INTERNATIONAL INSTITUTE OF INFORMATION TECHNOLOGY
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Technology, Social Impact

Dynamic reorganization of transcriptome during liver regeneration

INTRODUCTION

Being an important metabolic organ, liver plays a vital role in the body, including the production of plasma proteins, clotting factors, synthesis of triglycerides, cholesterol, glycogen, detoxification etc.

Interference with these liver functions have serious repercussions leading to several metabolic disorders like hepatic steatosis, NAFLD(Non-alcoholic fatty liver disease), NASH(Non-alcoholic steatohepatitis), HCC(hepatocellular carcinoma).

Liver transplantation and partial liver resection(PHx) have been suggested as possible treatment options to fight such diseases to some extent, but they are prone to recurrence after few years.

In this direction we attempt to explore recent advancements in this area along with various mathematical tools that can be utilized to gain systems-level understanding of patho-physiology of metabolic disorders.

METHODS

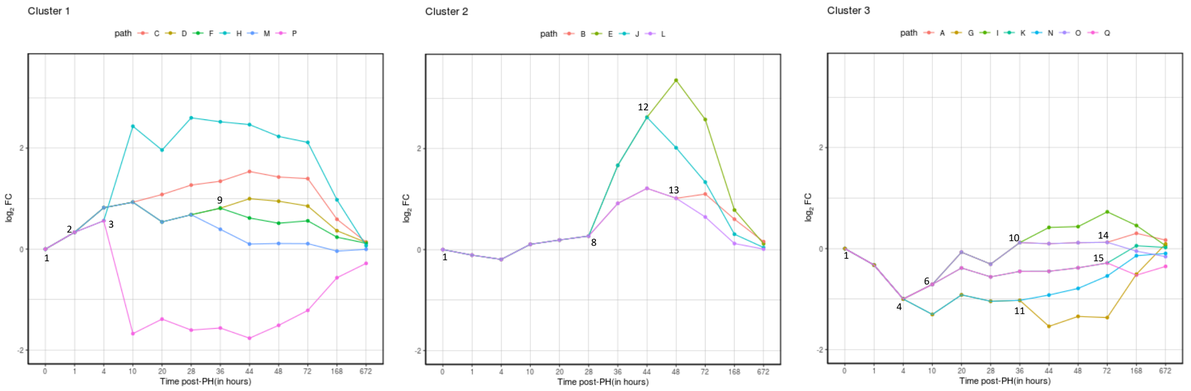
❖ Analyzing temporal transcriptomics data(RNA-seq) for differentially expressed genes using LIMMA.

❖ Associating cluster-wise temporal changes in gene expression to transcription factors(TFs) using Input-Output Hidden Markov Model(IOHMM), Dynamic Regulatory Events Miner(DREM).

❖ DREM integrates time series gene expression data with TF-gene target association(from ChIP-seq data).

❖ The output is a model with different clusters highlighting bifurcation points(BPs) and TFs potentially responsible for them.

RESULTS



1-2	CEBPB, NFATC2, NFATC3, NFATC1, NFATC4, JUN, JUNB, FOS, FOSB, JUND, FOSL2, SRY, BACH2, ALX4, NFE2L1, XBP1, SRF, GATA4, FOSL1, CD40, ARHGEF7, ETS1, SPIB, POU2F2, SLC22A1, STAT6, STAT1, POU3F1, ATF1, STAT5A, PRDM1, OTX1, OTX2, ERF, LEF1, STAT4, NFKB1, TBP
1-8	E2F4, RB1, E2F5, E2F2, PTGDR, SRPR, E2F1, TFDP1, TFDP2, E2F7, NFYA, UBE4A, UBE4B, NFYB, PITX2, TRAF4, ALX1, NRF1
3-H	STAT3, GABPA, WT1, NFE2, ZIC2, NFE2L2, TCF4, SMAD4, RELA, ZBTB7A
4-6	AHR, TRP53, RXRA
6-10	NF1, ZIC2, ZBTB7A, ZFP355C
8-12	POU3F2
8-13	HNF4A, SP3
9-D	GIF1, G1F1B
10-14	RXRA, SRY, VDR
11-N	CEBPBD, ARNT, NFYB, GATA1, POU2F1, FOXF2, NFYA, NF1
12-E	IL10, TGIF1
13-B	FOS, JUNB, JUND, PGR, TMEM37, FOSB
13-L	TFDP2, E2F4
15-K	IRF1, IRF7, IRF8, IRF3, IRF4, PPARA, IRF5

