

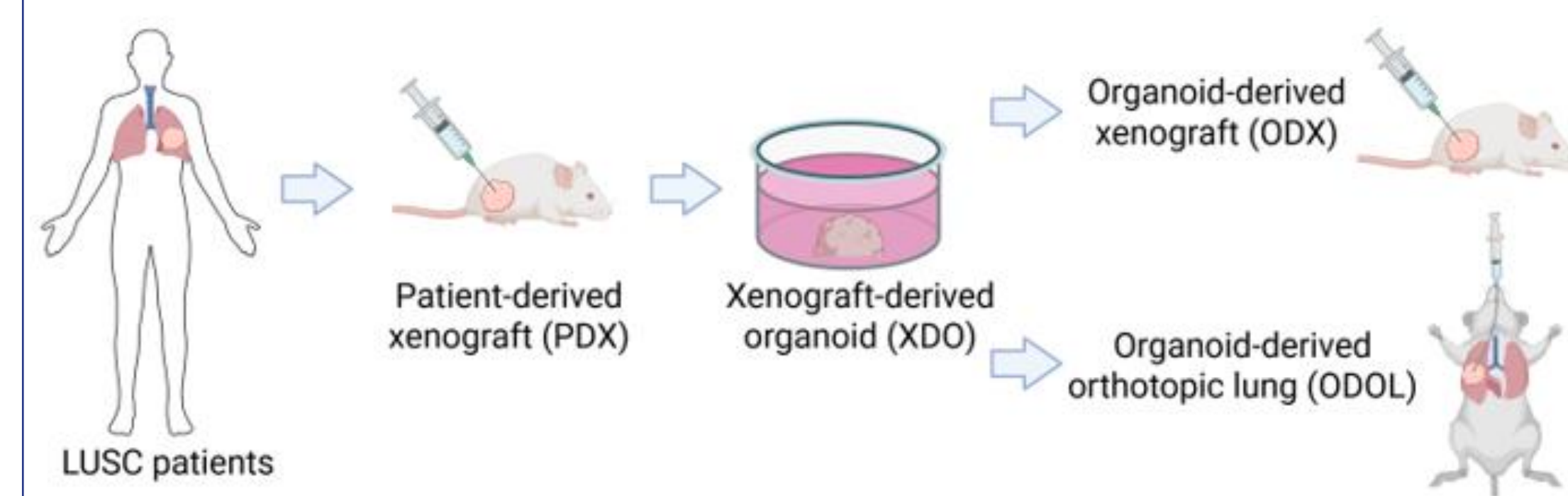
INTRODUCTION

- Lung squamous cell carcinoma (LUSC) is the second most common NSCLC subtype with limited treatment options
- A better understanding of the **molecular mechanism and pathogenesis** of LUSC is needed

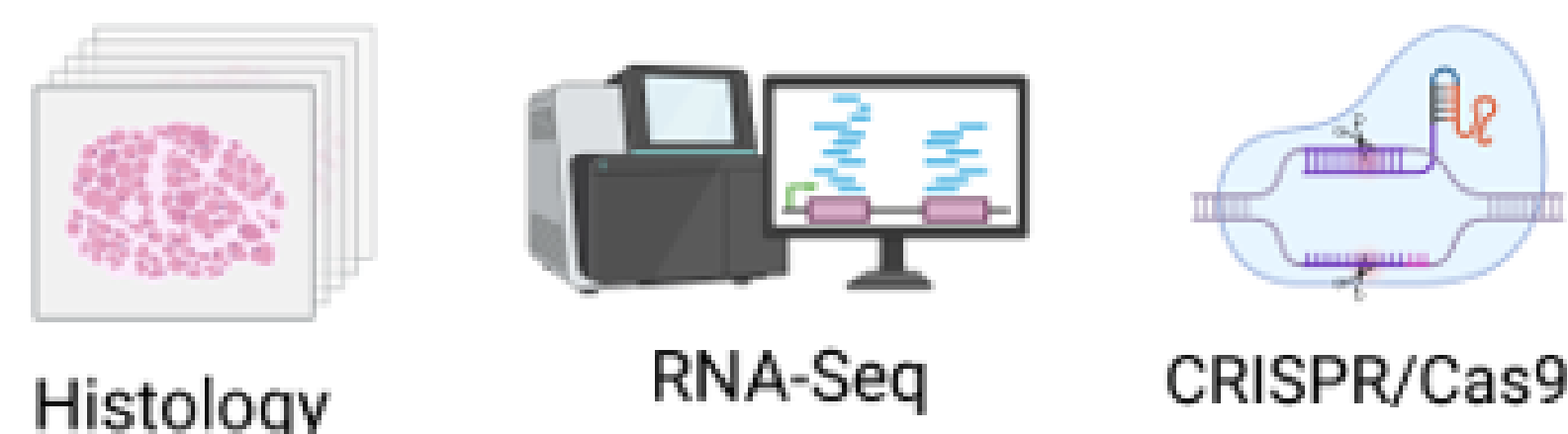
Objective: Investigate how the **tumor microenvironment (TME)** influences LUSC phenotypes using a **novel orthotopic patient-derived organoid model**

