

TDP-43 MITOCHONDRIAL LOCALIZATION INHIBITOR FOR THE TREATMENT OF NEURODEGENERATIVE DISEASE

RELATED APPLICATION

[0001] This application claims Priority from U.S. Provisional Application No. 62/328,484, filed April 27, 2016 and 62/319,580 filed April 7, 2016, the subject matter of which are incorporated herein by reference in their entirety.

GOVERNMENT FUNDING

[0002] This invention was made with Government Support under Grant No. 1R01NS089604 awarded by the national institutes of health. The United States Government has certain rights in the invention.

BACKGROUND

[0003] Amyotrophic lateral sclerosis (ALS) is the most common motor disease characterized by progressive motor neuron degeneration in the brain stem and spinal cord, while frontotemporal dementia (FTD) is the second most common form of early-onset dementia caused by neuron loss in the frontal and temporal cortex. The vast majority of ALS or FTD cases, referred to as sporadic ALS or FTD, are not genetically transmitted and their causes remain unknown. Currently, there is no effective treatment for both ALS and FTD.

[0004] TDP-43 is a small ubiquitously expressed RNA/DNA binding protein containing two tandem RNA recognition motifs RRM1 and RRM23. Previous studies have revealed that TDP-43 primarily binds mRNA, and regulates post-transcriptional RNA processing including RNA splicing, transportation and translation. Autosomal dominant mutations in TDP-43 are associated with sporadic and familial ALS, and the redistribution of TDP-43 from the nucleus to cytoplasm has been recognized as a pathological hallmark for most forms of ALS and most frequent subtypes of FTD. In fact, the mis-localization of TDP-43 to the cytoplasm also represents a key pathological feature of other major neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and Huntington's disease.

SUMMARY

[0005] Examples described herein generally relate to compositions and methods of inhibiting TAR DNA Binding Protein 43 (TDP-43) mitochondrial localization in a neural cell and particularly relates to compositions and methods for treating neurodegenerative diseases or disorders in a subject in need thereof. The methods can include administering to a neural

cell or the subject in need thereof a therapeutically effective amount of an agent that inhibits TDP-43 mitochondrial localization.

[0005a] In one aspect, the present disclosure refers to use of a TDP-43 mitochondrial localization inhibitor in the manufacture of a medicament for treating a neurodegenerative disease in a subject, wherein the medicament includes a synthetic therapeutic peptide of 5 to 10 amino acids and a transport moiety that is linked to the synthetic therapeutic peptide and facilitates uptake of the synthetic therapeutic peptide by a cell, the synthetic therapeutic peptide inhibiting TDP-43 mediated disassembly of mitochondrial respiratory complex and including an amino acid sequence selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.

[0006] In some examples, the neurodegenerative disease or disorder can include neurodegenerative diseases or disorders characterized and/or associated with aberrant TDP-43 mitochondrial localization, TDP-43 neuronal toxicity, and/or mutations of TDP-43. The neurodegenerative disease can include, for example, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, dementias related to Alzheimer's disease, Parkinson's, senile dementia, Huntington's disease, Gilles de la Tourette's syndrome, multiple sclerosis, or hereditary motor and sensory neuropathy.

[0007] Other examples relate to methods of treating motor-coordinative and cognitive dysfunction associated with mutant TDP-43 expression. The methods can include administering to a neural cell or the subject in need thereof a therapeutically effective amount of an agent that inhibits TDP-43 mitochondrial localization.

[0008] In some examples, the agent or TDP-43 mitochondrial localization inhibitor includes a therapeutic peptide of about 5 to about 10 amino acids having an amino acid sequence that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% identical to about 5 to about 8 consecutive amino acids of a mitochondrial internal targeting signal of TDP-43. For example, the therapeutic peptide can include an amino acid sequence that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% identical to about 5 to about 7 consecutive amino acids of M1 (SEQ ID NO: 1), M3 (SEQ ID NO: 3), or M5 (SEQ ID NO: 5) or TDP-43. In some examples, the therapeutic peptide can include, consist essentially of, or consist of a peptide having an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 7.

[0009] In other examples, the agent includes a transport moiety that is linked to the therapeutic peptide and facilitates uptake of the therapeutic peptides by the cell. For example, the transport moiety can be an HIV Tat transport moiety.

[0010] In still other examples, the cell is in a subject being treated, and the therapeutic agent is administered locally or systemically to the subject being treated.

[0011] In yet other examples, the therapeutic peptide is expressed in the neural cell.

Having described the invention, the following is claimed:

1. Use of a TDP-43 mitochondrial localization inhibitor in the manufacture of a medicament for treating a neurodegenerative disease in a subject, wherein the medicament includes a synthetic therapeutic peptide of 5 to 10 amino acids and a transport moiety that is linked to the synthetic therapeutic peptide and facilitates uptake of the synthetic therapeutic peptide by a cell, the synthetic therapeutic peptide inhibiting TDP-43 mediated disassembly of mitochondrial respiratory complex and including an amino acid sequence selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.
2. The use of claim 1, the synthetic therapeutic peptide including an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 7.
3. The use of claim 1, the synthetic therapeutic peptide including an amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 8.
4. The use of claim 1, the transport moiety comprising a TAT peptide.
5. The use of claim 1, the TDP-43 mitochondrial localization inhibitor having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 13, 15, and 16.
6. The use of claim 1, wherein the neurodegenerative disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia, Alzheimer's disease, Parkinson's disease, and Huntington's disease.
7. The use of claim 1, wherein the neurodegenerative disease is frontotemporal dementia.
8. The use of claim 1, wherein the neurodegenerative disease is amyotrophic lateral sclerosis.

9. The use of claim 1, the TDP-43 mitochondrial localization inhibitor is to be administered to the subject via continuous subcutaneous infusion.