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Targeting the angiocrine with a selective ROCK2 inhibitor in liver fibrosis

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Liver fibrosis, a hallmark of chronic liver diseases including metabolic dysfunction-associated steatohepatitis (MASH), remains a leading cause of global morbidity and mortality. Current therapies targeting metabolism or inflammation show limited efficacy against fibrosis and largely overlook the hepatic microvasculature. Blood vessels are not passive conduits but active signaling centers that secrete angiocrine factors. Here we identify ROCK2 as a key regulator of a pro-fibrotic angiocrine niche. The selective ROCK2 inhibitor TDI01 demonstrates potent anti-fibrotic effects in a minipig model and has shown favorable safety with trends of disease reversal in clinical trials, offering a novel "angiocrine" – based therapeutic strategy.

INTRODUCTION: THE UNMET NEED AND BOTTLENECK

Chronic liver injury leads to progressive extracellular matrix (ECM) deposition, driving the transition from metabolic dysfunction-associated steatohepatitis (MASH) to cirrhosis and hepatocellular carcinoma (HCC).[1] Recent metabolic modulators—such as thyroid hormone receptor-beta (THR-β) and glucagon-like peptide-1 (GLP-1) receptor agonists—work well on early metabolic dysregulation in MASH, but what is still missing is a therapy that can directly and effectively reverse established fibrosis. Targeting hepatocytes alone or dampening systemic inflammation is unlikely to be enough. Real structural reversal will require looking beyond the hepatic parenchyma and directly addressing the intercellular crosstalk that sustains the fibrotic microenvironment.[2] The concept of "angiocrine" signaling has changed how we think about this: endothelial cells are not just passive vessels but active secretors of growth factors, cytokines, and matrix proteins that shape organ regeneration, homeostasis, and disease.[3,4] While the concept of angiocrine signaling in liver fibrosis is well established, the discovery of vascular ROCK2 as a key, druggable node within this signaling axis offers a promising new direction for anti-fibrotic drug discovery (Figure 1).[5]

THE ANGIOCRINE AS A PROMISING THERAPEUTIC TARGET

The liver is highly vascularized, and its unique microvascular network is lined by specialized LSECs. Under homeostatic conditions, these fenestrated endothelial cells maintain a quiescent microenvironment. However, chronic insult triggers LSEC capillarization—characterized by the complete loss of fenestrae and the formation of a continuous basement membrane. This structural collapse is not merely a consequence of disease but a primary driver of fibrogenesis. Capillarized LSECs undergo a transcriptomic reprogramming, transforming the vascular niche into an "angiocrine" hub that actively secretes pro-fibrotic factors. These aberrant signals, in turn, directly activate perivascular HSCs, promoting their transdifferentiation into matrix-producing myofibroblasts. Thus, the angiocrine niche represents the pathological epicenter of liver fibrosis.

ROCK2 IN ENDOTHELIAL CELLS IS CENTRAL TO THE ANGIOCRINE

Our initial characterization of the fibrotic microenvironment pointed to the RhoGTP signaling pathway as a key regulator. However, since Rho GTPases themselves are notoriously difficult to drug, we turned our attention downstream to their effectors, ROCK1 and ROCK2. Single-cell transcriptomic profiling and pathological analyses of human fibrotic livers (Hu et al. Cell 2026 Figures 1C-1E) then revealed a striking upregulation of ROCK2 specifically within the vascular and perivascular compartments, predominantly localized to the LYVE1$^+$ subpopulation of LSECs.[5] Unlike broad-spectrum kinase targets, vascular ROCK2 functions as a dual-action molecular switch: it physically drives LSEC defenestration through cytoskeletal hypercontractility, while simultaneously orchestrating the transcriptional release of key pro-fibrotic angiocrine factors like Galectin-3, a process potentially mediated by its influence on cytoskeletal dynamics that alters downstream transcriptional events. Importantly, although pan-ROCK inhibitors have historically failed due to severe systemic toxicities—such as hypotension caused by ROCK1 inhibition—selectively targeting ROCK2 avoids these on-target, off-tissue toxicities. This positions vascular ROCK2 as a highly druggable and precise point for reprogramming the fibrotic microenvironment.

