6 Summary

Norrie disease (ND) is a rare X-linked recessive congenital blindness, sometimes associated with deafness and mental retardation. In this thesis the molecular pathogenic mechanisms of this syndrome should be elucidated using the *Ndph* knockout mouse model. Gene expression studies but also histology and protein biochemistry were used to characterize the affected organs, eye and brain. Gene expression analyses of eyes at p21 using cDNA subtraction in combination with microarrays and blot hybridization did not lead to the identification of differentially expressed genes. This might be due to low expression differences early on in the disease. However with quantitative Real Time RT-PCR we could show differential expression of many angiogenic factors during postnatal retinal development, suggesting an early effect of Norrin in the extracellular matrix on endothelial cells. Its lack leads to the block in the development of deep retinal capillary networks. Subsequently hypoxia develops after p10, which we could show to be an important pathogenic factor for Norrie disease. It is likely that it is also the molecular basis for similarities of the clinical Symptoms of the related diseases familial exudative vitreoretinopathie, coats disease and retinopathy of prematurity. Global gene expression studies in the brain of ND-mice identified a reduction of growth hormone expression. This reduction occurs specifically in the brain, but not in pituitary, where the endocrine active growth hormone (*Gh*) is produced. The brain-specific reduction of the *Gh* transcript might provide for the first time a possible explanation for the mental retardation in Norrie disease patients, although the molecular link remains to be elucidated. Also for the first time, the infertility of homozygous *Ndph* knockout female mice was found. The underlying cause was identified to be a disturbance in decidualization. Around E7 maternal bleedings into implantation sites have been discovered leading to loss of embryos by resorption. Additionally, the expression of *Ndph/NDP* in deciduae of mice and in human placenta also suggested an important function of this gene in female reproduction. In addition, recombinant Norrin was produced. The obtained polyclonal anti-sera detected the antigen but could not detect Norrin in tissue homogenates. The functional characterization of the recombinant Norrin in a cornea vascularization assay could not prove the role of Norrin in angiogenesis. Altogether the here obtained data suggested angiogenic defects as an important basis for pathogenesis in Norrie disease.