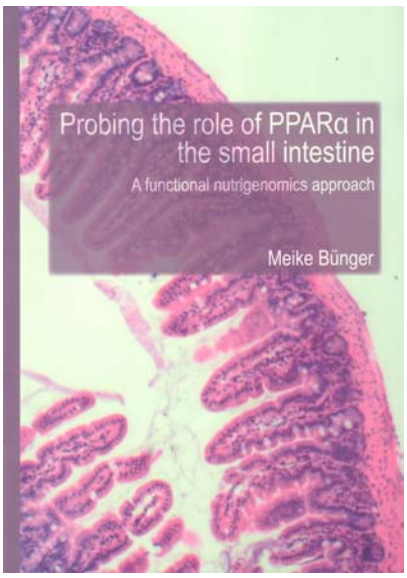

Samenvatting proefschrift
Meike Bünger

'Probing the role of PPARα in the small intestine, a functional nutrigenomics approach'

Promotiedatum: 12 september 2008
Wageningen Universiteit

Promotor:
Prof. dr. M. Müller

Co-promotor:
Dr. G.J.E.J. Hooiveld

Background: The peroxisome proliferator-activated receptor alpha (PPARα) is a ligand-activated transcription factor known for its control of metabolism in response to diet. Although functionally best characterized in liver, PPARα is also abundantly expressed in small intestine, the organ by which nutrients, including lipids, enter the body. Dietary fatty acids, formed during the digestion of triacylglycerols, are able to profoundly influence gene expression by activating PPARα. Since the average Western diet contains a high amount of PPARα ligands, knowledge on the regulatory and physiological role of PPARα in the small
intestine is of particular interest.

Aim: In this thesis the function of PPARα in the small intestine was studied using a combination of functional genomics experiments, advanced bioinformatics tools, and dietary intervention studies.

Results: Detailed analyses on the expression of PPARα in small intestine showed that PPARα is most prominently expressed in villus cells of the jejunum, coinciding with the main anatomical location where fatty acids are digested and absorbed. Genome-wide transcriptome analysis in combination with feeding studies using the synthetic agonist WY14643 and several nutritional PPARα agonists revealed that PPARα controls processes ranging from fatty acid oxidation and cholesterol-, glucose- and bile acid metabolism to apoptosis and cell cycle. In addition, we connected PPARα with the intestinal immune system. In a more focussed study we showed that PPARα controls the barrier function of the intestine. By comparing the intestinal and hepatic PPARα transcriptome we found that PPARα controls in these two organs the expression of two distinct, but overlapping sets of genes. Finally, by performing a range of functional studies deduced from the transcriptome analysis, we demonstrated that PPARα controls intestinal lipid absorption.

Conclusion: By maximally utilizing the unique possibilities offered in the post-genome era, the studies described in this thesis reported on the function of PPARα in small intestine. We conclude that intestinal PPARα plays an important role, is relevant for nutrition, and its effects are distinguishable from the hepatic PPARα response. Our results provide a better understanding of normal intestinal physiology, and may be of particular importance for the development of fortified foods, and prevention and therapies for treating obesity and inflammatory bowel diseases.