

Hypoxia Drives HIF-1α/YAP-AXL-Mediated Adaptive Resistance to Osimertinib in EGFR-Mutant NSCLC



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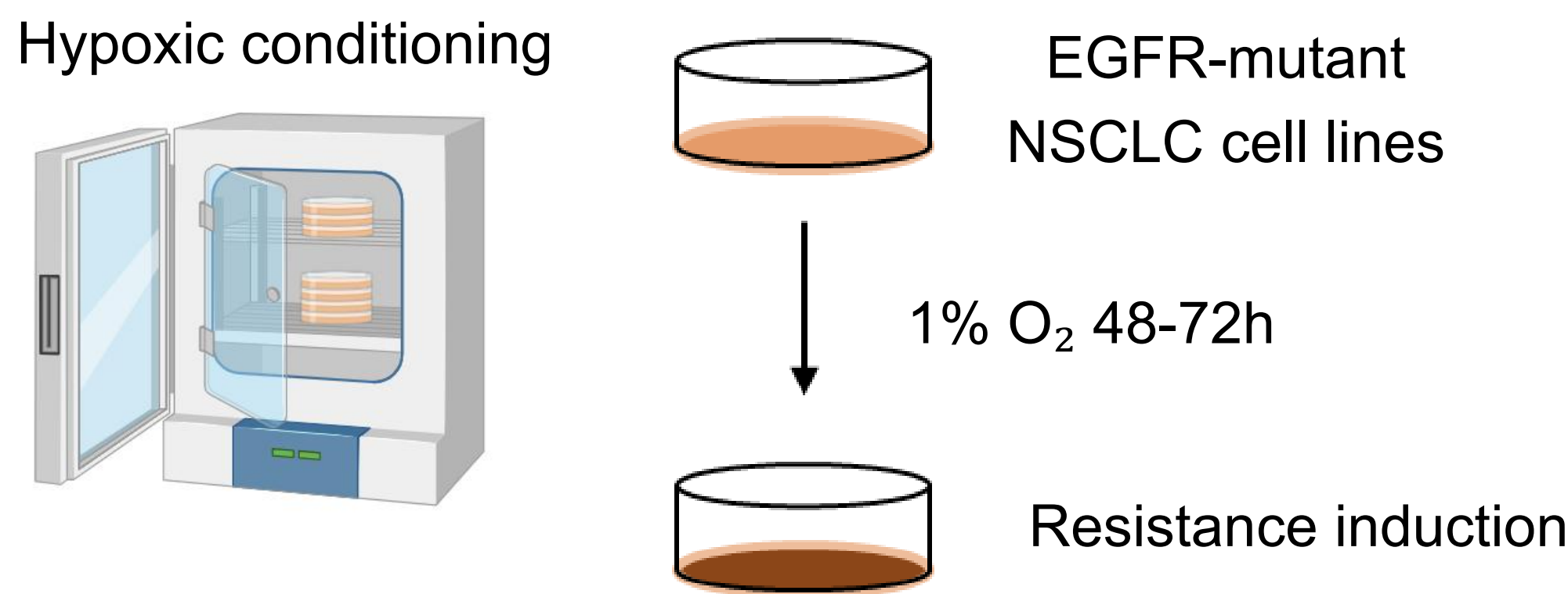
Background

Non-small cell lung cancer (NSCLC) harboring activating EGFR mutations often shows marked initial responses to EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, these responses are rarely durable, and adaptive resistance remains a major clinical challenge. AXL has been implicated in adaptive resistance to EGFR-TKIs, and the AXL inhibitor ONO-7475 has been reported to suppress AXL-mediated drug-tolerant cells (1). Hypoxia is a common feature of the tumor microenvironment in solid tumors and may promote cell survival under therapeutic stress. In other cancer types, hypoxia has been reported to regulate AXL signaling (2). However, whether AXL mediates hypoxia-induced adaptive resistance to osimertinib in EGFR-mutant NSCLC remains unclear.

Objective

We investigated whether hypoxia promotes adaptive resistance to osimertinib in EGFR-mutant NSCLC and explored the underlying signaling mechanisms and therapeutic vulnerabilities.

