From knowledge base of the pathogenic astrocyte-motoneuron communication in amyotrophic lateral sclerosis to therapeutic approaches

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Country

Switzerland

Title of project or programme

From knowledge base of the pathogenic astrocyte-motoneuron communication in amyotrophic lateral sclerosis to therapeutic approaches

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SNSF

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01/02/2015

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3

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Research Abstract
Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by the progressive loss of motoneurons in the spinal cord, brainstem and motor cortex. Although the majority of ALS cases (>90%) are considered to be sporadic, the identification of genetic factors associated with

familial forms has largely contributed to our understanding of pathogenesis. In particular, animal and cellular models have been generated based on missense mutations in the SOD1 gene linked to autosomal dominant inheritance of the disease. Exploring the etiology of ALS in SOD1 models has revealed a complex array of cellular dysfunctions collectively leading to muscle denervation and motoneuron death as a function of intrinsic cellular vulnerability. These models have also highlighted the important contribution of non cell-autonomous mechanisms. In particular, astrocytes have been implicated in ALS progression. However, the molecular mechanisms underlying the pathogenic interaction between astrocytes and motoneurons have remained elusive.
Our objective is to further decipher the pathologic interaction between astrocytes and motoneurons in the perspective of developing therapies for ALS. Towards this goal, this project brings together three expert teams in motoneuron diseases, in order to provide complementary technologies applicable to animal and cellular models of ALS, such as gene transfer to the brain and spinal cord and genome-wide analysis of gene expression. The research project is articulated in three main workpackages, with the following specific aims:
1. Identify the non cell-autonomous signals derived from of astrocytes that affect motoneuron susceptibility to disease and motoneuron regenerative programs in SOD1 ALS.
2. Elucidate how diseased motoneurons affect neighboring astrocytes in SOD1 ALS.
3. Determine the effects of the identified target genes and pathways on the ALS pathology and design novel therapeutic approaches to achieve neuroprotection and improve neuromuscular function in ALS.
To achieve these objectives, we will take advantage of gene delivery to either motoneurons or astrocytes in mouse spinal cord using adeno-associated viral (AAV) vectors, to locally and selectively silence the expression of mutated human SOD1 in a given cell type. The non-cell-autonomous effects of suppressing mutated SOD1 in astrocytes will be determined by measuring the gene expression changes in the neighboring motoneurons. Conversely, we will assess how SOD1 silencing in motoneurons affects gene expression in astrocytes.
This experimental framework will provide the base for the rationale identification and validation of key pathways involved in the pathologic interaction between astrocytes and motoneurons in the SOD1 pathology. Comprehensive gene expression data sets related to the motoneuron-astrocyte axis will be made accessible to the ALS scientific community. We will further explore the therapeutic potential of the main target genes and determine if the identified targets are also relevant to other forms of ALS.

Further information available at:

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Switzerland

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