Lentiviral vectors in neurodegenerative disorders

Aspects in gene therapy and disease models

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ABSTRACT

The PhD dissertation was conducted at Section of Neurogenetics, Panum Institute, Faculty of Health Sciences, University of Copenhagen during 2005-2008.

Neurodegenerative disorders remain a complex group of diseases (i.e. Huntington's disease, HD) that are characterized by progressive loss of neurons resulting in movement disorders, cognitive decline, dementia and death. There is no cure for these diseases and treatment relies on symptomatic relief, which is most often only satisfactory in the initial phase of the disease. Gene therapy is a novel treatment strategy intended to treat or alleviate disease by genetically modifying cells by introducing nucleic acids into the cells. Lentiviral vectors hold great promise as gene transfer vectors and are able to transduce post-mitotic cells i.e. terminally differentiated neurons, making them ideal candidates for gene transfer to the brain and as experimental tools.

In this study vectors expressing miRNA embedded shRNA from pol II-promoters were constructed for RNA interference (RNAi) in vitro and in vivo. Robust gene knock-down was shown using a ubiquitous promoter (CMV) and for the first time neuron specific RNAi was obtained using a neuron specific promoter (NSE). Furthermore, optimization of lentiviral vectors was conducted using an insulator element (cHS4) in order to enhance transgene expression and escape transgene silencing during differentiation of neural stem cell lines. However, insulator vectors appeared to be impaired in functionality, which has importance for the future use of insulators in viral vectors. Finally, cell based models of HD was constructed to elucidate the association between HD and diabetes as well as for screening of peptide compounds for possible efficacy against HD.