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Precision-Cut Tissue Slice Assay to Advance Drug Discovery

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Abstract

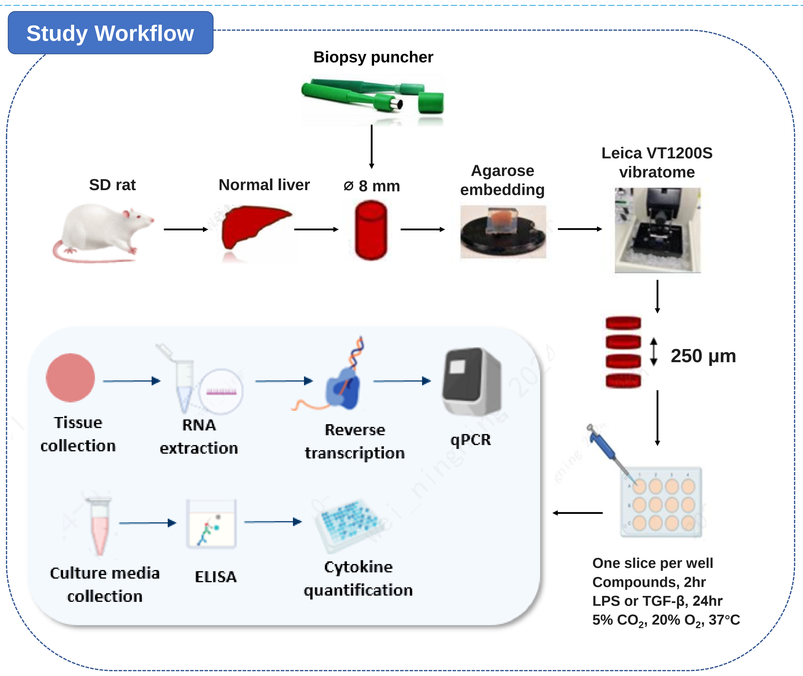
Precision-cut tissue slices (PCTS) serve as an effective *ex vivo* model for studying human diseases. PCTS retain the complex tissue microenvironment including immune components and the extracellular matrix, rendering them a valuable tool for drug discovery.

We have successfully established *ex vivo* fibrosis and inflammation models using precision cut liver slices (PCLS) from rats. Following treatment with TGF-β for 24h, mRNA levels of IL-6, TNF-α, COL1A1, α-SMA, TGF-β1, IL-1β, etc., significantly increased compared to untreated PCLS controls. These changes were downregulated upon treatment with the anti-inflammatory drug dexamethasone or anti-fibrotic compounds such as SB525334 and Nintedanib.

Moreover, upon LPS induction, mRNA levels of IL-6, TNF-α, COL1A1, α-SMA, TGF-β1, IL-1β, IL-10, CTGF and iNOS significantly increased. Immune suppression drug like Tacrolimus and JAK inhibitor Baricitinib significantly decreased LPS-induced upregulation of these inflammation- and fibrosis-related genes.

PCTS treatment responses can be assessed using multiple readouts, including tissue viability, RNA and protein analyses, histology, and live-cell imaging. These readouts enhance PCTS's potential as a translational tool, bridging *in vitro* assay findings with *in vivo* efficacy. Ongoing studies showed promising results for advancing drug discovery.

Experimental design



Results

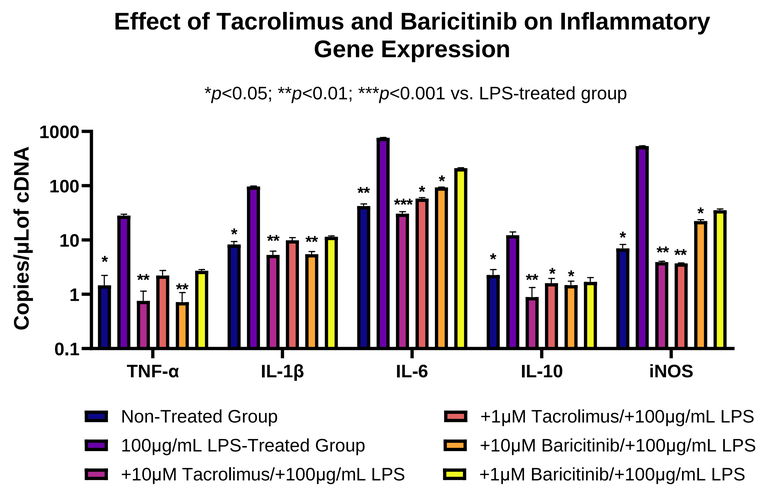


Figure 1. Droplet Digital PCR (ddPCR) analysis of inflammation-related genes in LPS-induced inflammatory PCLS.

