SciMedCentral

Journal of Neurology & Translational Neuroscience

Editorial

Astroglia and Protein Aggregation Diseases

Parminder J S Vig*

Department of Neurology, Biochemistry and Neurobiology & Anatomical Sciences, University of Mississippi Medical Center, USA

Corresponding author

Vig PJS, Neuroscience Division, Department of Neurology, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA, E-mail: pvig@umc.edu

Submitted: 09 August 2013

Accepted: 16 August 2013

Published: 19 August 2013

Many neurodegenerative disorders like Alzheimer's, Parkinson's, prion and polyglutamine diseases are caused by gain-of-function mechanisms in which the disease-causing protein accumulates in the form of insoluble protein aggregates or inclusion bodies [1,2]. Whether these aggregated proteins directly cause neurodegeneration is still controversial; however, it is widely believed that soluble form of the proteins and/or micro-aggregates are more toxic than the larger inclusions. Spinocerebellar ataxia 1 (SCA1) is one such protein aggregation disease, characterized by loss of motor coordination due to the degeneration of cerebellar Purkinje cells (PCs) and brain stem neurons [3]. In SCA1, the expanded mutant ataxin-1 protein aggregates into nuclear inclusions (NIs) [4]. However, before the appearance of NIs, SCA1 PCs exhibit cytoplasmic vacuoles rich in astroglial derived S100B protein, which is exclusively expressed in Bergmann glia (BG) of the cerebellum [5]. These S100B containing cytoplasmic vacuoles appear as early as 16 days postnatally in PCs of the asymptomatic SCA1 transgenic (Tg) mice. No S100B vacuoles were seen in wildtype animals and A02 Tg line with normal CAG repeats [5].

Astrocytes play a crucial role in the regulation of synaptic formation and function by ensheathing axon–dendrite connections [6]. BG of the cerebellum form rosettes around PCs in the cerebellar cortex, encasing their dendrites and synapses to maintain and regulate their structure and function [7,8]. However, abnormalities in BG cause degeneration of PC dendrites and impair motor coordination [9]. Furthermore, BG involvement in SCA1 pathogenesis is also supported by a recent report on SCA1 knockin (Ki) mice, which suggests that the functional deficiency of BG may contribute to PC pathology in SCA1 [10]. In the mouse model of polyglutamine disease SCA7, the mutant ataxin-7 expression restricted to BG, not the target PCs caused striking PC loss [11] suggesting a non-autonomous role of mutant proteins prone to form aggregates.

Further, in our SCA1 studies, immunohistochemical and specialized silver stain analysis revealed that vacuolar formation is associated with alterations in the morphology of dendritic spines of PCs [5]. In addition, we found that PC pathology is preceded by an increase in the cerebellar S100B mRNA levels in asymptomatic SCA1 mice [5]. Furthermore, our cell culture experiments indicated that S100B may directly influence toxicity or solubility of the ataxin-1 protein [5,12]. Our recent data demonstrated that S100B may be associated with oxidative damage pathway in SCA1 [13]. To determine if the pathology observed in the mouse model of SCA1 also occurs in the human disease, we immunostained human cerebellar tissue sections for S100B. Interestingly enough, surviving PCs of SCA1 patients showed S100B containing cytoplasmic vacuoles [5,14].

Gene expression profiling of 2 wk old wildtype and SCA1 heterozygous mice cerebella using Affymetrix microarrays showed a dysregulation of genes involved in BG-PC cell interactions, especially cell-cell adhesion and signaling [unpublished data; 15]. We believe that two-way communication between PCs and BG is essential for normal functioning of the cerebellum during development and throughout adult life. These bidirectional interactions are prerequisite for the survival of either cell-type in the cerebellum.

Currently, there are no specific or effective treatments to delay or halt the progression of SCA1. Thus, the identification of promising therapeutics and methods to target potential pathogenic pathways is vitally important to developing treatments for SCA1 and other cerebellar ataxias. Motivated by the limitations of current therapeutics, our long-term goal is to develop a therapeutic approach that can overcome the challenges of blood brain barrier (BBB) delivery and can target and inhibit specific pathogenic pathways. We are presently using SCA1Tg and Ki mouse models to evaluate the efficacy and safety of therapeutic interventions prior to clinical trials. To combat the neuronal damaging effects of S100B in SCA1, we have designed a therapeutic polypeptide, which consists of a thermally responsive polypeptide, a TRTK12 S100B inhibitory peptide and a cell penetrating peptide, SynB1, to enhance intracellular delivery. The peptide TRTK12 has been shown to have a high binding affinity for S100B with the capability to block S100B interaction with S100B target proteins [14,16,17]. Previously, we have shown that the TRTK12 peptide is therapeutic to SCA1 mice, where animals given TRTK12 displayed a significant improvement in ataxic behavior [12]. We believe that the genetically engineered polypeptide based technology has a great potential to thermally target therapeutics to the cerebellum and possibly other areas of the brain to treat multiple CNS disorders, especially the cerebellar ataxias.

