Regulatable viral vectors for neuroregeneration

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Regeneration of the injured central nervous system (CNS) is hampered by a lack of neurotrophic support, the formation of scar tissue and the expression of neurite outgrowth inhibitory proteins in and around the lesion. Therefore, cell- and gene therapy-based strategies are studied that promote functional regeneration of the brain and spinal cord. Adeno-associated viral vectors (AAV) and third generation lentiviral vectors (LV) are used as therapeutic gene-delivery agents in combination with Schwann cells and olfactory ensheating glia cells to locally change the molecular and cellular properties of the injured CNS. Expression of neurotropic factors should be switched off in the lesion area after axon regeneration has started so that "trapping" of the axon sprouts in the in vivo engineered trophic environment can be prevented. Ideally, expression at sites in the direction of the denervated targets should then be switched on. For this purpose, we have constructed regulatable viral vectors based on the Tet-on system, that should allow to switch on expression and control its level over a therapeutic range with an orally taken inducer, the tetracyclin analogue doxycycline, and, to shut off expression when intake is stopped. This system was made in the context of AAV and LV viral vectors: the tTS^{kid} repressor and the therapeutic gene are under control of a bi-directional tet operon on one vector, whereas the rtTA activator is expressed constituitively from a second regulator vector. Sofar, in vitro studies with these vectors revealed effective induction of transgene (GFP) expression, while leak-expression was minimal. Currently, we are about to evaluate the system in vivo.

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