



C. Grothe

Claudia Grothe

- 1981** Diploma in Biology at the Free University of Berlin
- 1983** Ph.D. at the Free University of Berlin
- 1991** Habilitation at the Philipps-University of Marburg
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Current Research

Growth factors are involved in the development, degeneration, and regeneration of the nervous system. Current projects include the analysis of the role of growth factors, like basic fibroblast growth factor (FGF-2), during neuronal development and in neurodegenerative diseases. In addition, their possible use in the establishment of new therapeutic strategies is in the center of interest. Studies are carried out on neuronal and glial cell cultures and in *in vivo* animal models. Furthermore, biochemical and molecular interactions, particularly of FGF-2, are under current investigation to clarify the cascades of the effects of the growth factor.

Mouse mutants for the FGF system

To gain a better understanding of the physiological role of the endogenous FGF-2 and its receptors, the peripheral nervous system is extensively investigated in FGF-2- and FGF receptor 3-deleted mice and in the tgFGF-2 mouse model with and without specific lesions. First results show that FGFR3 signaling seems to be involved in processes of damage-induced neuron death and of axonal development. Furthermore, according to our regeneration studies in FGF-2-deleted mice, we suggest that endogenous FGF-2 is crucially involved in the early phase of peripheral nerve regeneration presumably by regulation of Schwann cell differentiation.

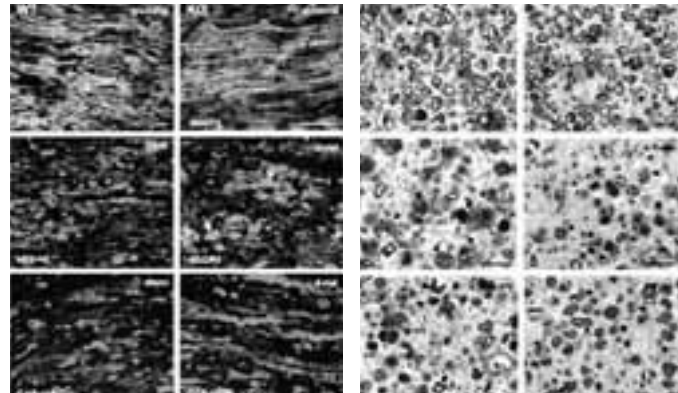


Fig. 1: Double labeling for NSE and GAP-43, respectively, with P0 in the proximal and distal part of the crushed sciatic nerve in FGF-2 wild-type and knock-out mice. Representative semithin cross-sections performed at the crush site, 0.5 mm and 1.0 mm distally of lesioned wild-type (WT: A, C, E) and knock-out (KO: B, D, F) mice.

The role of FGF-2 in the regenerating peripheral nervous system

Regeneration and cellular expression of FGF-2 and its high affinity receptors are assessed quantitatively and qualitatively in the nervous system following nerve injury. The velocity and extent of regeneration is morphometrically and functionally evaluated. Adult rat sciatic nerve transection is used as a lesion model. The nerve stumps are inserted into the opposite ends of silicone chambers filled with genetically modified Schwann cells which overexpress distinct FGF-2 isoforms. With regard to autologous cell transplants and a possible clinical use of these interponats, the establishment of highly enriched adult Schwann cells (rat and human), their genetical modification and their propagation is currently investigated.

The role of FGF in the dopaminergic nigrostriatal system

The effects of growth factors (FGF-2, FGF-20) on survival and differentiation of dopaminergic neurons or dopaminergic progenitor cells are analyzed in dissociation cultures and after transplantation into the rat model of Parkinson's disease induced by neurotoxin injection. Dopaminergic progenitor cells are genetically modified to over-express FGF-2 or FGF-20. In addition to the phenotypical and functional characterization in vitro, these cells are also evaluated with regard to the anatomical and functional integration after intrastriatal transplantation into the neurotoxin-lesioned rat brain.

Intracellular functions of FGF-2: FGF-2 and Spinal Muscular Atrophy

Spinal muscular atrophy is a neurodegenerative disease with a progressive loss of motoneurons caused by a deletion of the carboxyterminus of the survival of motoneuron protein (SMN). SMN is an assembly factor for the spliceosomal machinery. We have found that intracellular FGF-2 is able to interact directly with SMN opening an exciting pathway for direct modulation of splicing by a neurotrophic growth factor.

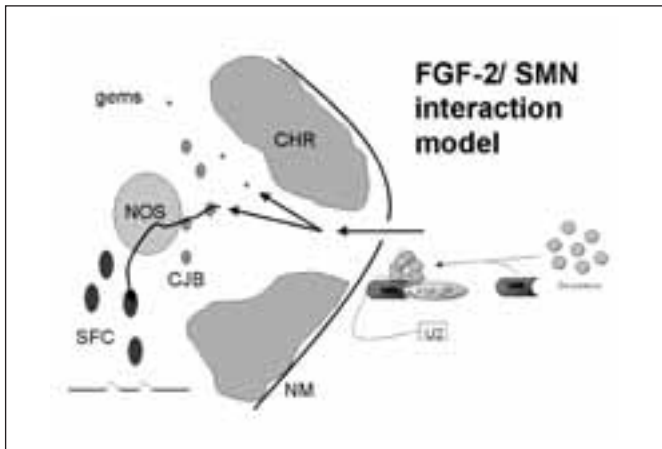


Fig. 2: FGF-2 directly interacts with SMN, an assembly factor for the spliceosomal machinery. After assembly the complex is imported into the nucleus where SMN is directed to highly mobile nuclear bodies (gems), whereas the ribonucleoprotein particle is processed in Cajal bodies (CJB), in the nucleolus (NOS) and eventually localize to the splicing compartments (SFC). NM, nuclear membrane; CHR, chromosome territories.

Selected Publications

- [1] Grothe C., Schulze A., Semkova I., Muller-Ostermeyer F., Rege A., Wewetzer K.: The high molecular weight fibroblast growth factor-2 isoforms (21,000 mol. wt and 23,000 mol. wt) mediate neurotrophic activity on rat embryonic mesencephalic dopaminergic neurons in vitro. **Neuroscience**. 2000; 100: 73-86.
- [2] Grothe C., Meisinger C., Claus P.: In vivo expression and localization of the fibroblast growth factor system in the intact and lesioned rat peripheral nerve and spinal ganglia. **J Comp Neurol**. 2001; 434: 342-57.
- [3] Claus P., Doring F., Gringel S., Muller-Ostermeyer F., Fuhlrott J., Kraft T., Grothe C.: Differential intranuclear localization of fibroblast growth factor-2 isoforms and specific interaction with the survival of motoneuron protein. **J Biol Chem**. 2003; 278: 479-85.
- [4] Timmer M., Robben S., Muller-Ostermeyer F., Nikkiah G., Grothe C.: Axonal regeneration across long gaps in silicone chambers filled with Schwann cells overexpressing high molecular weight FGF-2. **Cell Transplant**. 2003; 12: 265-77.
- [5] Jungnickel, J., Gransalke, K., Timmer, M., Grothe, C.: Fibroblast growth factor receptor 3 signaling regulates injury-related effects in the peripheral nervous system. **Mol. Cell. Neurosci.**, 2004; 25: 21-29.

Group Structure

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