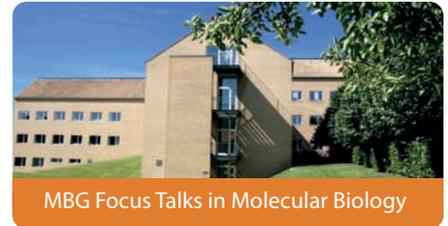


MBG FOCUS TALK

hosted by Erik Østergaard Jensen



Thursday October 27, 2016 at 9:15 - 10:00

Science Park, conference room (3130-303)

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Protein Dosage and Neurological Disorders

The family of neurodegenerative disorders known as proteinopathies - whose most famous members are Alzheimer's disease, Parkinson's disease and Huntington's disease - involve problems with protein folding and clearance. In most cases there is a mutation that alters the conformation of the disease-causing protein in a way that alters its function and causes it to accumulate over time in neurons. Recent work, however, has shown us that even wild-type proteins can wreak havoc when they are expressed at too-high levels. For example, duplication of the amyloid precursor protein (APP) locus causes autosomal dominant early-onset Alzheimer's disease, and duplications or triplications of alpha-synuclein (SNCA) are associated with familial Parkinson's disease. In animal models, extremely high (30x - 40x) levels of wild-type ataxin-1 (Atxn1) cause disease reminiscent of spinocerebellar ataxia type 1 (SCA1). This raises the reasonable question: could less extreme elevations of protein levels also cause disease? In particular, could aberrant RNA processing and post-transcriptional regulation of specific proteins alter their steady-state levels sufficiently to cause neurodegeneration? The coordinated activities of microRNA (miRNA) and RNA-binding proteins (RBPs) regulate mRNA turnover, localization and translation, and orchestrate hundreds of circuits that are responsible for proper cognitive function. Yet little is known about the role of miRNA and RBPs in brain development or disease. Pursuing this line of thought, I investigated the regulation of two proteins involved in neurological disease: ATXN1 (whose mutant form causes the adult-onset neurodegenerative disease SCA1) and MeCP2 (whose mutant form causes the postnatal neurodevelopmental disorder Rett syndrome). In this seminar I will describe my findings and their ramifications for neurological disease.