Integrative Multi-Omics Analysis to Decipher the Molecular Tipping Point and Biomarkers of NAFLD Progression

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Non-Alcoholic Fatty Liver Disease (NAFLD), recently redefined as Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), affects approximately 25% of the global population. A major clinical challenge remains the "Obese Control" puzzle: understanding why only a subset of patients progresses to Non-Alcoholic Steatohepatitis (NASH/MASH) [3]. This study integrates human transcriptomics with mouse signaling profiles to identify the molecular "tipping point" of this transition.

Our analysis revealed a distinct three-stage transcriptomic progression in humans: Stage 1 involves lipid metabolism and cytoskeleton remodeling; Stage 2 is characterized by metabolic failure and early inflammatory signaling; and Stage 3 exhibits systemic immune activation with advanced fibrosis. Parallel signaling profiling in mouse models uncovered a critical temporal shift in kinase networks: early-stage adaptation is driven by proliferative signals such as EGFR and INSR, whereas chronic progression triggers a transition toward pro-fibrotic remodeling signals coordinated by SRC and the matrix stiffness sensor PTK2. Network analysis further identified synergistic drivers shared by NAFLD and Type 2 Diabetes, highlighting key nodes including COL1A1, GDF15, and IGFBP7.

To translate these mechanistic findings, future work will employ a simplified machine learning framework. Specifically, a binary classification model (e.g., Random Forest) will be constructed using the identified core markers, PTK2 and SRC, to accurately distinguish NASH from simple steatosis, providing a robust tool for non-invasive clinical diagnosis [1, 2].

References

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