FROM RATIONAL DRUG DESIGN TO CLINICAL VALIDATION

Exploiting ROCK2 as a therapeutic target demands exceptional pharmacological selectivity. For years, the development of ROCK-targeting drugs has been hindered by the high sequence homology between the kinase domains of ROCK1 and ROCK2. Conventional pan-ROCK inhibitors such as Fasudil fail to distinguish between the two isoforms, often causing severe systemic side effects like hypotension due to ROCK1 inhibition, which has repeatedly stalled their clinical translation. Through computer-aided drug design and high-throughput screening, we developed TDI01. Structural analysis revealed that TDI01 stabilizes the inactive DFG-out conformation and exploits a key residue difference (leucine 210 in ROCK2 versus phenylalanine 194 in ROCK1) to achieve selective binding via the displacement of the αC-helix. This gives TDI01 approximately 600-fold selectivity over ROCK1 (IC_{50}: 10.31 nM for ROCK2 vs. 6159 nM for ROCK1), allowing potent ROCK2 suppression while completely avoiding ROCK1-mediated toxicities.

Crucially, this biochemical selectivity translates directly to cellular environments. Quantitative proteomics using a biotin-labeled TDI01 derivative in human primary ECs and HSCs (LX2 cells) confirmed that ROCK2 is the highest-intensity interacting protein, and TDI01 exhibited dose-dependent, selective inhibition of ROCK2 activity over ROCK1 in these cellular contexts. Furthermore, while Belumosudil is an FDA-approved selective ROCK2 inhibitor for chronic graft-versus-host disease (GVHD), TDI01 distinguishes itself through a substantially higher selectivity index and distinct binding mechanism. This highly optimized pharmacological and safety profile allows TDI01 to be therapeutically positioned not only for GVHD but also for a broader spectrum of severe fibrotic conditions, prominently including liver fibrosis (MASH) and pulmonary fibrosis.

To validate the angiocrine therapeutic concept, we tested TDI01 in animal models of fibrosis. In standard mouse models of liver fibrosis, TDI01 significantly reduced collagen deposition and improved histological outcomes. We then moved to the Bama minipig model of MASH, which closely mirrors human anatomy, metabolism, and disease progression. In these animals, TDI01 effectively restored LSEC fenestration, halted capillarization, and markedly reversed extensive collagen deposition.

These preclinical results supported the move to clinical testing. A Phase I trial (ChiCTR2200058868) in healthy volunteers confirmed that TDI01 has a favorable safety profile and predictable pharmacokinetics, demonstrating that selective ROCK2 inhibition avoids the toxicities seen with pan-ROCK blockade. An extended trial (ChiCTR2400082056) in patients with liver fibrosis then provided evidence of target engagement and clinical activity. Post-treatment biopsies showed reduced phosphorylated ROCK2 in the liver, along with improvements in fibrotic pathology and liver stiffness measurements. Together, these data mark the successful transition of TDI01 from preclinical discovery to early clinical validation.

