

Nogo Inhibition to Enhance Regeneration and Functional Recovery in SCI

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Small injuries of the brain or spinal cord often have a good prognosis with extensive functional recovery. After injury of the central nervous system, damaged fiber tracts spontaneously react with a short-lasting repair response including a short period of axonal sprouting and up-regulation of growth-associated proteins in the nerve cell body. It is well documented for the cortex that intact brain areas can functionally compensate for areas which have been injured. Similar compensatory changes (e.g. due to fiber growth or sprouting) can also occur in the spinal cord, where they contribute to functional recovery following smaller tissue destructions. Extent and length of fiber growth is, however, very limited in the adult central nervous system. This is in contrast to peripheral nerves, where injured axons often regenerate back to their target where they make functionally meaningful connections. Our group has discovered the presence of specific nerve growth inhibitory factors in central nervous system myelin, among which the membrane protein Nogo-A. Nogo-A is a very potent nerve growth inhibitor of the adult central nervous system.

After large spinal cord injuries or stroke, sensory and motor functions are affected in many cases. The nature of both sensory and motor-controlled mechanisms such as sensation, locomotion or fine digit movements can often be studied best in animal models. Regenerative processes seen on the cellular or anatomical level must be meaningful in the context of the whole nervous system as shown by behavioral analyses for functional recovery. Importantly, animal models must be clinically relevant to be able to transform gained knowledge to a human setting. We have therefore generated reagents (anti-Nogo-A antibodies) which block Nogo-A function and have applied them to rats and macaque monkeys with spinal cord injuries as well as animals with strokes. Animals treated with such reagents showed molecular changes which strongly suggest that the growth machinery of the nerve cells is turned on, similar to the situation during development. On the anatomical level, different changes indicating long-distance regeneration of certain nerve fiber tracts as well as plastic events were induced. Behavioural experiments for locomotion as well as skilled fine finger movements showed marked improvements of functional recovery in the Nogo-A antibody treated injured animals. In collaboration with Novartis, an anti-human Nogo-A antibody was generated and extensively tested toxicologically. A Phase I clinical trial (coordinated by Novartis, Basel) is currently ongoing in a European Network of Spinal Cord Injury Centres (EM-SCI, coordinated by Volker Dietz, Zurich), using this anti Nogo-A antibody in acutely injured paraplegic patients. For Phase II elaborate functional readouts are being developed to gain detailed information on any sensory or motor improvements occurring.