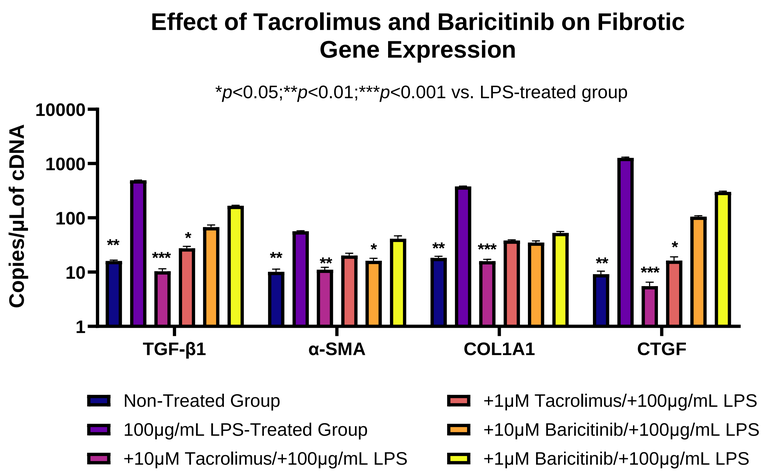


Figure 2. Droplet Digital PCR (ddPCR) analysis of pro-fibrotic genes in LPS-induced inflammatory PCLS.

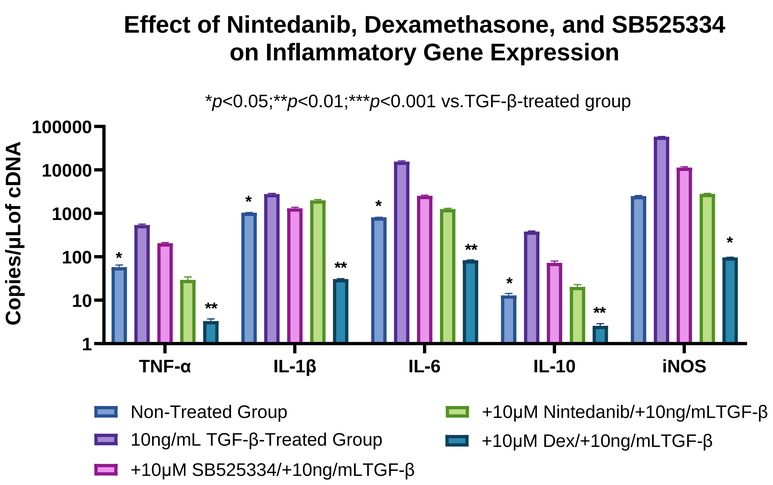


Figure 3. Droplet Digital PCR (ddPCR) analysis of inflammation-related genes in TGF-β-induced fibrotic PCLS.

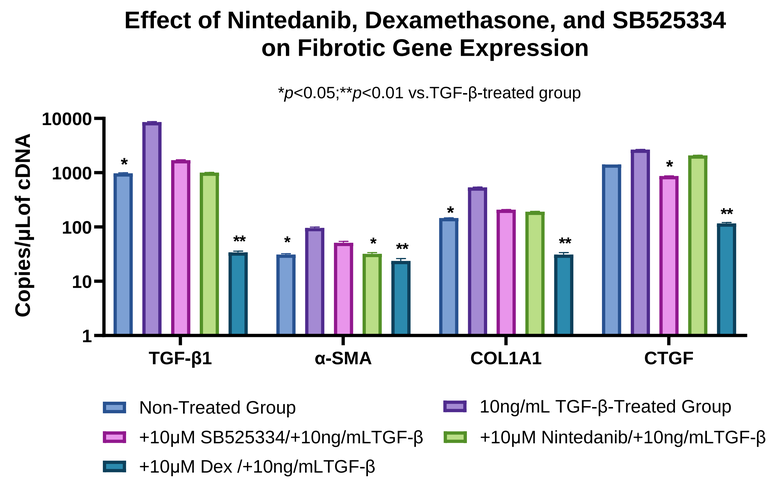


Figure 4. Droplet Digital PCR (ddPCR) analysis of pro-fibrotic genes in TGF-β-induced fibrotic PCLS.

Summary

- An inflammatory and a fibrotic PCLS model were successfully established by LPS and TGF-β induction, respectively.
- In the inflammatory PCLS model, Baricitinib and Tacrolimus dose-dependently inhibited the mRNA expression of TNF-α, IL-1β, IL-6, IL-10, iNOS, TGF-β1, α-SMA, COL1A1, and CTGF.
- In the fibrotic PCLS model, Nintedanib and Dex decreased the mRNA expression of TNF-α, IL-6, IL-10, iNOS, TGF-β1, α-SMA, COL1A1, and CTGF.

References

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