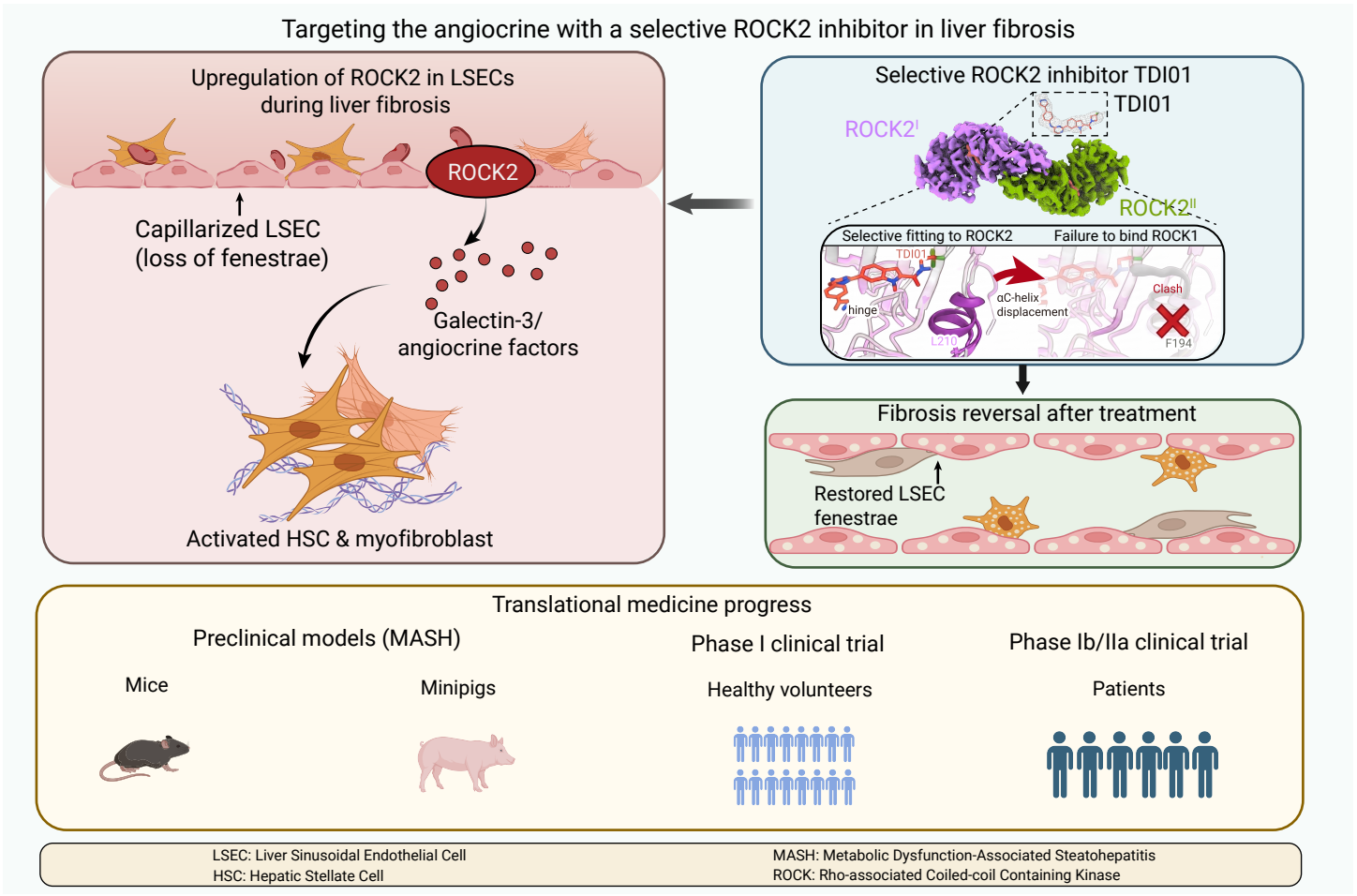

Figure 1. Targeting the angiocrine with a selective ROCK2 inhibitor in liver fibrosis The figure describes the mechanism and translational progress of selective ROCK2 inhibitor TDI01 against liver fibrosis. Fibrosis triggers liver sinusoidal endothelial cell (LSEC) capillarization and ROCK2 upregulation, driving hepatic stellate cell activation. TDI01 selectively binds ROCK2 via αC-helix displacement, sparing ROCK1 due to a structural clash at the F194 site. Preclinically validated in MASH models (mice, minipigs), the candidate has advanced to Phase I trials in healthy volunteers and Phase Ib/IIa studies in patients.

FUTURE DIRECTIONS AND CONCLUDING REMARKS

The core finding of this study, that the angiocrine factor ROCK2 is a druggable anti-fibrotic target, represents a conceptual breakthrough in hepatology. Although selective ROCK2 inhibitors have shown encouraging efficacy in early clinical trials, whether they can truly extend patient survival and how broadly they can be applied still need rigorous validation through large-scale double-blind randomized controlled trials. In addition, combining TDI01 with metabolic regulators may produce synergistic effects in patients with complex MASH. Furthermore, given the shared pathological feature of LSEC capillarization and macrophage-driven inflammation in alcohol-associated liver disease (ALD), this angiocrine ROCK2 mechanism likely applies to ALD and other fibrotic diseases. As our understanding of the vascular microenvironment deepens, selective ROCK2 inhibitors like TDI01 may help advance mechanism-driven precision anti-fibrotic therapy.

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AUTHOR CONTRIBUTIONS

X. Y conceived the concept and wrote the manuscript. B. D reviewed and edited the manuscript. All authors accepted the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

Not applicable.