The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors involved in energy homeostasis. Their natural ligands are fatty acids and there are three different PPAR isoforms; PPARα, PPARγ and PPARδ. They are encoded by separate genes and have distinct functions, due to different tissue expression and affinity for ligands. PPARα controls genes involved in fatty acid oxidation, PPARγ regulates genes important for fatty acid storage, and PPARδ controls genes implicated in lipid oxidation and lipoprotein metabolism. Primates and humans treated with a PPARδ agonist (GW501516) resulted in improved insulin sensitivity, increased HDL and decreased LDL cholesterol levels, making it a putative drug candidate for treatment of metabolic disease. PPARδ has recently been assigned a beneficial role in macrophages, by inducing a switch from proinflammatory (M1) to antiinflammatory (M2) macrophages.

To characterize additional target genes of PPARδ involved in the lipoprotein metabolism, the effect of PPARδ activation on the apolipoprotein A-II (apoA-II) gene was investigated in human hepatoma cells. ApoA-II is one of the major proteins in the HDL particles. Treatment with GW501516 increased apoA-II promoter activity and mRNA levels in hepatoma cell lines. A site located at -737/-717 in the promoter was identified as the functional PPAR response element (PPRE). These results suggest that increased expression of the apoA-II gene is one of the reasons for the beneficial effects on lipoprotein metabolism after treatment with the PPARδ agonist.

To investigate whether PPARs could regulate the alanine aminotransferase (ALT) genes, the effect of PPARα, γ and δ agonist treatment was studied. ALT activity in plasma is used as a marker for hepatotoxicity in humans. During a clinical trial with the PPARα ligand, AZD4619, the plasma ALT activity increased in some patients and in vitro studies showed that ALT1 protein and mRNA expression was induced by treatment with PPARα agonists in primary hepatocytes. Similarly, transient transfection of a promoter construct of ALT1 in HuH-7 cells showed increased activity mediated via a PPRE located at -574 after treatment with PPAR agonists. This study shows that the ALT1 gene is regulated by PPARs and that PPAR drugs might contribute to increased ALT activity in serum.

To explore regulation of the PPARδ gene by posttranscriptional events, 5'- and 3'-RACE were performed on cDNA obtained from placenta, adipose tissue and pancreas. Both 5'- and 3'-alternative splicing of PPARδ was identified. Coupled transcription/translation showed that the length and number of upstream AUGs in the 5'-UTR had a major impact on translational efficiency. Further, the promoter located upstream of exon one was verified as the major promoter, using reporter gene assays. A 3'-splice variant encoding a truncated PPARδ protein, PPARδ2, was shown to be a negative regulator of the full length receptor, PPARδ1, in transient transfection assays.

To identify whether PPARδ is regulated by microRNA (miRNA), the 3'-UTR was analysed in silico. Two putative miRNA target sites were identified in the PPARδ 3'-UTR; miR-9 and miR-29. The miR-9 was verified as a functional miRNA targeting PPARδ. However, PPARδ mRNA levels remained unaffected by miR-9 expression, indicating that only the translation of PPARδ was inhibited. Since both miR-9 and PPARδ have been shown to play important roles in the inflammatory response of monocytes, the regulation of PPAR expression by miR-9 was investigated in these cells. A suppressive role of miR-9 on PPARδ expression was identified in monocytes after LPS treatment but not in M1 or M2 macrophages, suggesting that the regulatory role of miR-9 on PPARδ is exerted in monocytes, before differentiating into macrophages.

In summary, this thesis describes additional functions and ways of regulation of the ubiquitously expressed transcription factor PPARδ with a major role in both health and disease.