

Research Profile



Herbert Hildebrandt

- 1990 Diploma in Biology, Eberhardt-Karls-University Tübingen
- 1991 Research Fellow at the University of Nevada, Reno, USA
- 1994 Dr. rer. nat., Free University of Berlin
- 1994-2005 Research Assistant and Assistant Professor (C1, C2) at the University of Hohenheim, Stuttgart
- 2001 Habilitation, Venia legendi in Zoology
- Since 2006 Professor of Neuroglycobiochemistry (W2) at the Dept. of Cellular Chemistry, Hannover Medical School

Objects of Research

The research of my group is focused on the analysis of cell interactions via the neural cell adhesion molecule NCAM and particularly its functional modification by glycosylation with a sugar polymer called polysialic acid. In the nervous system, polysialic acid is widely expressed during development and reduced to regions of persistent plasticity in the adult brain. As a marker of adult neurogenesis and some forms of synaptic plasticity, polysialic acid expression gradually declines during ageing. Its putative role in neural repair mechanisms is emphasized by numerous reports describing alterations of polysialic acid expression together with changes of neural precursor proliferation, migration and differentiation in a wide range of neurological disorders. In addition, high expression levels of polysialic acid have been directly correlated to malignant progression of several neuroectodermal tumors.

1. Impact of polysialic acid and NCAM on nervous system-derived tumor cells

Previous work from my group established that polysialic acid promotes growth of tumor cells and helps to maintain them in an undifferentiated state. On the other hand, down-regulation

or experimental removal of polysialic acid allows NCAM to interact and, as a consequence, leads to reduced proliferation, enhanced survival and differentiation. Thus, masking interactions of NCAM provides a possible mechanism how the expression of polysialic acid promotes the genesis and malignant progression of polysialic acid-positive tumors. Together with our previous studies on the regulation of polysialic acid synthesis, these results clearly identify the contributing enzymes as potential therapeutic targets. In continuation of this work, we elaborate the NCAM-induced signaling pathways and focus on the engagement of NCAM in multimeric transmembrane complexes, the interactions of NCAM signaling with growth factor receptor functions and the possible modulation of such interactions by polysialic acid.

2. Nervous system defects in polysialic acid-deficient mouse models

Mice lacking the two key enzymes of polysialic acid synthesis are completely devoid of polysialic acid but express normal levels of NCAM. These mice show severe defects of brain wiring, high incidence of progressive hydrocephalus and impaired postnatal development with >80% of the animals dying within four weeks after birth. Remarkably, these drastic defects were selectively rescued by additional deletion of NCAM, demonstrating that they originate from a gain of NCAM functions due to polysialic acid-deficiency. Highly consistent with the model based on our findings in tumor cells these data demonstrate that polysialic acid is a key regulator of NCAM-mediated functions. Analyzing the genesis of these defects *in vivo* as well as *in vitro* using explant and primary culture systems will shed light on the underlying cellular mechanisms.

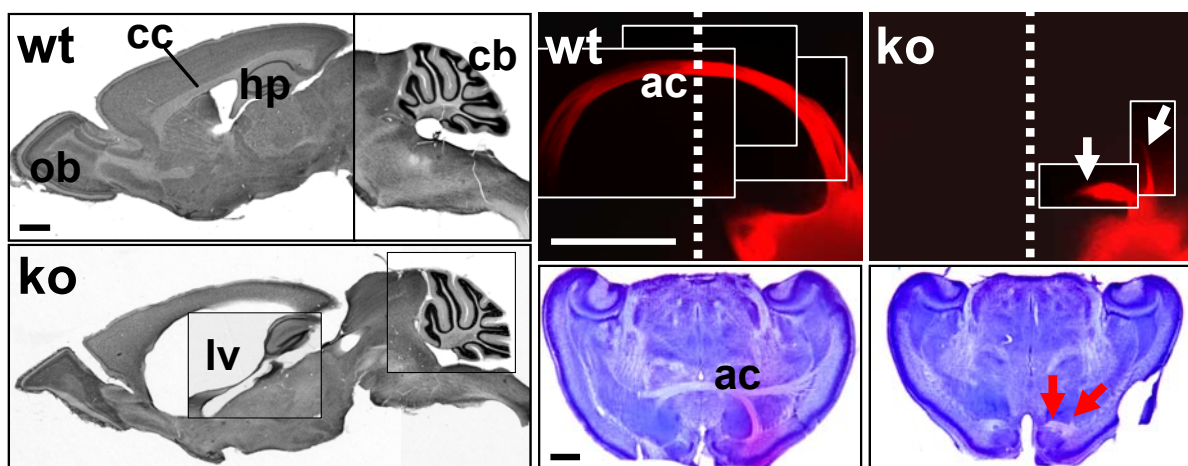


Fig. 1: Brain defects of polysialic acid-negative mice.

Left: Cresyl violet stained sagittal brain sections from a wildtype (wt) control and a polysialic acid-negative (ko) mouse suffering from hydrocephalus with expanded lateral ventricles (lv), thinning of the cortex and corpus callosum (cc), and distortion of the hippocampus (hp). Scale bar: 1mm.

Right: Anterior commissure (ac) in the wildtype (wt) and its agenesis in polysialic acid-negative (ko, arrows) mice, illustrated by tracing with the lipophilic dye Dil (upper) and cresyl violet staining of horizontal sections (lower panels). Scale bars: 500 μ m.

