Dissecting Molecular Mechanisms in DM2: Muscle defects and Misbehaving Molecules

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Type 2 Myotonic Dystrophy (DM2) is a genetic multi-systemic disease that primarily affects skeletal muscle. It is caused by the expansion of the quadruplet sequence CCTG in intron 1 of the CNBP gene. The molecular mechanisms underlying DM2 are not fully understood, particularly the relative roles of CNBP downregulation and CCTG expansion, which remain a matter of debate. Here, we elucidate the relative contributions of CNBP reduction and protein repeat toxicity to DM2 pathogenesis using *Drosophila* as an animal model. We demonstrate that CNBP deficiency causes locomotor defects linked to a significant decrease in polyamine content, and that polyamine metabolism is also altered in human DM2 muscle tissues. Moreover, we found that the expression of DM2 toxic tetrapeptide induces stress granule formation and autophagy defects.
These results reveal critical aspects of DM2 pathogenic mechanisms, which form the basis for developing novel therapeutic strategies.