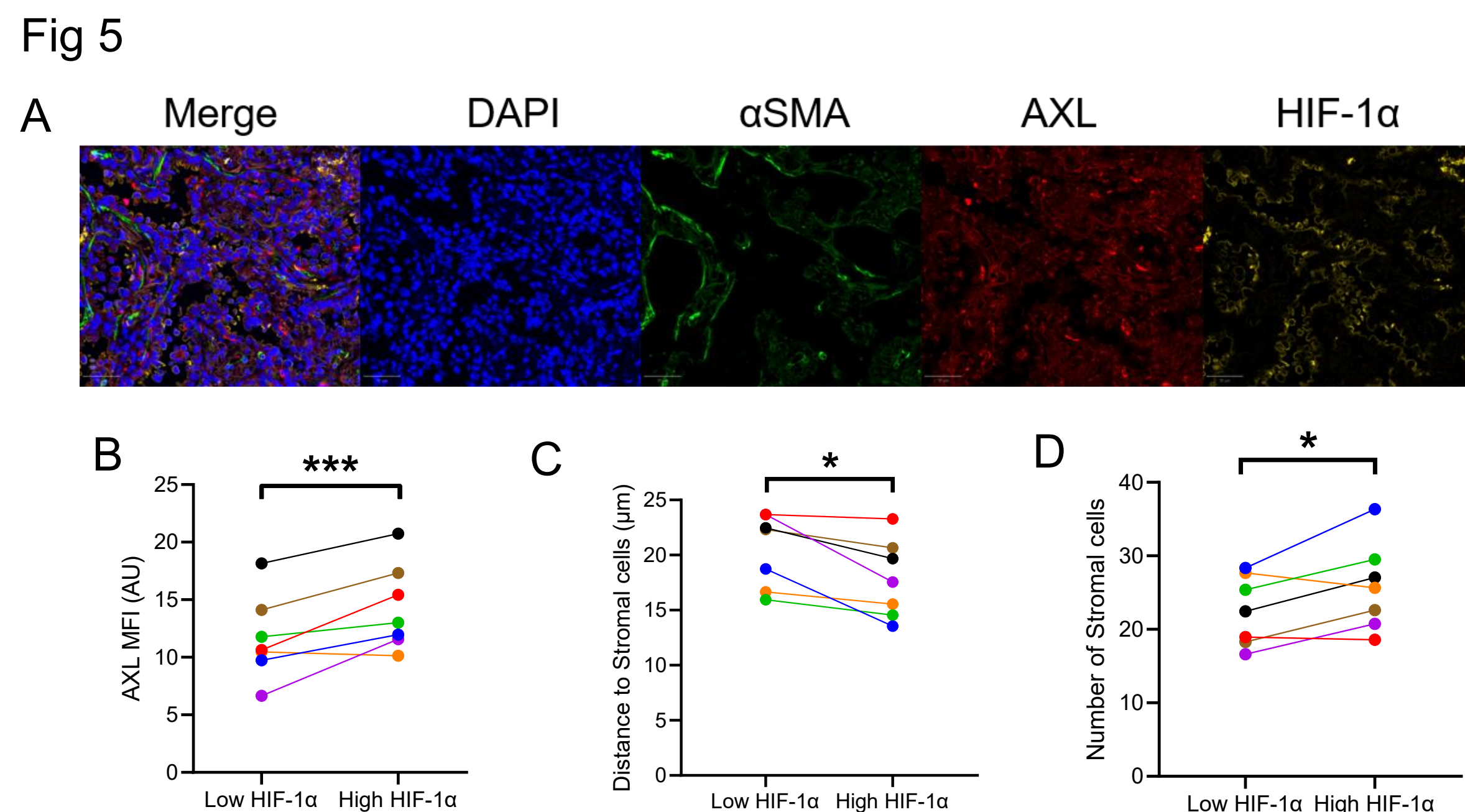
