Scientific summary

The regulation of metabolism has direct impact on the health of an organism and the proliferation and survival capacities of cells. Therefore, a deregulated metabolism results in the development of diseases at the organismal (e.g. diabetes) and cellular (e.g. cancer) level. Many proteins involved in the regulation of metabolism are tumour suppressors or oncogenes. It is shown that a heterogeneous deletion (e.g. *IGF1R*, *MYC*) or pharmacological inhibition (mTORC1 by rapamycin) of some proto-oncogenes leads to a lifespan extension and healthy metabolism in mammals.

In this thesis, we describe that C/EBPβ-LIP translation is controlled by mTORC1 signalling. Deficiency in C/EBPβ-LIP translation causes healthy metabolism in mice, which resembles the phenotype of other mouse models with reduced mTORC1 signalling or protein translation. Further, we show that C/EBPβ-LIP is able to reduce fatty acid oxidation and increase glucose metabolism and energy level in the cell. We identified the let-7 family of tumour suppressive microRNAs as novel C/EBPβ targets and the let-7 target and stem cell factor LIN28B as an important mediator of LIP induced metabolic reprogramming. Furthermore, LIP reprograms the cytoplasmic NADH utilisation by stimulating the malate-aspartate-shuttle and the usage of electrons from cytoplasmic NADH in OXPHOS and thereby possibly increases *de novo* biosynthesis from glucose. Moreover, we show that high LIP level impose a metabolic vulnerability on cells. Glucose starvation or inhibition of glycolysis causes low NADH level and thereby leads to apoptosis specifically in cells with high LIP level.

Our data suggests C/EBPβ-LIP as an important mediator of metabolic signalling since its expression is responsive to nutrient levels (though mTORC1) and it controls cellular metabolism (through let-7/LIN28B). Therefore, we suggest a nutrient level based negative feedback loop for LIP expression in the cell. Furthermore, we speculate that a loss of this feedback loop results in activation of apoptosis under nutrient limiting conditions, which should be exploited for future therapeutic strategies for cancer types that are characterized by high LIP levels.