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Transkriptionale Regulation der Adipozytenformation durch die Kernrezeptoren liver receptor homologue-1 und small heterodimer partner

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Obesity and its associated health effects are an increasing problem in the westernized world. Although the relationship between obesity, insulin resistance and cardiovascular diseases is well recognized, the underlying mechanisms remain relatively poorly understood. A deep knowledge of the processes involved in adipogenesis and the research of potential target genes are essential steps to help combat obesity. We show here that the nuclear factors Shp and Lrh1 are deregulated in murine, as well as in human obese subjects and show a link with the development of obesity.

The expression of Shp in adipose tissue is reduced in obese mice as well as in obese and especially obese, diabetic patients, while Lrh1 expression is induced in all three cases. Based on the findings that a loss of functional Shp is associated with the development of obesity and Shp, as well as Lrh1, are supposed to influence differentiation processes, we aimed to analyze the role of Lrh1 and its co-repressor Shp in the control of adipocyte formation. Both factors are exclusively expressed in the pre-adipocyte containing stromal vascular fraction (SVF) and expression of both factors is rapidly downregulated during adipocyte differentiation. This exclusive expression of Lrh1 and Shp in the SVF indicated that these factors might be important during the process of adipocyte differentiation. We could show in a 3T3-L1 differentiation assay that Shp was induced early in differentiation and sharply declined thereafter, while Lrh1 expression was rapidly reduced after induction of Shp expression. As such, an induction of Shp has also been linked to the entry of meiosis in germ cells. Thus, it might be possible that differentiation processes in other cell types are also regulated by short term Shp activation.

Viral modification of Shp and Lrh1 expression in 3T3-L1 cells and murine SVF revealed the stimulatory effect of Shp and the inhibitory effect of Lrh1 on adipocyte differentiation. In line with the finding that Shp suppresses Lrh1, while Lrh1 induces expression of Shp and

consistent with the observed Shp peak during adipocyte differentiation, our results point to an Lrh1 mediated repression of adipogenesis, which can be abolished through increased Shp levels. The effect of most pro-adipogenic factors seems to be mediated to a certain extent through activation of Pparγ expression or activity. Consistently, we could show that Shp partially exercised its stimulatory effect on adipogenesis through induction of Pparγ activation, as well as Pparγ expression.

Additionally, this study proposes that the transcription factors Shp and Lrh1 control adipogenesis at least in part by modulating estradiol conversion through regulation of Cyp19a1 gene expression. Consistent with the measured Lrh1 mRNA levels, Cyp19a1 was markedly upregulated in obese mice, as well as in obese and obese, diabetic patients. We could show that Cyp19a1 is also exclusively expressed in the pre-adipocyte containing SVF and simultaneously declines with Lrh1 during adipocyte differentiation. We suggest that Shp represses the Lrh1 mediated induction of Cyp19a1 expression and therefore releases the inhibition of adipocyte differentiation through aromatase.

In vivo, the direct injection of adenovirus, which transferred Cre recombinase into the epididymal fat depots of $Shp^{fl/fl}$ and $Lrh1^{fl/fl}$ mice, caused an ablation of the floxed Shp or Lrh1 gene, respectively. In line with cell culture experiments, loss of Lrh1 led to induced adipogenesis, while loss of Shp induced Lrh1 and reduced adipogenesis in vivo. Furthermore, insulin levels, as well as FFA, were significantly increased in $Shp^{fl/fl}$ mice, while both parameters were decreased in $Lrh1^{fl/fl}$ mice. Similar alterations in metabolic parameters could be found in obese and obese, diabetic patients, indicating that the deregulation of Lrh1 and Shp in murine and human subjects might cause the alterations in adipocyte differentiation and metabolic control. Taken together this thesis investigates the Lrh1/Shp network as a novel pathway in the transcriptional regulation of adipogenesis, which might contribute to a new therapeutic approach for obesity and type-2 diabetes.