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Hepatic enhancer activities and transcription factor networks in response to fasting

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The liver is a first-line-responder to fluctuations in food intake, adapting gene expression (GE) programs by recruitment of specific transcription factors (TFs) to promoter and enhancer regions. Transcriptionally engaged TFs have been described to bind enhancers, resulting in the generation of enhancer RNAs (eRNAs). To investigate fasting-selective eRNAs we established qPRO-seq for complex tissues and applied it to mouse livers sampled at several time points over a 24-hour fasting period. Various bioinformatics tools and custom scripts were used. Differential GE analysis from qPRO-seq time series delivered dynamics of known fasting-regulated genes, such as induction of gluconeogenesis (Pck1) as early as 3 and peaking after 24 hours and repression and, paradoxically, induction after 3 hours of de novo fatty acid synthesis (Fasn) already 1 hour after food withdrawal, showing the strongest repression after 12 hours. GO annotation of fasting-activated enhancers (from around 140 up to 1300, depending on time point) neighboring genes showed an overrepresentation of metabolic processes regarding various metabolites, protein transport and cell signaling processes after 1, 12 and 24 hours respectively. This stark temporal difference suggests dynamic regulation of numerous pathways throughout fasting. Finally, enriched TF motifs within each set of fasting-activated enhancers were compiled. This revealed regulatory dynamics of known nuclear receptor TFs, like PPAR α and forkhead TFs, such as FOXA1, as well as less described TFs like NR2F1, NR2F6 and Rfx6. Currently our results suggest a timely coordination of fasting GE by specific TF clusters a genome-wide enhancer activation in fasted liver. In future analyses, we will focus on individual (super-) enhancer clusters and TF networks to reveal novel regulatory mechanisms in the fasting context.