METHODS

- Established **xenograft-derived organoids (XDO377 and XDO149)** from two LUSC-patient-derived xenograft (PDX) models
- Generated **subcutaneous (ODX)** and **orthotopic lung (ODOL)** tumors using organoids
- Compared tumor growth, histology, protein expression, and transcriptomic profiles
- Performed CRISPR/Cas9-mediated **HIF1α** or **SOX2** knockout followed by functional analyses



Comparative analyses



RESULTS

Fig. 1 TME regulates LUSC phenotypes

- Reduced tumor growth (A), squamous differentiation (B), and collagen organization (ECM remodeling) (C) in ODOL compared to ODX
- Despite no genomic differences by WGS (D), ODOL tumors showed suppressed hypoxia-, HIF1α-, and SOX2-associated transcriptional programs (E)

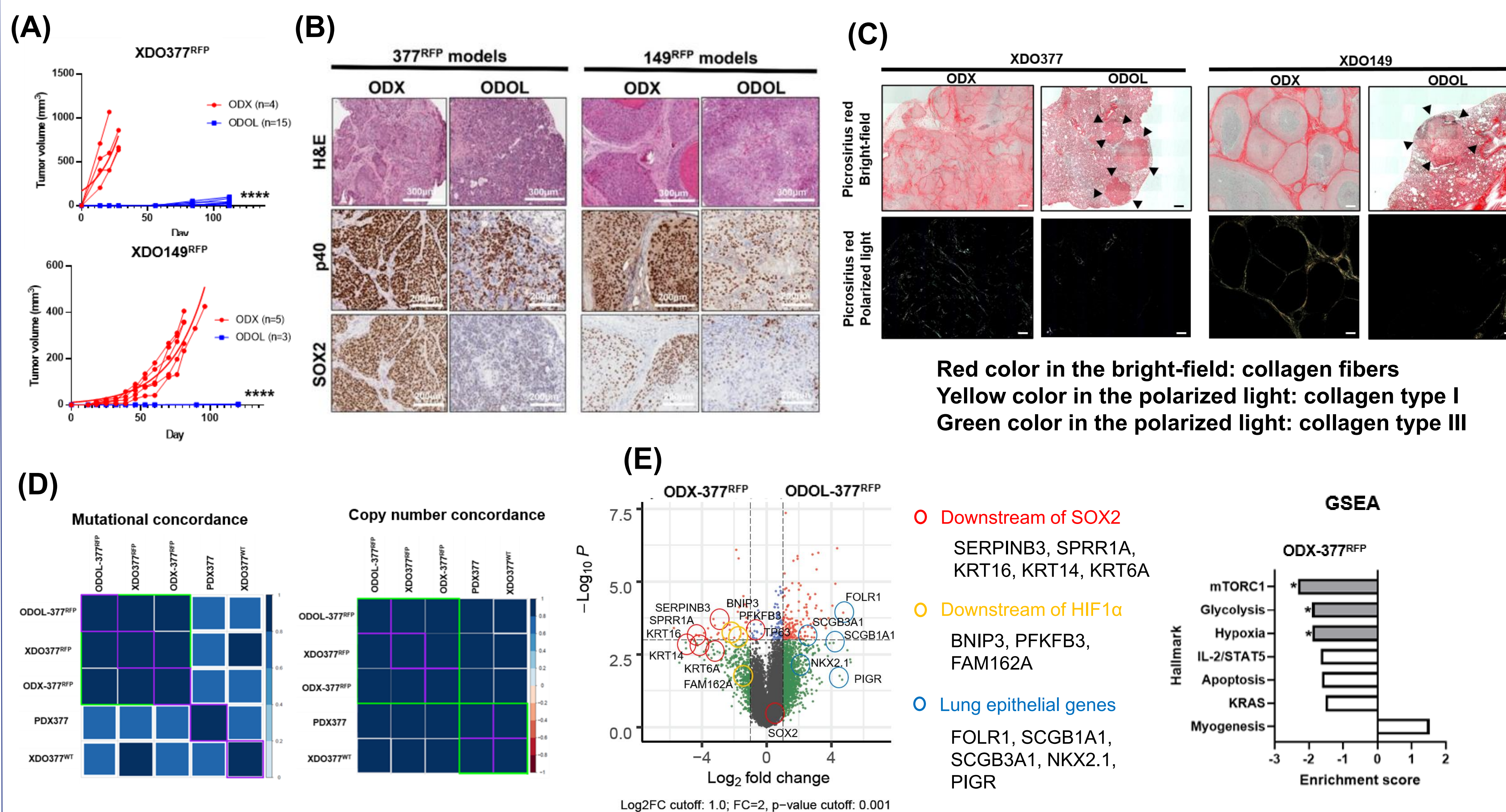


Fig. 2 HIF1α regulates SOX2 (lineage oncogene) and ECM remodeling

- HIF1α KO: ↓ tumor growth (1A), ↓ SOX2 (1B), ↓ collagen organization (1B)
- SOX2 KO: ↓ tumor growth only (2A, 2B)

