Summary

Transcriptional regulation plays an intricate role in metabolic adaptation. Cellular metabolism is thus regulated through a system of transcriptional activators and repressors. These coregulators are able to modulate transcription of various metabolic programs to maintain energy homeostasis in response to altered energy demands or environmental cues. Peroxisome proliferator-activated receptor (PPAR) coactivator 1 alpha (PGC-1α) is a transcriptional coactivator, which is import for cellular metabolic adaptation. PGC-1α is expressed in mitochondria-rich tissues and regulates distinct metabolic gene programs, such as fatty acid oxidation and mitochondrial oxidative phosphorylation through interaction with various transcription factors. The pervasive role of PGC-1α in metabolic regulation has made this transcriptional coregulator a promising therapeutic target in several disorders with a mitochondrial bioenergetic etiology. However, to comprehend the therapeutic potential of PGC-1α activation, it is essential to gain a full understanding of the transcriptional networks modulated by this coactivator and its impact on cellular- and organismal physiology. Moreover, it is important to validate whether PGC-1α activation is necessary to mediate the beneficial metabolic effects (i.e. increased energy expenditure or improved glucose tolerance) of various pharmacological compounds. Such experiments will confirm the potential use of PGC-1α as a therapeutic target, and will give a better insight into the molecular mechanisms how these compounds exert their effects. Ultimately, the characterization of PGC-1α as a therapeutic target will aid in the design of more efficient drug therapies.

The role of PGC-1α is well established in organs such as liver and skeletal muscle. However, despite the prevalence of mitochondrial dysfunction in the pathogenesis of renal disorders, the role of PGC-1α in kidney physiology and its potential therapeutic use in this organ is still unknown. To define the role of PGC-1α in renal physiology, we generated and characterized a nephron-specific PGC-1α knockout mouse model. We observed that deletion of PGC-1α in kidney led to a reduced transcription of gene programs involved in mitochondrial oxidative metabolism. PGC-1α was also required for the induction of PPARα target genes and renal fatty acid oxidation during high fat diet feeding. Renal deletion of PGC-1α resulted in mild hypertension and increased urinary sodium excretion. However, mice deficient for PGC-1α in the kidney could still adapt their salt and water homeostasis in response to salt stress. This indicates that PGC-1α is dispensable for the adaptive regulation of tubular reabsorption and secretion. However, due to the high basal energy demand of the kidney, there is a strong link between mitochondrial dysfunction and renal disorders. While the loss of PGC-1α did not affect basal renal physiology, it has a central role as a regulator of metabolic and mitochondrial transcriptional programs in the kidney. Hence,

PGC-1α could be a potential therapeutic target to ameliorate renal metabolic disorders associated with mitochondrial dysfunction and lipotoxicity.

In the second study, we investigated the role of skeletal muscle PGC-1α in mediating the therapeutic effects of the SIRT1-activaiting compounds resveratrol (RSV) and SRT1720. The beneficial systemic effects of these compounds, such as an enhanced metabolic rate and improved glucose tolerance, were independent of skeletal muscle PGC-1α. PGC-1α was however necessary for transcriptional activation of mitochondrial genes in skeletal muscle with RSV and SRT1720 treatment. Intriguingly, while postulated to act through the same signaling pathways, we could also demonstrate differential effects of RSV and SRT1720 treatment on mitochondrial and metabolic processes in liver and white adipose tissue (WAT). Importantly, both RSV and SRT1720 enhanced transcription of PGC-1α target genes in WAT and liver, respectively. Finally, in the third part of this thesis, we investigated the role of PGC-1α in the regulation of skeletal muscle ketone body oxidation. Ketone bodies are important metabolic fuels during prolonged starvation and dietary ketosis has been postulated to possess several therapeutic effects, such as improved epileptic seizure control, reduced cancer growth rates and enhanced mitochondrial biogenesis in brown adipose tissue and brain. However, relatively little is known how ketolytic capacity in skeletal muscle is regulated. We demonstrated that PGC-1α, together with the estrogen-related receptor alpha (ERRα), regulates transcription of ketolytic enzymes in skeletal muscle, both in a basal state and in response to exercise. Importantly, modulation of PGC-1α levels in skeletal muscle affected systemic ketone body homeostasis during exercise, fasting and feeding of a low-carbohydrate ketogenic diet. Moreover, elevation of PGC-1α levels in skeletal muscle was sufficient to ameliorate diabetic ketoacidosis in mice. Hence, we identified PGC-1α as a potential therapeutic target to reduce hyperketonemia in diabetic patients.

In summary, the work presented in this thesis describes several new aspects of PGC-1α biology. We have revealed novel insights into the role of PGC-1α in renal physiology and its potential role as a therapeutic target in kidney. Additionally, we have evaluated the role of skeletal muscle PGC-1α as a molecular effector of the beneficial effects of RSV and SRT1720 on whole body metabolism. Finally, we have described a novel role of PGC-1α as a transcriptional regulator of ketone body oxidation. Collectively, our findings demonstrates a crucial role of PGC-1α in many different biological processes which are all ultimately connected to mitochondrial metabolism. These data expand our knowledge on the transcriptional networks and cellular processes regulated by PGC-1α and will help to develop more efficient therapeutic strategies against metabolic disorders.