December 23, 2008

MOLECULAR MECHANISMS OF NEURODEGENERATION IN POLYGLUTAMINE DISEASE

Maria Pennuto, PhD
Senior Research Investigator
Department of Neurology
University of Pennsylvania
Philadelphia, PA

ABSTRACT OF THE TALK

Polyglutamine diseases are a family of nine neurodegenerative diseases caused by expansion of a tract encoding glutamine in diverse genes. Polyglutamine proteins share common features. Nonetheless, expansion of polyglutamine causes degeneration of specific regions in the brain. This suggests that the polyglutamine domain is not the only responsible for pathogenesis, and that regions outside the polyglutamine tract contribute to toxicity. One example in which the protein context is critical for disease pathogenesis in spinobulbar muscular atrophy (SBMA), which is caused by expansion of polyglutamine in the androgen receptor (AR) gene. SBMA is characterized by loss of motor neurons in the spinal cord and brainstem and skeletal muscle atrophy. A unique feature of SBMA is that the disease is gender-specific, as only males are fully symptomatic. The reason of this is that the disease is initiated by the androgen-dependent conversion of AR into a toxic molecule. The mechanisms underlying this process remain to be elucidated. I will discuss new insights into the molecular mechanisms of disease pathogenesis. In particular, I will show that ligand-induced post-translational modifications of mutant AR can impact its toxicity and that this information can lead us to identify novel therapeutic avenues for patient treatment.