## Summary (English)

Functional genomics is an emerging approach used for understanding the role of gene regulation in polygenic disease development. One disease that belongs to this category is type II diabetes and its precursor, the metabolic syndrome. A morbid and, in some cases, life-threatening aspect of these pathological states is an inability of the body to cope with fluctuating nutrient levels after a meal. While the role of the liver in regulating postprandial homeostasis is well established, there are still open questions regarding the key players that regulate the gene and enhancer activity during a feeding response in the liver. More specifically, only few studies have addressed the acute transition from a fasted to a fed state in a genome-wide scale, and there is lack of research that would address the problem through a circadian-relevant approach.

The aim of this thesis is to examine mechanisms involved in hepatic feeding-regulated gene expression and the chromatin landscape by using genomics-based approaches. This includes a special focus on finding the points of crosstalk between insulin signalling and glucocorticoid signalling pathways, which are relevant to hepatic circadian and feeding regulated gene expression and enhancer activity.

We first characterized gene expression and chromatin remodelling during an acute hepatic feeding response by using functional genomics approaches such as RNA-seq, DNase-seq and ChIP-seq in an in vivo setting (**Section 2**). We found that in mice which are entrained to a circadian-integrated feeding regime, the postprandial decrease in corticosterone in coordination with the acute postprandial hyperinsulinemia cooperatively regulates hepatic transcriptional output. Through characterising the chromatin landscape dynamics in the transition from a fasted to a fed state, we identified and further investigated the involvement of FoxO1 and GR in the coordination of feeding-repressed gene expression. We showed that pharmacological manipulation of GR and insulin receptor activity can fully reactivate feeding repressed genes in the liver, and that discordance in both signalling pathways explains certain gene expression profiles in mice harbouring genetic disruption of GR and IRS, as well as in diet induced obese mice.

We then focused on finding the crosstalk points between glucocorticoid and insulin signalling pathways in a cell culture model (H4IIE rat hepatoma cells) - a setting which is independent of systemic signals other than insulin and glucocorticoid input (Section 3). We observed that GR binding to chromatin and the majority of glucocorticoid induced gene expression is reduced in the presence of insulin. By overexpressing a constantly active FoxO1 mutant in these cells, we observed that GR activity is likely affected both by FoxO1 and by kinases downstream of the insulin signalling pathway.

Together, these results elucidate regulatory complexity between glucocorticoid and insulin signalling pathways in coordinating the transcriptional networks when the liver switches from a fasted state to a fed state. These results also encourage finding drug strategies which target the crosstalk between GR and insulin signalling to improve glycemic control.