3. Polysialic acid as a regulatory element of postnatal neurogenesis

Based on our findings on tumor cell growth the aim of this project is to analyze, whether polysialic acid and NCAM are of similar importance for postnatal neuro- and gliogenesis using *in vivo* analyses of the polysialic acid-deficient mouse models combined with *in vitro* approaches. Isolation, *in vitro* expansion and differentiation of neural progenitors from the postnatal mouse forebrain has been successfully established and first results indicate a significant role of polysialic acid in their proliferation and differentiation. These studies aim at the use of polysialic acid-positive precursor cells in transplantation strategies of neural repair.

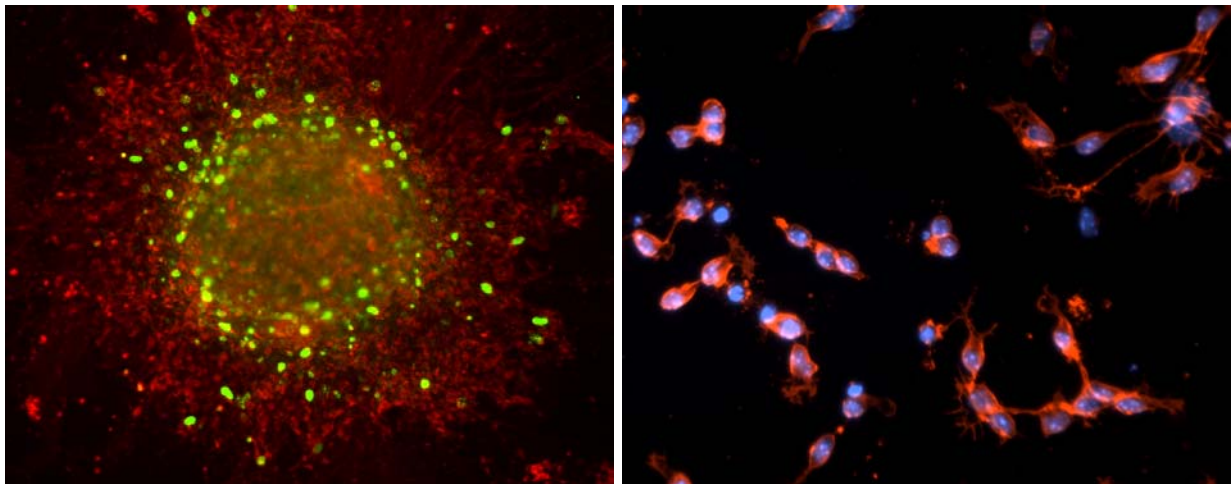


Fig. 2: Neural progenitors derived from the subventricular zone of postnatal day 2 mice grown *in vitro* as proliferating neurospheres (left) or as differentiating neuroblasts under adherent conditions (right). Red: polysialic acid. Green: proliferation marker BrdU. Blue: nuclei stained with DAPI.

Future aims

Our major goals are to understand the cellular and molecular mechanisms how polysialic acid influences nervous system and tumor development, its role in adult neurogenesis and its potential use in neural repair strategies. Future work will focus on analyses of peripheral nervous system development in polysialic acid-negative mice and on the differential contribution of the two polysialic acid-producing enzymes to their phenotype. We will further exploit the *in vitro* approach to ask for the molecular mechanisms and signaling cascades as well as changes in gene expression and cell cycle progression underlying polysialic acid- and NCAM-dependent steps in neuro- and gliogenesis. In addition, we would like to extend these approaches to embryonic and mesencephalic stem cell-derived neurogenesis.

Selected Publications:

1. Seidenfaden R. and Hildebrandt H. (2001) Retinoic acid-induced changes in NCAM polysialylation and polysialyltransferase mRNA expression of human neuroblastoma cells. **J. Neurobiol.** 46, 11-28.
2. Seidenfaden R., Krauter A., Schertzinger, F., Gerardy-Schahn R., Hildebrandt H. (2003) Polysialic acid directs tumor cell growth by controlling heterophilic NCAM interactions. **Mol. Cell. Biol.** 23: 5908-5918.
3. Valentiner U., Carlssona M., Erttmann R., Hildebrandt H., Schumacher U. (2005) Ligands for the peroxisome proliferator-activated receptor-gamma have inhibitory effects on growth of human neuroblastoma cells in vitro. **Toxicology** 213:157-168.
4. Weinhold B., Seidenfaden R., Röckle I., Mühlhoff M., Schertzinger F., Conzelmann S., Marth J.D., Gerardy-Schahn R., Hildebrandt H. (2005) Genetic ablation of polysialic acid causes severe neurodevelopmental defects rescued by deletion of the neural cell adhesion molecule. **J. Biol. Chem.** 280:42971-77.
5. Seidenfaden R., Krauter A., Hildebrandt H. (2006) The neural cell adhesion molecule NCAM regulates neuritogenesis by multiple mechanisms of interaction. **Neurochem. Int.** 49: 1-11.

Group Structure:

Group leader: Prof Dr. Herbert Hildebrandt

Graduate student: Dipl Biol. Iris Röckle

Technicians: Hannelore Burkhardt

Further graduate students are currently recruited.

Contact:

Prof. Dr. Herbert Hildebrandt

Department of Cellular Chemistry -OE 4330-

Hannover Medical School

Carl-Neuberg-Str. 1

30625 Hannover

Phone: +49 511 532 9808

Fax: +49 511 532 3956

e-mail: hildebrandt.herbert@mh-hannover.de