Towards gene therapy in amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a fatal paralytic neurodegenerative disease characterised by specific motoneuron death. Although the exact pathogenesis of ALS is still not clear, glutamate excitotoxicity seems to play an important role in motoneuron cell death. By overexpressing the glutamate transporter EAAT2, and thereby lowering the glutamate concentration in the surroundings of motoneurons, we aim to confer neuroprotection in the G93A-hSOD1 ALS mouse model. Gene therapy with the use of lentiviral vectors (LVV) seems to be a promising approach to deliver therapeutic proteins to the central nervous system, notably the spinal cord. LVVs encoding EAAT2 or green fluorescent protein (GFP) were constructed to examine the pattern of transduction and the neuroprotective efficacy of LVV-EAAT2. In a first experiment organotypic spinal cord cultures were transduced and the cellular protein expression of the transgenes was investigated. Immunohistochemical analysis showed that LVV-GFP preferentially transduced the astrocytes compared to neurons. Likewise, when G93A-hSOD1 mice were injected with LVV-GFP at the level of vertebra L1, with the use of a spinal adaptor, immunohistochemical analysis showed again that mainly astrocytes were transduced. Next, using the paw grip endurance test, the beam balance test, and body weight as clinical parameters, the neuroprotective efficacy of LVV-EAAT2 was evaluated in G93A-hSOD1 mice. No difference was found in survival and onset between the LVV-EAAT2 treated mice, LVV-GFP treated mice, and naive mice, respectively. The outcome of this study and its clinical implications will be discussed.

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