Molecular Mechanisms in the Pathology of Myotonic Dystrophy

--- Internship possibilities at the Department of Cell Biology, RIMLS, Radboudumc ---

SCIENTIFIC BACKGROUND

Myotonic dystrophy type 1 (*dystrophia myotonica*; DM1) is an autosomal dominant, multisystemic disorder, which can affect all age groups and involves many different organs, including skeletal muscle, heart and brain. At the basis of the disease is a (CTG)n trinucleotide repeat expansion mutation located in the 3' untranslated region of the DMPK gene and the promoter area of the SIX5 gene (Fig. 1). Above a threshold of ~37 triplets the repeat becomes unstable between generations and during ageing in somatic cells. Hence, length of the (CTG)n repeat is highly variable. (CTG)n repeat length does correlate with severity and age of onset of the disease in patients.

How does a non-coding (CTG)n repeat cause the highly variable constellation of symptoms of DM1? Most of the current experimental evidence supports a toxic RNA gain-of-function model for DMPK RNA carrying a long expanded (CUG)n repeat. The (CUG)n segment aberrantly binds RNA-binding proteins like MBNL and CUGBP1, which in turn leads to dysregulation of splicing and transcription in cells where the DMPK gene is expressed (Fig. 1). In addition, we postulate that the (CUG)n RNA-protein aggregates also have wider implications on the cell's well being and may be considered a continuous source of cell stress.

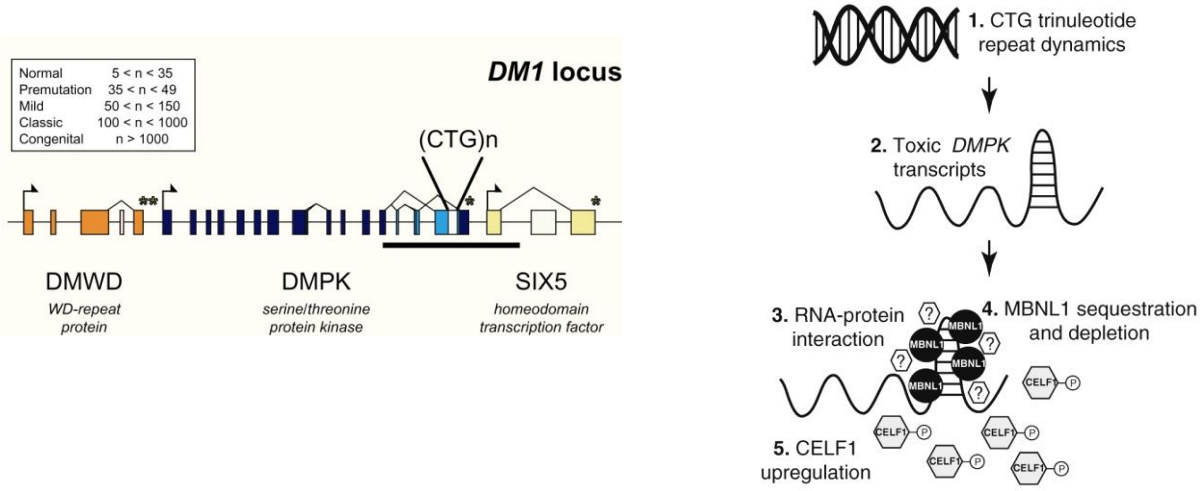

Figure 1. LEFT: A schematic representation of the DM1 locus and the relationship between repeat length and disease severity. RIGHT: Schematic representation of downsstream effects of an expanded (CTG)n repeat.

CURRENT TOPICS

Our group has been studying the molecular pathogenesis of DM1 for more than 20 years now. Topics and approaches have changed throughout the years. Publications can be found at www.ncbi.nlm.nih.gov/pubmed?term=wansink%20wieringa).

The following research projects currently run in the DM group (2015/2016):

(i) (CUG)n RNA protein aggregation, proteostasis and cell stress
(ii) Peptide-mediated uptake of therapeutic antisense oligonucleotides for DM1 (with Dept. of Biochemistry)
(iii) DMPK RNA structure probing and RNP assembly
(iv) CRISPR/Cas9-mediated cell models to study fundamental aspects in DM

In our research we use various techniques ranging from molecular and biochemical techniques to state-of the-art microscopy. Starting date depends on the availability of the intern, the supervisor and work space in the lab. In general, an interview is part of the selection process. The intern will be given a personal project to carry out, fitting within the general research theme of the group. The precise topic of a project will depend on ongoing research at the start of the internship and will be composed in close collaboration with the applicant, according to his/her research interests.

INTERESTED? DO NOT HESITATE TO CONTACT FOR MORE INFORMATION OR AN INFORMAL MEETING:

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