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Glial response to polyglutamine-mediated stress

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Abstract

Neurodegenerative trinucleotide (CAG) repeat disorders are caused by the expansion of polyglutamine tracts within the disease proteins. Some of these proteins have an unknown function. How does expanded polyglutamine cause target neurons to degenerate, is not clear. Recent evidence suggests that intercellular miscommunication may contribute to polyglutamine pathogenesis in CAG repeat disorders. Polyglutamine induced degeneration of the target neuron can be mediated via glia-neuron interactions. Here we hypothesize during neurodegenerative process the failure of cell: cell interactions have more severe consequences than alterations in intracellular neuron biology. We further believe that bidirectional communication between neurons and glia are prerequisite for the normal development and function of either cell-type. Understanding intercellular signaling mechanisms such as glial trophic factors and their receptors, cell adhesion or other well-defined signaling molecules provide opportunities for developing potential therapies.

INTRODUCTION

The polyglutamine diseases are a group of nine dominantly inherited neurodegenerative disorders caused by the expansion of an unstable translated CAG repeat located in different disease genes. These include Huntington's disease (HD), spinobulbar muscular atrophy (SBMA), dentatorubropallidoluysian atrophy (DRPLA), and six autosomal dominant spinocerebellar ataxias (SCAs) [1]. As would be expected for dominant mutations, polyglutamine expansions confer toxic properties on the host proteins [1–4]. Some of these, however, are novel proteins.

SCA1 is associated with progressive ataxia resulting from the loss of cerebellar Purkinje cells and neurons in the brainstem [1,5,6], SCA1 transgenic mice (line B05) express mutant ataxin-1 with 82 glutamines [7]. Overexpression of mutant ataxin-1 in Purkinje cells of these mice results in a progressive ataxia and Purkinje cell pathology that are very similar to those seen in SCA1 patients [7–9]. The toxic gain-of-function mechanisms by which the ataxin-1 induces neuronal Purkinje cell death are not fully understood. Alterations in transcriptional regulation, calcium homeostasis, glutamate signaling, and impaired protein degradation are few reported events in the pathogenesis in SCA1 [8,10,11]. The major challenge now is to determine how these responses account for the clinical manifestation of the disease symptoms and, ultimately, how this knowledge can be translated into the development of therapeutic strategies.

Throughout the development of the cerebellar cortex, Purkinje cells interact closely with Bergmann glia, a specialized form of astrocyte [12]. Lordkipanidze and Dunaevsky [13]

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analyzed the pattern of growth of Purkinje cell dendrites and reported that vertical growth of Purkinje cell dendrites occurs primarily in alignment with Bergmann glia processes and Bergmann glia processes provide structural substrates in the form of cell adhesion molecules for the directional growth of Purkinje cell dendrites, thus influencing the shape of the dendritic tree. We believe that Bergmann glia influence Purkinje cell differentiation and pathology in SCA1.

HYPOTHESIS

Neurodegenerative diseases are generally believed to be the result of dysfunction within the degenerating neuron. However, recent evidence suggests that intercellular miscommunication may also contribute to disease pathogenesis. For example, in neurodegenerative trinucleotide (CAG) repeat disorders polyglutamine induced degeneration of the target neuron can be mediated via glia-neuron interactions [14,15]. Therefore, we hypothesize that during neurodegenerative process the failure of cell: cell interactions have more severe consequences than alterations in intracellular neuron biology.

Aside expanded polyglutamine proteins, non-cell-autonomous interactions of mutant neurodegenerative disease proteins have been reported for other diseases [15,16]. In inherited ALS caused by the ubiquitous expression of cytoplasmic SOD1, conditional gene deletion in mice has demonstrated that mutant SOD1 produces disease by initiating damage within the target motor neurons. Whereas, mutant damage within microglia, dramatically accelerates disease progression [15]. Similarly, in a mouse model of multiple system atrophy, overexpression of alpha-synuclein in oligodendrocytes of mice results in degeneration of neurons in the CNS [16]. Furthermore, in the inherited form of Alzheimer disease, the wide and ubiquitous expression of mutant gene products cause generalized synaptic pathology, which could certainly involve cell-cell interactions [17]. Thus, abnormal cell interactions may represent common degenerative pathways in many aspects of pathogenesis.

In the mouse model of polyglutamine disease SCA7, the mutant ataxin-7 expression restricted to Bergmann glia, not the target Purkinje cells, caused striking Purkinje cell pathology [18]. These data are supported by our recent findings in SCA1 transgenic mice [19]. Unlike, 'dark' cell degeneration seen in SCA7 mice, SCA1 Purkinje cells show glial derived cytoplasmic vacuoles in Purkinje cells [19]. Further, the immunohistochemical analysis revealed that S100B though expressed exclusively in Bergmann glia was localized to these vacuoles. We observed S100B containing cytoplasmic vacuoles as early as 16 days postnatally in Purkinje cells of heterozygous SCA1 mice. This is the earliest morphologic abnormality seen in SCA1 mice to date [19]. Gene dosage had no effect on the time line of vacuolar development. These vacuoles were negative for Purkinje cell markers protein kinase C- γ , β -III tubulin and calbindin D28k. No S100B vacuoles were seen in wildtype animals and A02 transgenic line with normal CAG repeats [19]. Further, immunohistochemical and specialized silver stain analysis revealed that vacuolar formation is associated with alterations in the morphology of dendritic spines of Purkinje cells (unpublished observation). Furthermore, to determine if the pathology observed in the mouse model of SCA1 reflects that occurring in the human disease we immunostained human cerebellar tissue sections for S100B. Interestingly enough, surviving Purkinje cells of SCA1 patients showed S100B containing cytoplasmic vacuoles (unpublished data). In addition, gene expression profiling of 2 wk old wildtype and SCA1 heterozygous mice cerebella using Affymetrix microarrays showed a dysregulation of genes involved in Bergmann glia –Purkinje cell interactions (unpublished data). We believe that two-way communication between Purkinje cells and Bergmann glia 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. Further, decreased cell-cell adhesion and signaling leads to vacuole formation in SCA1 (Fig. 1).

Although expression of mutant ataxin-1 is believed to cause cell autonomous degeneration in Purkinje cells in SCA1 mice [7], the involvement of Bergmann glia in our study may open up new therapeutic avenues, as signaling molecules and receptors involved in intercellular communication may be more sensitive to therapeutic intervention than intracellular changes, such as protein misfolding and aggregation [20].

CONCLUSION

For the explanation for a wide range of neurodegenerative conditions, the status of neighboring glial cell of a target neuron cannot be ignored. Aiming therapeutic strategies at the mechanisms of cell: cell interactions could be more beneficial to patients suffering from neurodegenerative disorders.

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Mechanism of Purkinje cell-Bergmann glial crosstalk

Fig. 1.

A: Schematic diagram showing hypothetical mechanism of normal and impaired Purkinje cell (PCs) -Bergmann glia (BG) crosstalk. In SCA1 (**B**), impaired PC-BG interaction results in cytoplasmic vacuole formation in PCs (Steps 1–5). Mutant ataxin-1 (transcriptional repressor) early in development causes alterations in the expression of signaling and cell adhesion molecules like FGF7, neurocan and contactin 2. The neighboring BG respond by similar modulations, which produces a stress signal and glia react by releasing high levels of S100B protein. At higher concentrations, S100B either disrupts IFs or causes vimentin to aggregate, and to form vacuoles in PCs. This model was developed based on the preliminary results and

gene expression data of 2 wks old wildtype and SCA1 mice. **FGF7**: Fibroblast growth factor 7; **IF**: Intermediate filaments.