

## ABSTRACT

Peroxisomes are essential organelles for normal cell functions in all organisms from yeast to human. Their important contribution in different metabolic pathways is clearly visible by the severe phenotypes seen in the majority of peroxisomal diseases, where the symptoms often leads to an early death. Peroxisomes are involved in the synthesis of etherphospholipids and bile acids, in the metabolism of certain amino acids, purines and glyoxylate, and do also harbour an advanced system for degradation of various types of fatty acids and complex lipids. Peroxisomes are dynamic organelles that respond to different physiological and pharmacological changes by changing their number and contents of certain proteins.

We carried out a tissue expression and regulation study on the majority of all known peroxisomal proteins (here called the 'Pexiome') in mouse at mRNA level to investigate if and how the different pathways may differ in their expression through out the mouse body. We studied how the mRNA expression varies in liver, kidney and intestinal epithelial in response to 12 hrs fasting, and also the effect of peroxisome proliferator activating receptor  $\alpha$  (PPAR $\alpha$ ) agonist administration on gene expression in liver. The results show that indeed the mRNA expression of different genes varies markedly among tissues, while a number of genes seem to have a very wide tissue expression, which is in line with the content of peroxisomes in all cell types. Interestingly, fasting has a profound effect on the expression of the 'Pexiome' and also affects the peroxisomal gene expression in a strongly tissue specific manner. By examination of mouse livers from fasted and PPAR $\alpha$  agonist treated animals on PPAR $\alpha$ (+/+) and PPAR $\alpha$ (-/-) backgrounds, it was evident that the regulation of most of the peroxisomal genes by fasting is far more complex than just involving PPAR $\alpha$  activation.

We also carried out an in depth study on the mouse peroxisomal Nudix hydrolase 7 $\alpha$  (NUDT7 $\alpha$ ), which had previously been shown to act as a CoASH diphosphatase. Our data show that NUDT7 $\alpha$  preferably cleaves off 3',5'-ADP from the CoA-moiety of medium chain acyl-CoA's. The expression of the enzyme at mRNA level was down regulated during PPAR $\alpha$  activation in liver, and we also found that the total Nudix hydrolase activity was decreased in rat liver peroxisomes isolated from clofibrate treated mice. These findings suggest that NUDT7 $\alpha$  may be an important regulator of the peroxisomal CoASH pool, and likely also regulates the  $\beta$ -oxidation of fatty acids in the peroxisome at substrate level.

