

Seminar Announcement

Trinucleotide Repeat Disorders



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Over 30 neurological diseases are known to be caused by repeat expansion mutations, including expansions in coding regions of genes and larger expansions in non-coding DNA. This talk covers the clinical and genetic features of 4 representative repeat expansion diseases, what is known about the disease mechanisms, and the prospects for treatment.

Kennedy's disease (spinal and bulbar muscular atrophy) was the first repeat expansion to be identified, in 1991. It is an X-linked neuromuscular disorder with progressive muscle weakness and caused by an expanded CAG repeat encoding a polyglutamine tract in the androgen receptor. Huntington's disease is caused by a very similar mutation in the huntingtin gene, and 6 different spinocerebellar ataxias are also caused by similar CAG-polyglutamine expansions. The same kind of mutation in different genes causes different patterns of neurodegeneration and different clinical manifestations. In each disease the repeat length correlates inversely with age of onset and the expanded repeat is unstable. Cell culture and animal studies have shown that the mutant proteins with polyglutamine expansion are toxic and prone to aggregation. The toxicity likely involves transcriptional dysregulation. Therapeutic possibilities include targets that block the toxicity or enhance protective mechanisms, but the best prospects may be in reducing the levels of the mutant proteins, e.g., with antisense oligonucleotides that are now in clinical trials. Animal studies have shown that the damage can be reversed.

Friedreich's ataxia is an autosomal recessive disease caused by repeat expansion in the first intron of the frataxin gene. The expanded repeat in this case causes decreased gene expression and deficiency rather than toxicity of the frataxin protein. Frataxin is a nuclear-encoded mitochondrial protein involved in the synthesis of iron-sulfur complex-containing proteins. Deficiency of frataxin causes mitochondrial dysfunction. Therapeutic efforts are aimed at increasing frataxin expression, replacing the defective gene, and mitigating the effects on mitochondrial function.

Myotonic dystrophy is an autosomal dominant disease caused by repeat expansion in the 3'-untranslated region of the DMPK gene. The clinical features often increase from generation to generation with increasing repeat length, a phenomenon known as anticipation. The disease mechanism involves toxicity of the mutant mRNA with sequestration and depletion of RNA-binding proteins, particularly the splice factor muscleblind. A clinical trial of oligonucleotide treatment to reduce levels of the mutant transcript is now in progress.

A therapeutic intervention to reduce the size of expanded repeats would be applicable to all of these and other repeat expansion diseases.

Friday, October 28th, 2016

11:00 a.m. to 12:00 p.m.

Venue: Room GL-100

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