Summary

Over the past centuries, obesity has become one of the biggest threats to the public health primarily due to development of associated collateral diseases including type 2 diabetes mellitus and atherosclerosis. A central contributor to obesity-linked pathogenic progression is prevalence of adipose inflammation. This condition is caused by extensive lipid filling of adipocytes due to prolonged positive energy balance. This in turn leads to recruitment and activation of immune cells causing a pronounced inflammatory tone of the tissues. This is known to promote adipocyte dysfunction by inducing a shift from anabolic to catabolic lipid metabolism resulting in induced lipid release from the tissue. Excess free fatty acids are known to ectopically accumulate in other metabolically active tissues including skeletal muscle and liver. Development of steatoses in these tissues can in turn lead to decreased insulin sensitivity and through that progress cause systemic insulin resistance and type 2 diabetes mellitus.

In this thesis, the transcriptional mechanisms underlying development and progression of adipocyte dysfunction are addressed.

In the first part of this thesis, the transcriptional response to inflammation was mapped in human adipocytes by application of a wide range of genomics techniques. Here, we found that inflammatory stimuli primarily targets adipocyte genes central for defining cell-identity which are often controlled by the recently characterized class of enhancers known as super-enhancers. Moreover, our data indicate that inflammatory signaling represses adipocyte gene expression by indirect mechanisms, which we propose to involve competition for co-factors; a mechanism known as transcriptional squelching.

In the second part, we found that inflammatory signaling also affects transcription factor occupancy as we identify extensive redistribution of the adipocyte defining nuclear receptor Peroxisome proliferator activated receptor gamma (PPARγ) following inflammatory stimulation. Aside from the known anti-inflammatory activity of PPARγ, we identified a subset of inflammation-induced genes, which require PPARγ for full activation. This hints to a hitherto unknown cooperativity betweenPPARγ, and pro-inflammatory transcription factors.

In the third part of this thesis, we addressed the impact of dietary components (bioactives) on human adipocytes. These are known to harbor potent inflammation pro-resolving and anti-diabetic properties. We treated adipocyte cultures with the compounds and mapped both metabolic and transcriptional effects. We found that the bioactives have subtle, but significant anti-diabetic and anti-inflammatory effects on adipocytes by display of increased glucose uptake and decreased lipolysis accompanied by decreased secretion of pro-inflammatory cytokines. However, effects of these bioactives were found to be less dependent on transcriptional regulations.