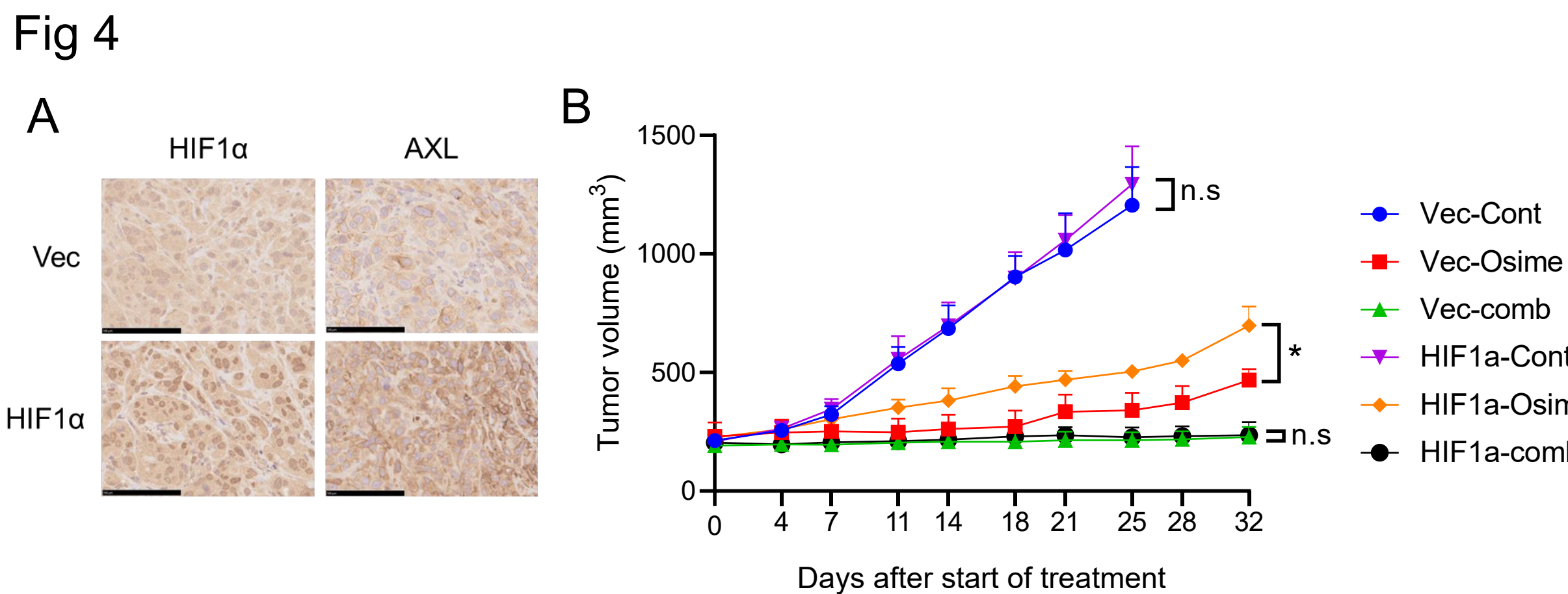
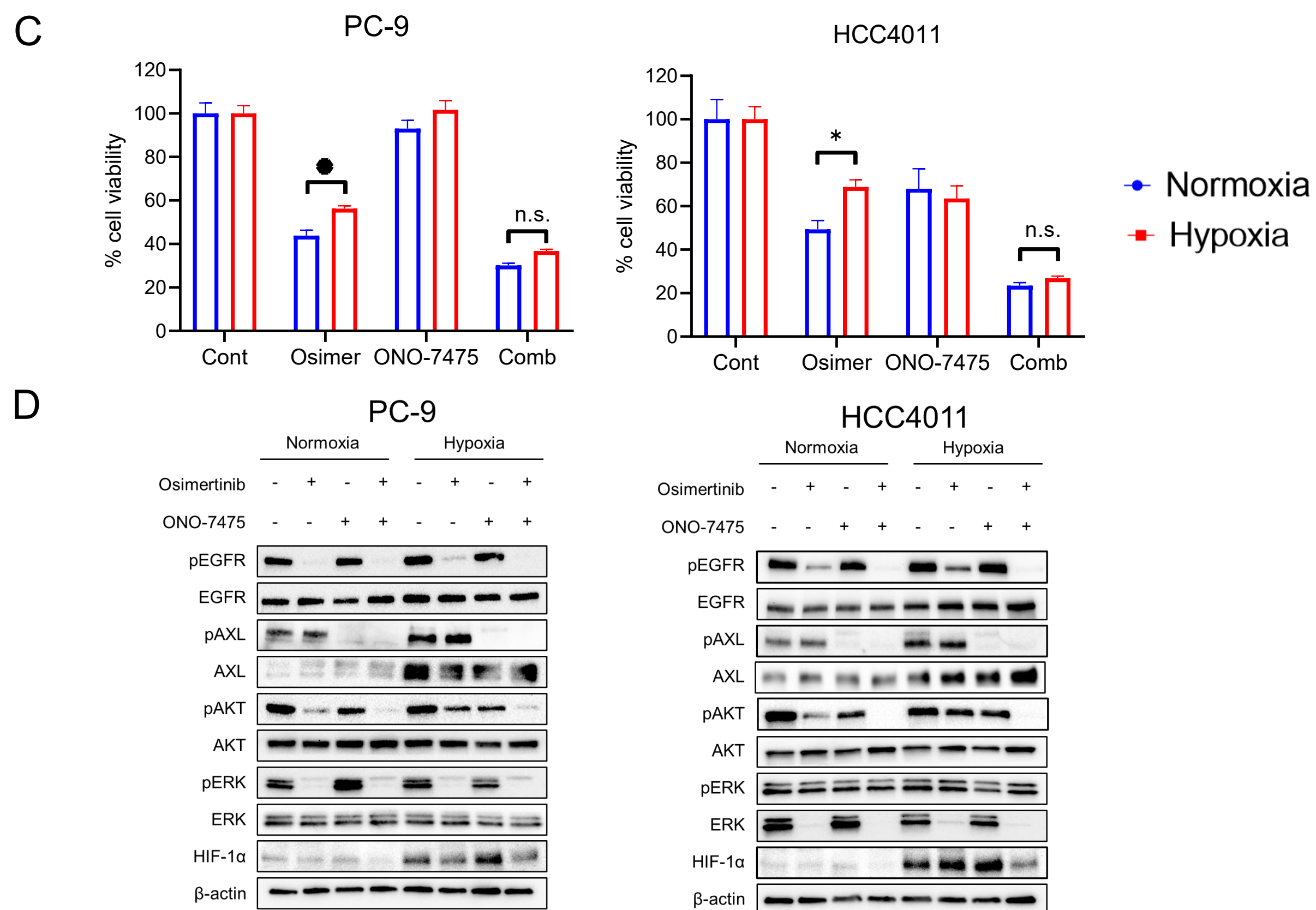