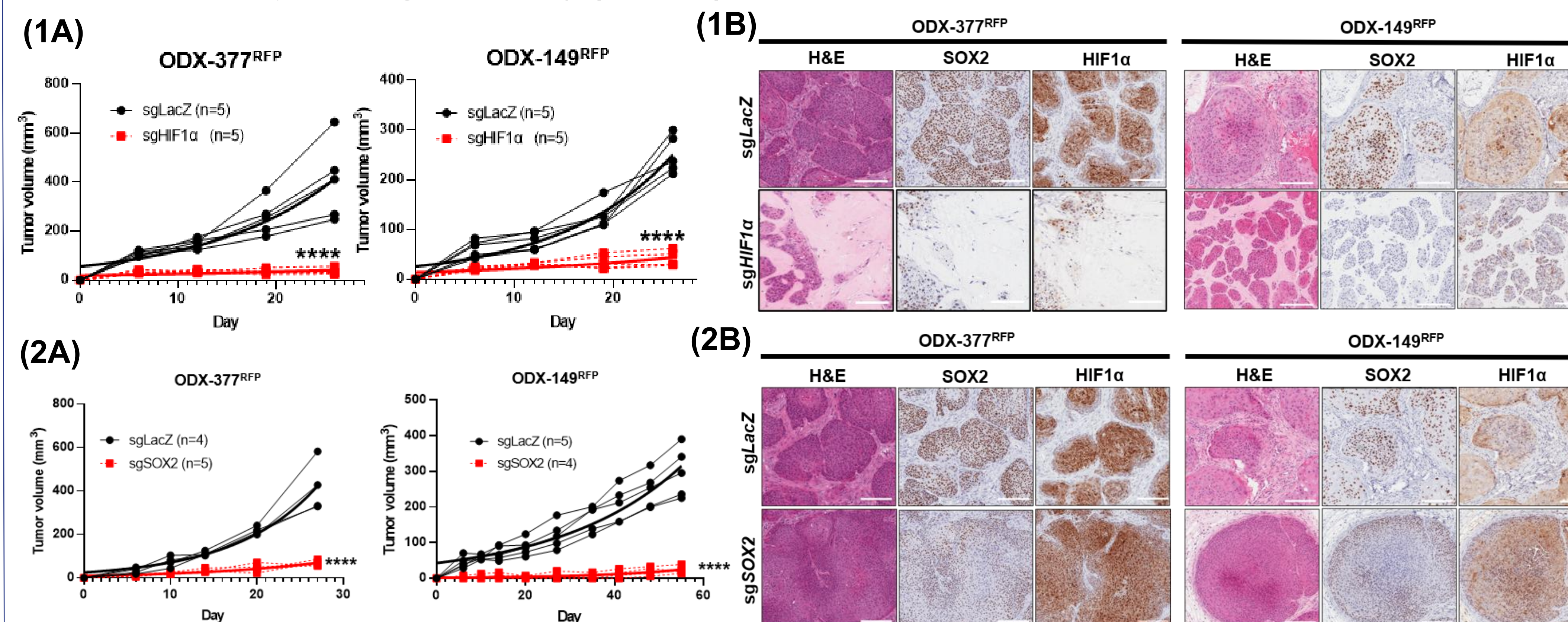
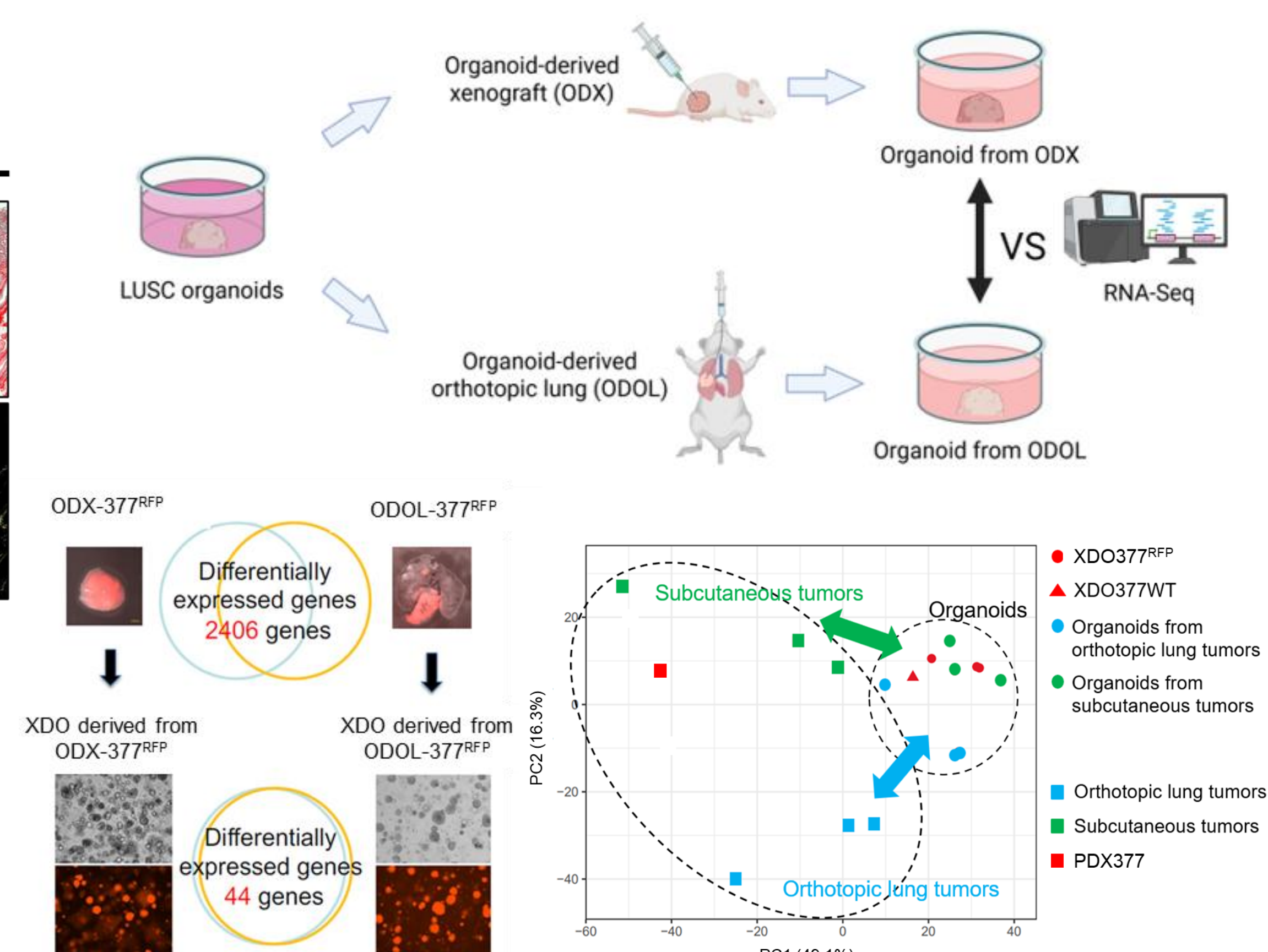


Fig. 3 Phenotypic plasticity is reversible

- Re-established organoids lost the ODX-ODOL differences



CONCLUSION

- We established a novel **orthotopic patient-derived organoid model** for studying LUSC
- HIF1α regulates TME-dependent squamous differentiation and ECM remodeling**
- LUSC phenotypes are reversible and governed by the TME**

REFERENCES & ACKNOWLEDGEMENTS

Reference: (1) Shi, et al. Clin Cancer Res 2020. (2) Bass, et al. Nat Genet 2009.

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AI Declaration: ChatGPT (OpenAI) was used solely to improve the readability and language of this presentation. The authors reviewed and edited all content as needed and take full responsibility for the content of the presentation.