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Multi-omics in one assay: qPRO-seq to decipher chromatin and transcriptional landscapes of fasting in adipose tissue

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Adipose tissue (AT) plays a central role in the regulation of systemic energy homeostasis. Transcriptome studies have shown that AT globally rewires its gene expression (GE) program upon fasting, but the regulatory determinants are not well understood. Key players of the fasting response are specific transcription factors (TFs) that bind to promoter and enhancer regions. Enhancer RNAs (eRNAs) are short and unstable RNAs, that are generated from TF-bound enhancers. For genome-wide determination of nascent RNAs in genes, promoters, and enhancers, quick precision nuclear run-on sequencing (qPRO-seq) of visceral AT of mice fed and fasted at different timepoints was performed. Data were analyzed using a customized bioinformatics pipeline. Validating our method, we found genes involved in ß-oxidation (e.g. Acads and Slc25a20) upregulated after three hours of fasting, while genes involved in lipid storage, including GK, were downregulated after one hour of fasting onset. Interestingly, GE analysis indicates signatures of immune cell infiltration (e.g. Il1r1, Reg4) as early as three hours after nutrient withdrawal. Moreover, we detected about 250 fasting-activated eRNAs cumulative over 6 hours of fasting. Motif enrichment analysis of fasting-selective enhancers identified several known AT-specific TFs, such as GRE, CEBP, RXR, as well as previously undescribed players, like the golgi-associated olfactory signaling receptor (GFY). Hence, we are first to apply qPRO-seq to complex tissues and show that, in combination with bioinformatics analyses, GE as well as the underlying regulatory events can be revealed in one genome-wide assay. In future, we will focus on analysis of fasting-evoked super enhancer clusters, TF networks, and their downstream pathways as well as on wet lab experiments to validate novel findings revealed by qPRO-seq. Since AT is very heterogenous and undergoes extensive remodeling upon fasting, cell-type specific approaches and models are currently tested.