

Remodeling of Protein Networks Across Cirrhosis Stages Reveals Molecular Signatures of Disease Severity and Therapeutic Targets

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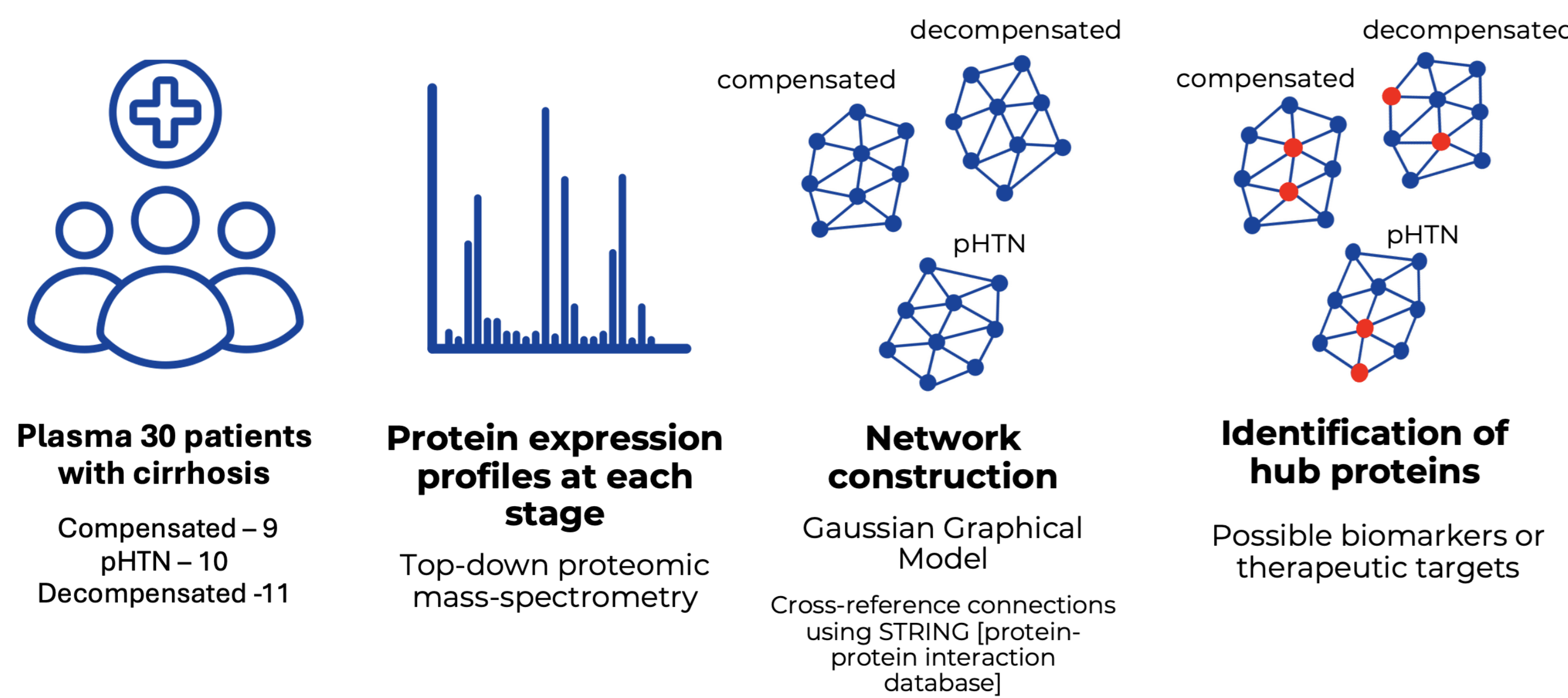
Background

- Currently available diagnostics cannot predict transition into decompensated cirrhosis¹
- Traditional analyses focus on individual proteins but miss critical protein interaction networks driving disease progression^{1,2}
- Rich-club proteins are highly interconnected hubs within protein networks, potentially acting as central coordinators of disease progression³

