Unraveling the Interaction of Poly(CUG)RNA with MBNL1 Protein

Sreenivasa Rao Ramisetty, Yuan Fu, Jonathan F. Arambula, Steven C. Zimmerman, and Anne M. Baranger

Trinucleotide repeat expansions are the genetic cause of numerous human diseases, including Huntington's disease, Fragile X mental retardation, and myotonic dystrophy type 1. Myotonic dystrophy (DM1) is an autosomal dominant neuromuscular disorder associated with a (CTG)n expansion in the 3'- untranslated region of the DM1 protein kinase (DMPK) gene. The disease is characterized by a waning of the muscles (muscular dystrophy), eye-lens opacity and myotonia. In DM1 the toxic poly(CUG)RNA binds to and sequesters key proteins, such as MBNL1 (muscleblind-like protein 1), preventing them from regulating proper splicing of different pre-mRNAs. The severity of DM1 correlates with the length of the CTG repeat tract in peripheral blood. Individuals with minimal expansions of 50-100 repeats generally have mild, late-onset symptoms, whereas those with 1000 or more repeats usually have severe disease in infancy. Expansions of 1000-4000 repeats affect skeletal muscle, heart, ocular lens and brain tissues.

We are investigating the interaction of the MBNL1 protein with poly(CUG)RNA. We are also investigating the RNA binding specificity of the MBNL1 protein and the binding site requirements, stoichiometry, and cooperativity of complex formation between the MBNL1 protein and poly(CUG)RNA. The inhibition of $(CUG)_4$ and $(CUG)_{12}$ RNA-MBNL1 complexes by a small molecule has been shown by gel-shift assays. The experiments for binding and inhibition studies of complexes formed between MBNL1 and higher repeats of poly(CUG)RNA are under progress.