＜特別講演 1＞

Past, present, and future of polyglutamine expansion disease

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The polyglutamine diseases are a set of nine neurodegenerative diseases caused by unstable CAG repeat expansions in widely expressed genes. Each disease has unique features due to the characteristics of the mutant protein and the population of neurons that degenerates, but there are common features of adult onset, gradual progression, and correlation of repeat length with age of onset and disease severity. Each disease has been reproduced by overexpression of the mutant protein in animal models. Intracellular inclusions of mutant protein are a common pathological feature in cell culture and animal models as well as in patients, and the expanded polyglutamine causes the proteins to aggregate in a repeat-length dependent manner. While there are indications of loss of normal function in some of the mutant proteins, the principal effect of the mutations is a toxic gain of function, which may cause transcriptional dysregulation, mitochondrial dysfunction, altered axonal transport, and other effects that lead to neuronal dysfunction and death. Various approaches to therapy have shown promise in animal models, including suppression of disease gene expression by RNA interference, targeted disruption of proteolytic processing or post-translational modification of the disease protein, enhancing the degradation of the mutant protein, and mitigating the downstream effects. Spinal and bulbar muscular atrophy, the first polyglutamine disease to be discovered, is unique in that the toxicity of the mutant protein (the androgen receptor) is ligand dependent. Androgen reduction therapy is effective in animal models. Demonstrating this effect in patients has been difficult because of the slow disease progression and perhaps also because the treatment needs to be started early in the disease course. The challenge now is to translate therapeutic interventions like this that show promise in preclinical studies into safe and effective treatment for patients in well designed clinical trials.

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