



R. Gerardy-Schahn

Rita Gerardy-Schahn

- 1989** Biochemist; Dr. rer. nat.; Johannes Gutenberg University of Mainz, Germany
- 1989 – 1990** Postdoc at the Medizinische Klinik in Mainz
- 1990** Independent research group started in November 1990, Department of Medical Microbiology, Medical School Hannover.
- 1997** *Venia legendi* Biochemistry and Molecular Biology
- Since 2000** Professor and Chair of Cellular Chemistry, Medical School Hannover

Current Research

Research in my team is focused by the interest in the cellular glycosylation pathways. Bound via lipids and proteins sugars form the glycocalyx, the outer rim, of the animal cell. According to theoretical considerations, about 10 % of the mammalian genome are used to generate the cellular *glycom*. Glycans are unprecedented in terms of structural diversity and thus in their potential to store information. Impressive prove for this has been obtained through the complex of "Congenital Disorders of Glycosylation" (CDG). CDGs are rare multisystemic disorders that all involve severe psycho-motor defects. In the context of this brochure our studies on the cellular sialylation machinery are of major importance.

1. The regulation of cell-cell contacts by the neural cell adhesion molecule NCAM and polysialic acid

The major reason for the negative charge of the animal cell surface is the negative charge provided by a 9-carbon sugar called sialic acid. Sialic acid occupies the terminal positions in many of the lipid and protein-linked sugar

trees of the glycocalyx. Moreover, sialic acids occur as di- and polymeric extensions of sugar trees on gangliosides and the neural cell adhesion molecule NCAM, respectively. Figure 1 schematically represents a alpha-2,8-linked sialic acid dimer (bottom) and a model of the secondary structure of a polysialic acid molecule. The extended helical structure is formed if the degree of polymerization rises >8.

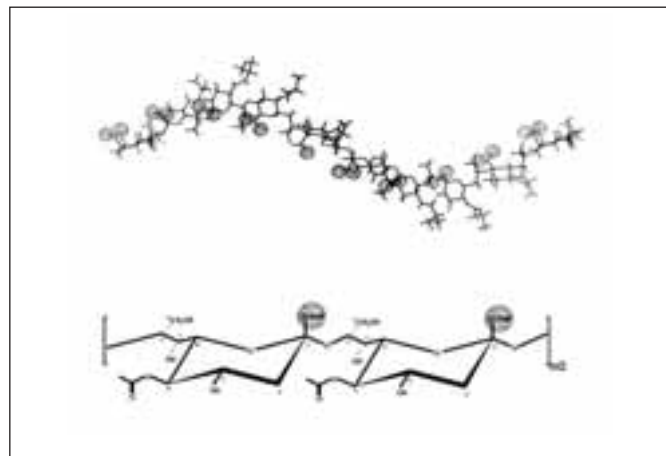


Figure 1

The dynamic process of neural development essentially depends on the coordinated performance of cellular adhesion events. NCAM, one of the best characterised molecules involved in these processes, acts as a molecule with a dual nature promoting and intervening with cellular adhesion events. Its ambiguity is due to the time- and situation-dependent expression of polysialic acid. As shown in Figure 2 the expression of polysialic acid interferes with the formation of tight cell-cell contacts and thus promotes cell motility (polysialic acid is a marker of neural stem cells).

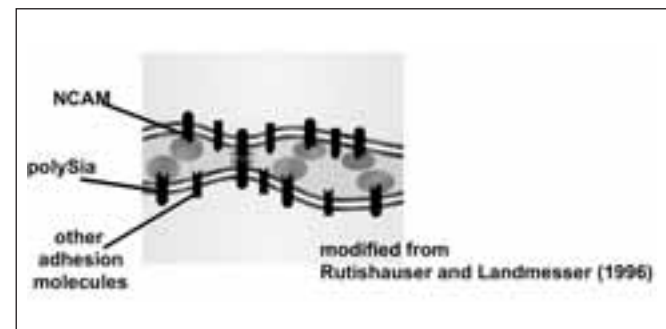


Figure 2

The addition of polysialic acid to NCAM is regulated by the activity of two enzymes the polysialyltransferases ST8SialII and ST8SialIV. These enzymes have been cloned and gene targeting strategies have been used to create animal models with altered polySia expression. ST8SialIV knock-out-mice have already been analysed and demonstrate severe deficits in learning and memory consolidation (see Figure 3). Mutants deficient in ST8SialII and animals lacking both polysialyltransferases are currently under investigation.

