Molecular mechanisms of pathogenesis in Norrie disease and vitreoretinopathies.

Summary / Zusammenfassung
Norrie disease (ND) is a rare X-linked recessive form of congenital blindness, mental retardation and deafness. The ND gene, designated NDP for Norrie disease pseudoglioma, was isolated by positional cloning and numerous disease-associated mutations have been described. The precise function of the ND gene and its protein product Norrin is yet unknown but recent findings suggest a role in angiogenic processes in the eye, ear and brain. Genotype-phenotype comparisons revealed remarkably variable disease symptoms in different patients even within the same family. NDP mutations do not only lead to the classic Norrie phenotype, but were also found in patients with exudative vitreoretinopathy (EVR), retinopathy of prematurity (ROP), and Coats’ disease. Strikingly, the same amino acid exchange can lead to different traits, suggesting a contribution of additional genetic or environmental factors. In order to study gene function, we have generated a mouse model for ND by gene targeting in embryonic stem cells. The results of initial ophthalmologic and audiologic examinations of mutant mice revealed characteristic symptoms, similar to the phenotype of ND patients. In addition we observed female infertility in homozygous knockout mice. Our results suggest an important role for Norrin in early blood vessel development and the regression of fetal vasculature in the eye as well as angiogenic processes in the female reproductive system. We have shown that Norrin-deficient mice develop early postnatal retinal hypoxia. However, retinal neovascularization, the consequence of hypoxic conditions, does not occur although several pro-angiogenic factors are transcriptionally activated. We will further use this mouse model to study disease-associated processes on the molecular and cellular level and identify signaling pathways which involve Norrin. It was shown by others in cell culture experiments that Norrin is a ligand of the Wnt-receptor Frizzled-4 (FZD4) and its co-receptor LRP5 and able to drive transcriptional activation of a reporter gene. Interestingly, mutations in FZD4 and LRP5 lead to EVR in humans and Fzd4-deficient mice show similar vascular defects as Norrie mice. These findings support the hypothesis of Norrin as a ligand for Frizzled-4. We will analyze the gene expression pattern on transcript and protein level in the eye and brain of our knockout mouse line, a unique source to identify in vivo target genes of this signaling cascade. These targets may provide additional genetic risk factors or modifiers not only for ND, EVR and ROP, but also for other, much more frequent vasoproliferative ocular diseases including diabetic retinopathy, age-related macular degeneration and retinopathy of prematurity. In this respect, it is also important to understand the transcriptional regulation of NDP itself. This will be addressed by reporter gene assays in order to detect regulatory DNA elements which are responsible for the tissue- and cell type-specific transcription of this gene.

Publications / Publikationen


**Keywords / Suchbegriffe**
Norrie Disease Pseudoglioma, exudative vitreoretinopathy, retinopathy of prematurity, angiogenesis, retina, blood vessels

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