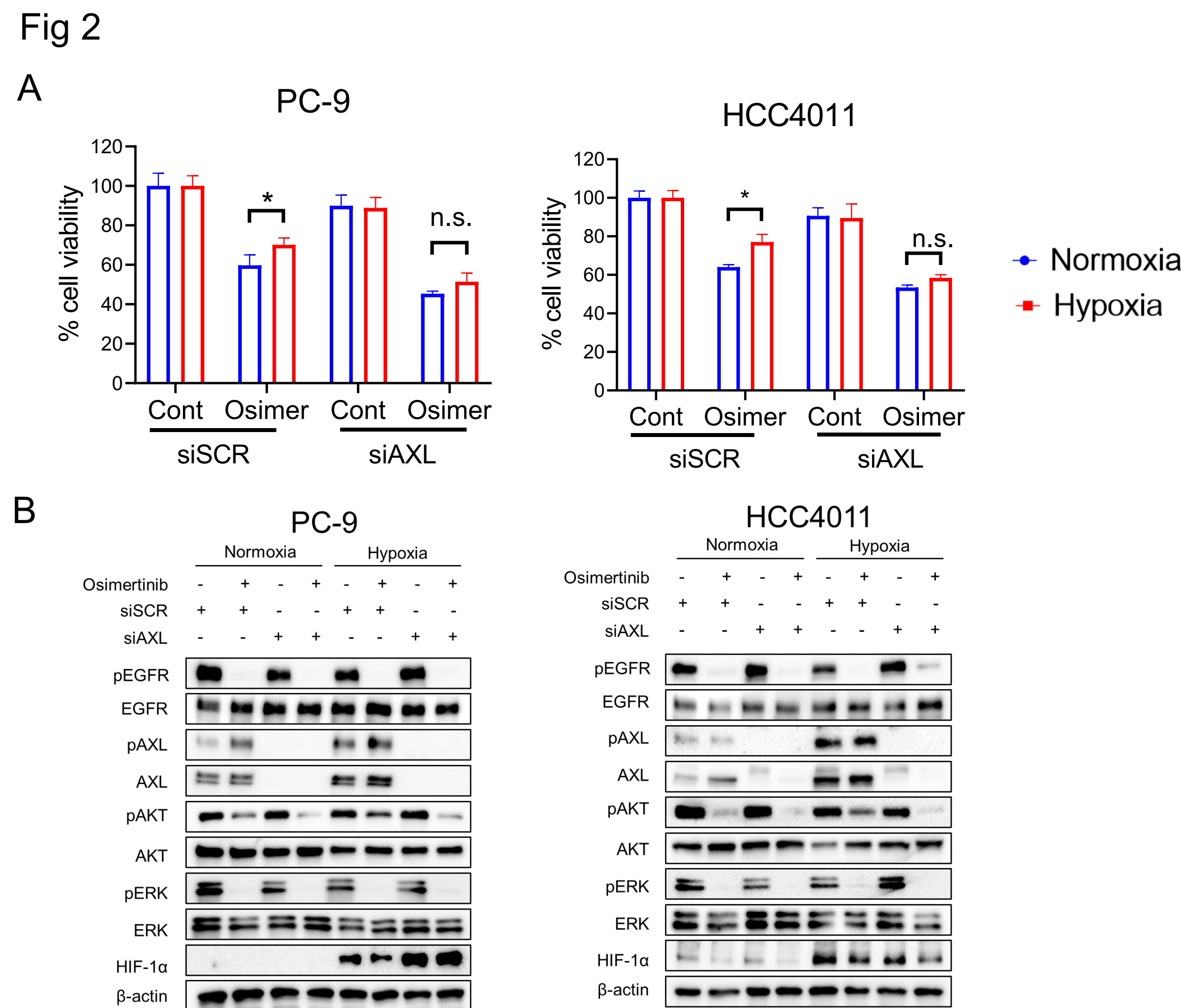