ACKNOWLEDGEMENTS

Some of the referenced work in this article was supported by grants from the National Institutes of Health and the National Ataxia Foundation, USA.

REFERENCES

1. Taylor JP, Hardy J, Fischbeck KH. Toxic proteins in neurodegenerative disease. Science. 2002; 296: 1991-1995.
2. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med. 2004; 10 Suppl: S10-17.
3. Zoghbi HY, Orr HT. Pathogenic mechanisms of a polyglutamine-mediated neurodegenerative disease, spinocerebellar ataxia type 1. J Biol Chem. 2009; 284: 7425-7429.
4. Lagalwar S, Orr HT. Regulation of ataxin-1 phosphorylation and its impact on biology. Methods Mol Biol. 2013; 1010: 201-209.
5. Vig PJ, Shao Q, Subramony SH, Lopez ME, Safaya E. Bergmann glial S100B activates myo-inositol monophosphatase 1 and Co-localizes to purkinje cell vacuoles in SCA1 transgenic mice. Cerebellum. 2009; 8: 231-244.
6. Eroglu C, Barres BA. Regulation of synaptic connectivity by glia. Nature. 2010; 468: 223-231.
7. Lordkipanidze T, Dunaevsky A. Purkinje cell dendrites grow in alignment with Bergmann glia. Glia. 2005; 51: 229-234.
8. Bellamy TC. Interactions between Purkinje neurones and Bergmann glia. Cerebellum. 2006; 5: 116-126.
9. Aamodt S. Focus on glia and disease. Nat Neurosci. 2007; 10: 1349.
10. Shiwaku H, Yoshimura N, Tamura T, Sone M, Ogishima S, Watase K, et al. Suppression of the novel ER protein Maxer by mutant ataxin-1 in Bergman glia contributes to non-cell-autonomous toxicity. EMBO J. 2010; 29: 2446-2460.
11. Custer SK, Garden GA, Gill N, Rueb U, Libby RT, Schultz C, et al. Bergmann glia expression of polyglutamine-expanded ataxin-7 produces neurodegeneration by impairing glutamate transport. Nat Neurosci. 2006; 9: 1302-1311.
12. Vig PJ, Hearst S, Shao Q, Lopez ME, Murphy HA 2nd, Safaya E. Glial S100B protein modulates mutant ataxin-1 aggregation and toxicity: TRTK12 peptide, a potential candidate for SCA1 therapy. Cerebellum. 2011; 10: 254-266.
13. Hearst SM, Walker LR, Shao Q, Lopez M, Raucher D, Vig PJ. The design and delivery of a thermally responsive peptide to inhibit S100B-mediated neurodegeneration. Neuroscience. 2011; 197: 369-380.
14. Hearst SM, Lopez ME, Shao Q, Liu Y, Vig PJ. Dopamine D2 receptor signaling modulates mutant ataxin-1 S776 phosphorylation and aggregation. J Neurochem. 2010; 114: 706-716.
15. Vig PJ, Wei J, Shao Q, Lopez ME, Halperin R, Gerber J. Suppression of calbindin-D28k expression exacerbates SCA1 phenotype in a disease mouse model. Cerebellum. 2012; 11: 718-732.
16. McClintock KA, Shaw GS. A logical sequence search for S100B target proteins. Protein Sci. 2000; 9: 2043-2046.
17. Charpentier TH, Thompson LE, Liriano MA, Varney KM, Wilder PT, Pozharski E, et al. The effects of CapZ peptide (TRTK-12) binding to S100B-Ca2+ as examined by NMR and X-ray crystallography. J Mol Biol. 2010; 396: 1227-1243.

Cite this article

Vig PJS (2013) Astroglia and Protein Aggregation Diseases. J Neurol Transl Neurosci 1: 1013.