

Abstract

The liver has a key role in the maintenance of metabolic homeostasis. It regulates central parts of glucose, lipid, amino acid and cholesterol metabolism in interplay with other key metabolic hubs like the adipose tissue and skeletal muscle. Endocrine signaling hormones, such as glucagon, insulin, glucocorticoid (GC) and thyroid hormone (TH) signal to the liver to induce transcriptional and posttranscriptional regulation facilitating metabolic adaptation of the liver in a context-specific manner. The coordinated signaling activates a complex network of transcription factors (TF), which in interplay with coregulators and chromatin remodelers, regulate the recruitment of the transcriptional machinery to specific genes to orchestrate a dynamic transcriptional response. These highly complex transcriptional changes in liver cells enable the organism to respond to changes in energy availability during the day. Disturbance of these endocrine signaling pathways, or the hepatic transcriptional response, are related to metabolic diseases highlighting the importance in understanding the underlying molecular mechanism.

TH and GC produced in the thyroid- and the adrenal gland, respectively, interact with their respective nuclear receptors the thyroid hormone receptor (TR) and the glucocorticoid receptor (GR), respectively. Both TR and GR function as important TFs regulating hepatic metabolism. Although the molecular mechanisms behind TR- and GR-mediated transcriptional regulation has been studied for years, many aspects are still unexplored.

The aim of this PhD project is to investigate the transcriptional mechanisms regulating the hepatic gene program induced by TH and GC activating TR and GR, respectively. First, we investigated enhancers regulated by TR and identified different types of enhancers differentially bound by coregulators. We found that at one type of TR-regulated enhancers the coactivator cAMP response element binding protein (CBP) is constitutively bound while the corepressor complex nuclear co-repressor 1 complex (NCoR) works as an acetylation rheostat. This observation challenges current models. In the second part of the PhD project, we investigated the role of GR in regulating hepatic transcription in the fast-feeding transition and identified GR-dependent feeding-repressed and -induced genes. These findings add a new function to GR otherwise known to be a fasting-responsive TF.

Collectively, this PhD study elucidates some of the transcriptional regulatory functions of the nuclear receptors, TR and GR in the liver. The results presented and discussed in this dissertation encourage further studies in the transcriptional networks controlling liver metabolism to lay the foundation for understanding the mechanisms driving metabolic diseases like non-alcoholic fatty liver disease and diabetes.