

3. Dystrophy

Neuropathophysiology of Duchenne muscular dystrophy: involvement of the dystrophin isoform Dp71 in cell migration and proliferation.

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Background:

Individuals with Duchenne muscular dystrophy (DMD) often have lower intelligence than that of the general population. Furthermore, the prevalence of cognitive impairment, epilepsy, autism and attention deficit hyperactivity disorder (ADHD) are higher in DMD patients. Evidence suggests a role for the most predominant dystrophin isoform, Dp71, which is expressed in neuronal cells and glia.

Aims:

Due to limited knowledge of the brain of Duchenne patients and an unclear understanding of the function of Dp71, we sought to investigate how distal mutations in the *DMD* gene, which lead to an absence of Dp71 expression, are associated with the range of cognitive and behavioural phenotypes in these patients. We have modelled the loss of Dp71 by using DMD patient-derived fibroblasts (which naturally express the Dp71 isoform). We have also employed siRNA-mediated knockdown of Dp71 in a panel of neuronal and glial cell lines. We examined whether the loss of Dp71 was associated with defects in cell migration and proliferation given that alterations in these processes are associated with the cognitive and behavioural co-morbidities observed in DMD patients.

Methods:

Four patient-derived fibroblast cell lines, containing unique mutations of the *DMD* gene (resulting in the loss of Dp71) were examined using wound healing and proliferation assays as well as by RT-PCR and immunoblotting. The associated clinical data confirmed that patients exhibit cognitive and/or behavioural symptoms, which were severe for two individuals.

Results:

We demonstrate that DMD patient fibroblasts lacking Dp71 had reduced metabolic activity than control cells and migrated more rapidly. The increased level of cell migration is accompanied by an increase in focal adhesion kinase (FAK, a regulator of cell migration) expression.

Conclusion:

Our data highlights a role for Dp71 in cell migration and proliferation; alterations in these cellular processes are known to be associated with behavioural disorders prevalent in DMD patients such as autism. These findings have potential to inform the development of effective brain-targeting treatments.