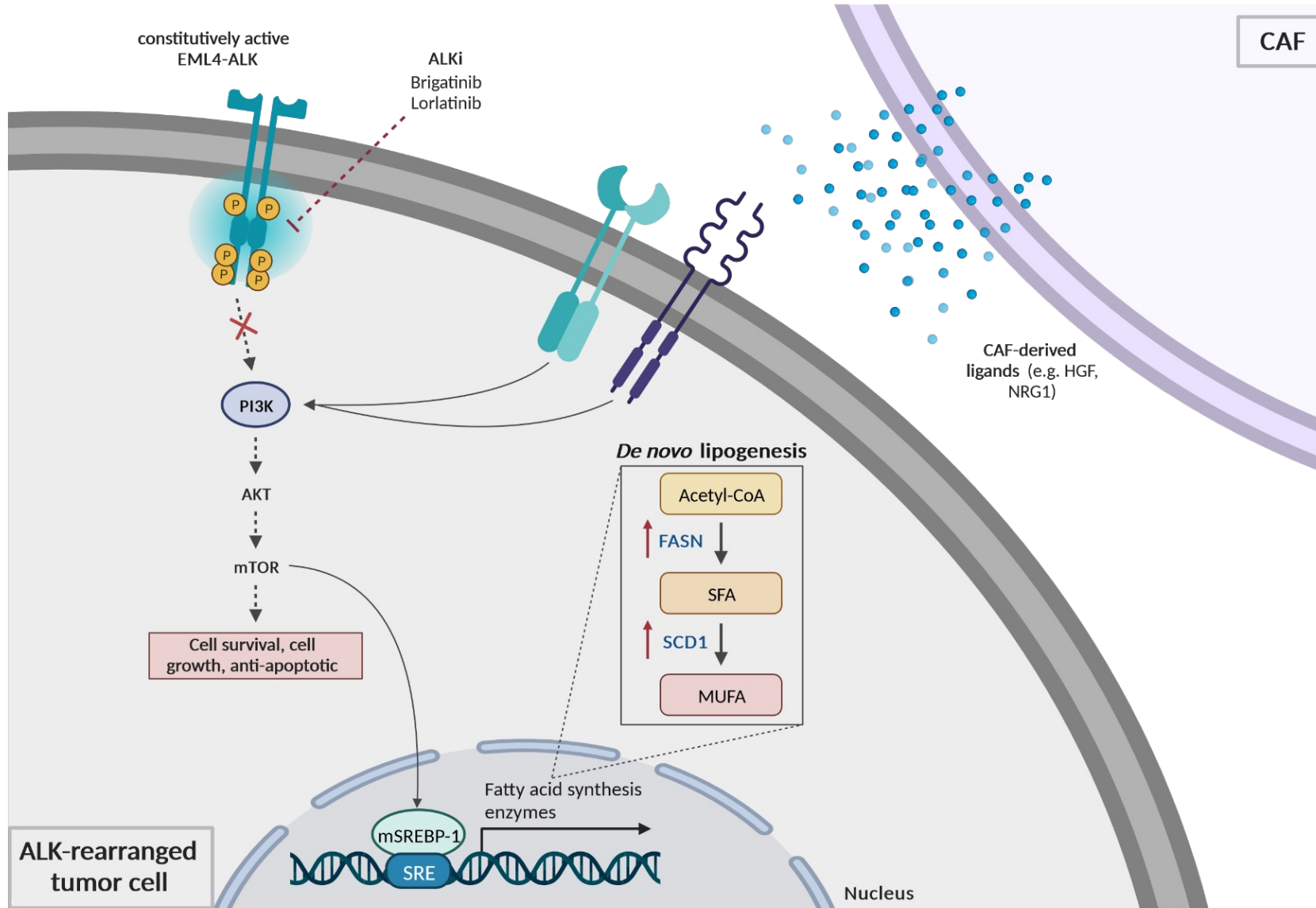


CAFs interfere with ALK-TKI induced AKT signaling perturbations

Expression of AKT signaling proteins



Wrap-up



Interested in more details?



Daum et al., preprint BioRxiv, 2023

Acknowledgements



Div. of Cancer Genome Research



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Thank you for your attention!



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