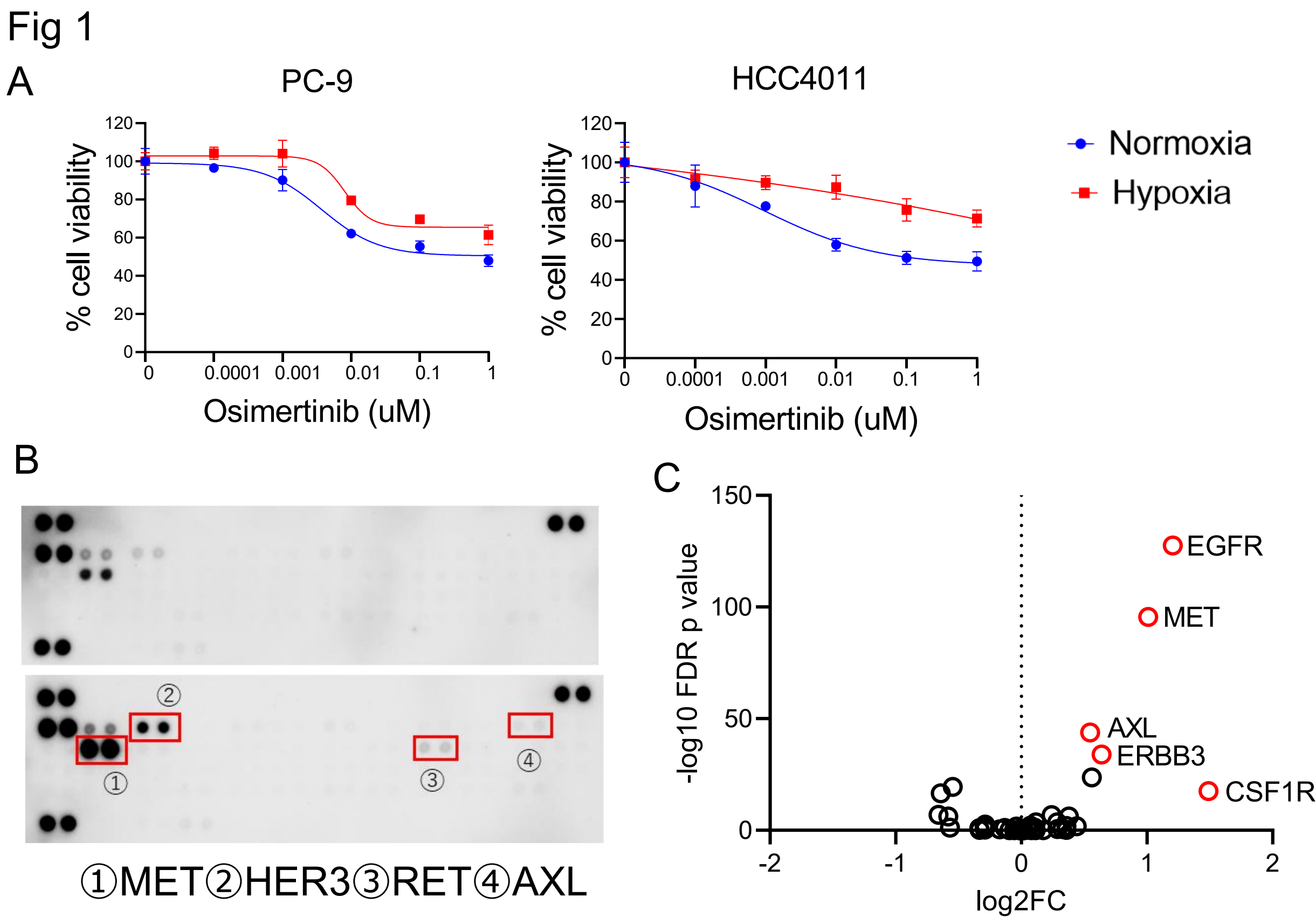
Methods



