



**Karolinska  
Institutet**

**Institutionen för Mikrobiologi, Tumör- och Cellbiologi (MTC)**

# Tissue- and site-specific effects of PPAR $\gamma$ activation and its role in chronic inflammation

AKADEMISK AVHANDLING

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## Abstract

Developmental programming, metabolism, immune function and tissue homeostasis in multicellular organisms are regulated by a plethora of stimuli. Transcription factors (TFs) convert incoming signals to appropriate transcriptional responses of the genome. Nuclear receptors (NRs), a particular family of TFs, are especially well suited for this task given their capacity to influence gene regulation in multiple tissues and conditions. In this work, I addressed how environmental cues affect the expression of NRs and how gene regulation is mediated in different tissues.

My thesis comprises a set of four separate manuscripts of which the first paper established how an important environmental factor, the gut microbiome, modulates NRs, including the peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), *in vivo*. The ligand-activated TF PPAR $\gamma$  is a key regulator of adipogenesis and glucose homeostasis, and possesses profound anti-inflammatory properties. In the subsequent manuscripts (paper II-IV), I have used PPAR $\gamma$  as a model to gain insights into the mechanisms that guide tissue-specific activity of NRs on a genome-wide level. To this end I have identified PPAR $\gamma$  binding sites in a genome-wide manner using chromatin immunoprecipitation combined with high-throughput sequencing (ChIP-seq) in adipocytes, macrophages and intestinal epithelium. These data were superimposed with information from gene-expression profiling to facilitate identification of direct PPAR $\gamma$  target genes.

Specifically, our comprehensive genomic analysis of PPAR $\gamma$  binding during adipogenesis confirmed the role of PPAR $\gamma$  as key regulator of this process and, potentially, revealed novel adipogenic target genes of PPAR $\gamma$  (paper II). In addition, an inter-species comparison of PPAR $\gamma$  binding sites in human and mouse macrophages identified a core set of conserved PPAR $\gamma$  targets. In this study we also identified PU.1 as a co-factor necessary for PPAR $\gamma$  function in macrophages (paper III). In the final manuscript, I mapped the genomic landscape of PPAR $\gamma$ -DNA interactions in intestinal epithelial cells (paper IV). These studies revealed that PPAR $\gamma$  antagonizes the WNT/TCF4 signaling pathways potentially identifying a mechanism by which activation of PPAR $\gamma$  affects cell fate of intestinal epithelial cells.

My PhD work yielded important novel insights into general mechanisms related to PPAR $\gamma$ -dependent gene regulation. While in the tissues studied, PPAR $\gamma$  activation seemed to always induce a core set of lipid metabolic genes, tissue-specific utilization of PPAR $\gamma$  binding sites appeared to be dependent on cell type restricted transcription factors which may determine binding site accessibility at the chromatin level.

My studies further suggest that the regulation of lipid metabolism is the evolutionary most conserved function of PPAR $\gamma$  and additional functions might have developed later, representing adaptations to changing metabolic needs and environmental challenges. While not studied in depth, our data on tissue-specific mechanisms of TF binding might also have implications for the interpretation of population-wide genetic studies.

In conclusion, my work has revealed common principles that guide PPAR $\gamma$  activation in a tissue-dependent and -independent manner and has laid the fundament for further detailed molecular studies of NRs in general and PPAR $\gamma$  in particular.

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