Pathogenetic mechanisms and therapeutic approaches for myotonic dystrophy

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Myotonic dystrophy type 1 (DM1) is a dominantly inherited, multisystemic disorder caused by expanded CTG repeats in the 3’ untranslated region (3’UTR) of the DMPK gene. DM1 is the most common adult-onset muscular dystrophy characterized by progressive skeletal muscle weakness, myotonia, cardiac arrhythmia, smooth muscle dysfunction, and neurological abnormalities. The repeat regions do not result in protein mutation because they are located in the 3’UTR, but lead to transcript accumulation into nuclear foci that affect the localization and activities of RNA-binding proteins involved in splicing regulation. Therapeutic strategies aimed at neutralizing the toxic RNA provide only short-term effects unless repeated administration of the inhibitory molecules are applied. No effective long-lasting therapy is yet available for DM1.

Our research focuses on the study of the pathogenetic mechanisms of DM1 disease and the development of new therapeutic strategies, through two different but related projects:

1. Circular RNAs (circRNAs) are emerging as key new members of the gene regulatory milieu, which are produced by back-splicing events within gene transcripts. Many circRNAs have been found to be important regulators of cellular physiology and pathology by a variety of mechanisms, and perturbations of circRNA expression have been recently reported in association with disease, including DM1(1). Analysis of publicly available gene-expression datasets indicate a pervasive dysregulation of circRNA levels and we identified a subset of circRNAs that are significantly increased in muscle biopsies of DM1 patients (2). With the aim of understanding the role of circRNAs in DM1 pathogenetic mechanisms, we are further expanding the search for circRNAs dysregulated in muscle biopsies of DM1 patients and plan to functionally validate them in DM1 in vitro and in vivo models.

2. Being DM1 a monogenic disease, gene therapy approaches aimed at eliminating the pathogenetic mutation are feasible. We have previously obtained permanent elimination of the toxic mutant repeats by using the CRISPR/Cas9 methodology in DM1 patient-derived fibroblasts (3), and recently developed inducible and tissue specific CRISPR/Cas9 complex components that ensure a time-limited and cell specific gene editing. Now, we are applying the same strategy in a well characterized DM1 mouse model carrying a mutated human DMPK transgene. These mice exhibit a pathologic neuromuscular phenotype similar to that observed in human DM1 disease and we expect that genome editing in diseased animals will lead to reversal of the pathologic phenotype. Given that this treatment should potentially result in a durable therapeutic response in postmitotic adult tissue, this technology could open the way for future gene therapy application in humans, alone or in combination with other therapies.


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