Transcription factors governing the reorganization of gene expression into diverging paths

Path	KEGG Pathways
C	Complement and coagulation cascades; Ferroptosis; Fluid shear stress; HIF-1 signaling pathway; TNF signaling pathway; Adipocytokine signaling pathway; ECM-receptor interaction;
D	Protein processing in ER; Protein export; Complement and coagulation cascades; Amino sugar and nucleotide metabolism;
F	MAPK signaling pathway; IL-17 signaling pathway; Circadian entrainment;
M	PPAR signaling pathway; Arginine biosynthesis; Alanine, aspartate and glutamate metabolism; Fatty acid degradation; Fatty acid elongation; Biosynthesis of unsaturated fatty acids
H	Cell cycle; p53 signaling pathway; DNA replication; Fatty acid degradation; PPAR signaling; Cellular senescence;
P	Steroid hormone biosynthesis; PPAR signaling; Primary bile acid biosynthesis; Biosynthesis of unsaturated fatty acids; Glycolysis/Gluconeogenesis

Path	KEGG Pathways
E	Cell cycle; p53 signaling, ECM-receptor interaction
J	Cell cycle; DNA replication; Gap junction; Apoptosis; Mismatch repair; Base excision repair
B	Glycolysis/gluconeogenesis; Focal adhesion
L	Homologous recombination; DNA replication; Nucleotide and base excision repair; Cell cycle; RNA transport; Spliceosome

Path	KEGG Pathways
A	Leukocyte transendothelial migration; Regulation of actin cytoskeleton
O	Steroid biosynthesis; Purine and pyrimidine metabolism; Bile secretion; Cholesterol metabolism;
K	Amino acid metabolism; Pentose phosphate pathway
Q	Ribosome
N	Tryptophan metabolism; Glutathione metabolism; Linoleic acid metabolism
G	Steroid hormone biosynthesis; Cholesterol metabolism; PPAR signaling; Arachidonic acid metabolism

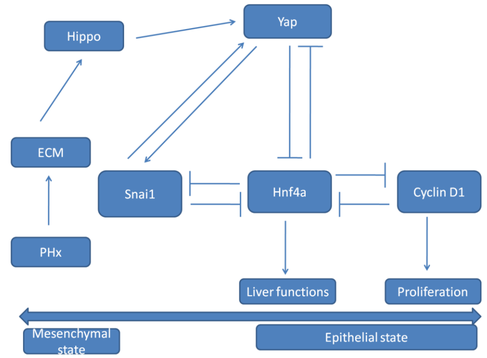
❖ During the course of regeneration transient changes are observed in the early phase between 0 to 4 hours post-PH

❖ Processes accompanying cell cycle are triggered in the mid-phase(28 hours post-PH). Along with cell cycle, repair mechanisms are also triggered during the same time window.

❖ Probabilistic modeling revealed coordination of metabolism and proliferation with some metabolic processes showing complex pattern.

❖ We found transient and sustained changes in metabolic process during liver regeneration.

❖ A mathematical model for liver regeneration is proposed.



A model for liver regeneration

REFERENCES

1. Schulz, M.H., Devanny, W.E., Gitter, A. *et al. BMC Syst Biol* **6,** 104 (2012).
2. Matias J. Caldez Philipp Kaldis, *et al.* Developmental Cell,Volume 47, Issue 4, 2018,Pages 425-438

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