Experimental framework

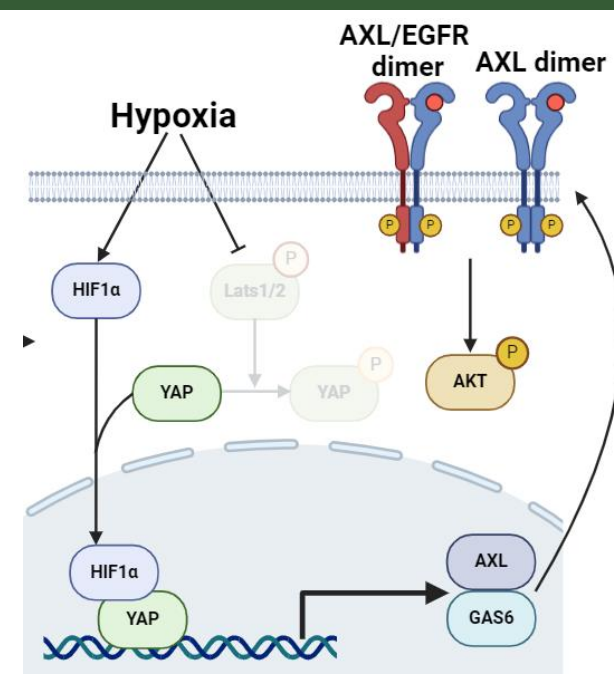
- Cell models: EGFR-mutant PC-9 and HCC4011 cell lines.
- Conditioning: normoxia (21% O₂) versus hypoxia (1% O₂) for 48 to 72 h.
- Readouts: cell viability, immunoblotting, phospho-RTK array, RNA-seq, siRNA, co-immunoprecipitation, and subcellular fractionation.

Results



Conclusions

Our findings identify a hypoxia-HIF-1α/YAP-AXL axis that contributes to adaptive resistance to osimertinib in EGFR-mutant NSCLC. Targeting this axis may represent a therapeutic strategy to overcome resistance within hypoxic tumor niches.



References

- Okura et al. Clin Cancer Res 26(9):2244-2256 2020.
- Rankin EB et al. Proc Natl Acad Sci U S A. 111:13373-13378 2014.