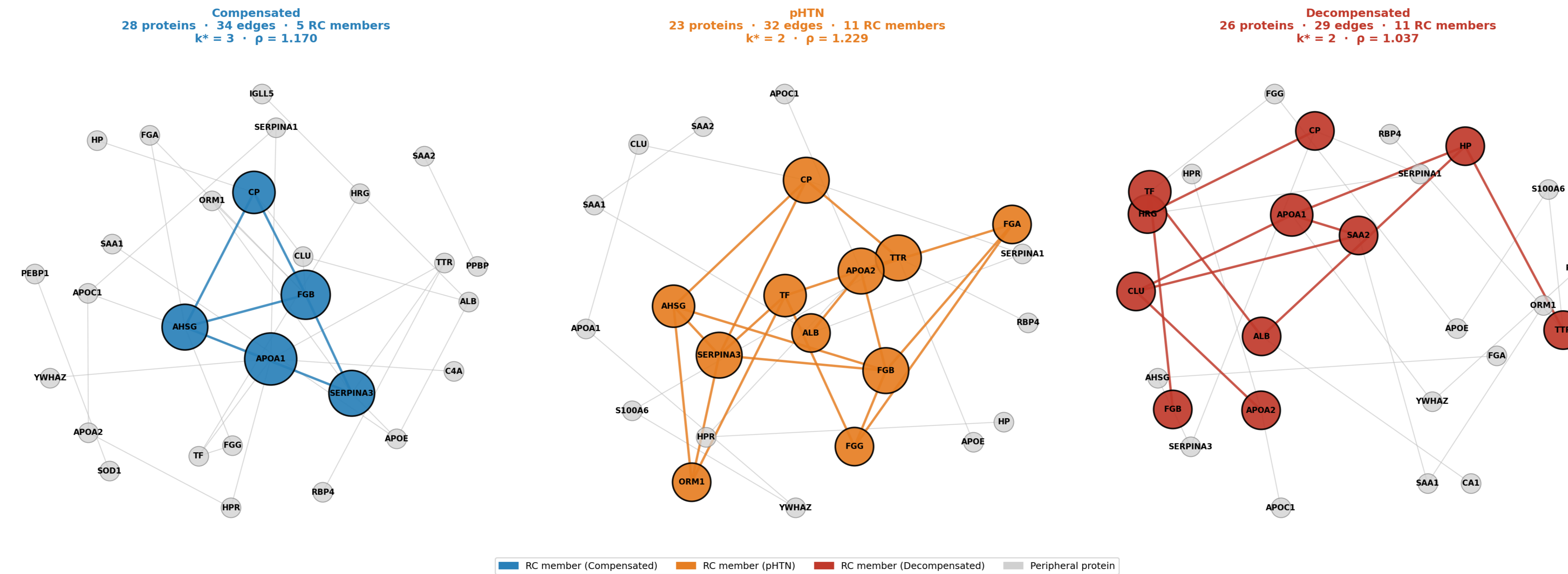
Goal

Uncover key proteins driving liver cirrhosis progression and inform future therapeutic strategies

Methods



Protein Network Degradation with Progression



Stage	Proteins	Edges	Density	RC Members
Compensated	28	34	0.090	5
pHTN	23	32	0.126	11
Decompensated	26	29	0.089	11

Networks share 17–24% of edges across stage pairs (Jaccard); RC overlap between Compensated and pHTN is significant (hypergeometric $p=0.047$)

Key Protein Targets and FDA Approved Drugs

Approved Drug Targets by Stage Transition — Upstream Regulators of RC Proteins

Regulator	Full Name	RC Proteins	Role	Key Approved Drugs
F2	Thrombin	FGA, FGB, FGG	Inhibit	Bivalirudin, Dabigatran, Argatroban
ITGA2B_ITGB3	Integrin α IIb/ β 3	FGA, FGB, FGG	Inhibit	Tirofiban, Eptifibatide, Abciximab
MMP13	MMP-13	FGA, FGB, FGG	Activate	Doxycycline
PPARA	PPAR α	APOA1, APOA2	Unknown	Fenofibric acid, Ciprofibrate, Pemafibrate
RXRA/B/G	RXR α / β / γ	APOA1, APOA2	Unknown	Bexarotene, Etretinate
IL6	IL-6	HP, SAA1	Inhibit	Siltuximab, Olokizumab
HNF4A	HNF4 α	APOA1, APOA2, TTR	Inhibit	Alverine

Confirmed in ≥ 2 of: DrugBank, OpenTargets, ChEMBL. Role = predicted direction of regulator activity.
■ Comp \rightarrow pHTN ■ Comp \rightarrow Decomp ■ pHTN \rightarrow Decomp

Conclusions

- Protein-Protein network architecture significantly changes as cirrhosis progresses
- RC identity shifts from coagulation at Compensated \rightarrow pHTN to lipoprotein and acute-phase proteins at Decompensated, with only CP and FGB conserved across all stages
- Stage-specific druggable upstream regulators were identified: thrombin inhibitors and integrin antagonists at early progression, and PPAR α agonists and IL-6 inhibitors at late-stage decompensation

References

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