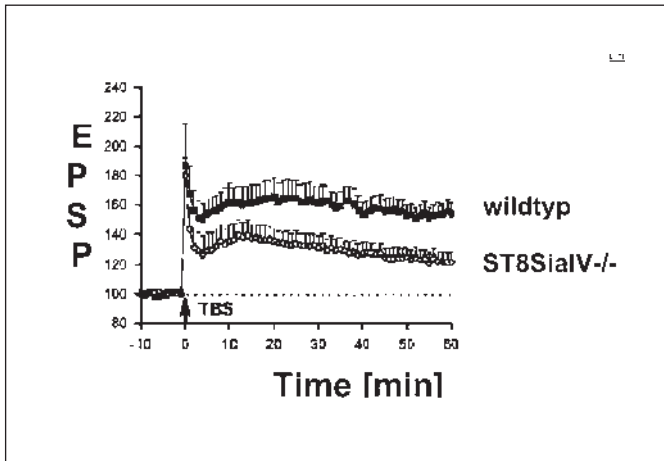


Figure 3

LTP in CA1 is altered in ST8SialIV^{-/-} animals. Theta-burst stimulation (TBS) of Schaffer collaterals evoked a high increase in the slopes of fEPSPs recorded in the CA1 region of slices from wild-type mice. In slices from ST8SialIV^{-/-} mice, the potentiation immediately followed by TBS appeared normal, but then the slope declined to a level significantly lower than in wild-type mice.

2. Polysialic acid and tumor biology

A second important topic concerns the role of polysialic acid and NCAM in tumor growth and malignancy. Malignant tumors of neuroectodermal origin express the polysialylated form of the NCAM at a high concentration. Polysialic acid is believed to facilitate the detachment of cells during the first steps of the metastatic cascade and to mask tumor specific antigens. Work in the laboratory is concentrated at defining the individual role of polysialyltransferases in tumor development. Moreover, we wish to develop new immunotherapeutic strategy for patients with neuronal tumors.

Future Projects and Goals

All the factors involved in the terminal cascade of polysialic acid synthesis have been cloned and animal models have been created with which the physiological role of sialic acids and polysialic acids can be studied in tissue- and developmental specific manners.

Selected Publications

- [1] Eckhardt, M., Bukalo, O., Chazal, G., Wand, L., Goridis, C., Schachner, M., Gerardy-Schahn, R., Cremer, H., Dityatev, A.: Mice Deficient in the Polysialyltransferases ST8SialIV/PST-1 Allow Discrimination of the Role of Neural Cell Adhesion Molecule Protein and Polysialic Acid in Neural Development and Synaptic Plasticity. *J. Neurosci.* 20:5234-5244 (2000).
- [2] Lühn, K., Wild, M.K., Eckhardt, M., Gerardy-Schahn, R., Vestweber, D.: The gene defective in leukocyte adhesion deficiency II codes for a GDP-fucose transporter. *Nat. Genet.* 28:69-72 (2001).
- [3] Mühlhoff, M., Manegold, A., Windfuhr, M. Gotza, B., Gerardy-Schahn, R.: The Impact of N-Glycosylation on the Functions of Polysialyltransferases. *J. Biol. Chem.* 276:34066-34073 (2001).
- [4] Mühlhoff, M., Stummeyer, K., Grove, M. Sauerborn, M. Gerardy-Schahn, R.: Proteolytic processing and oligomerisation of bacteriophage-derived endosialidases. *J Biol Chem.* 278:12634-12644 (2003).
- [5] Seidenfaden, R., Krauter, A., Schertzinger, F., Gerardy-Schahn, R., Hildebrandt, H.: Polysialic acid directs tumor cell growth by controlling heterophilic NCAM interactions. *Mol. Cell. Biol.* 23:5908-5918 (2003)

Group Structure

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