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A role for dystrophin Dp71 in cell migration: implications for Duchenne muscular dystrophy and cancer

Duchenne muscular dystrophy (DMD)

Although DMD is primarily a muscle disease, the loss of dystrophin in the brain is associated with a 'DMD neuropsychiatric syndrome[1].'

We are investigating the neuronal RNA processing of the *DMD* gene and the function(s) of the most predominant dystrophin variant in the brain, Dp71.

Our ultimate aim is to inform the development of brain-targeting treatments for DMD.

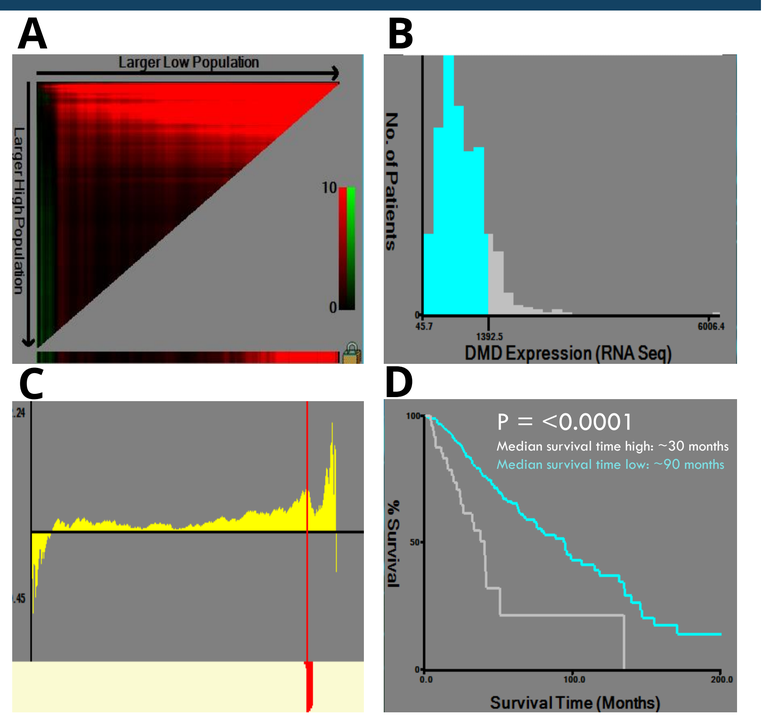
We identified a role for Dp71 in cell migration[2] and are investigating how this may contribute to the neuropathogenesis of DMD.

Cancer

Dystrophin has been identified as a tumour suppressor[3] and its expression may be an independent prognostic marker in several cancers.

Cancer	Hazard ratio	Meaning
Brain lower grade glioma	3.39	High expression associated with poor survival
Lung adenocarcinoma	0.51	High expression associated with longer survival
Breast invasive carcinoma	0.61	High expression associated with longer survival
Kidney renal papillary cell carcinoma	4.1	High expression associated with poor survival
Head and neck squamous cell carcinoma	0.69	High expression associated with longer survival
Pancreatic adenocarcinoma	0.34	High expression associated with longer survival
Mesothelioma	3.1	High expression associated with poor survival

High *DMD* expression is associated with poor survival in low grade glioma



X-tile analysis of low grade glioma survival based on high and low *DMD* expression. A: potential cut-points. Red colouration indicates an inverse correlation with survival and green direct associations. The optimal cut-point occurs at the brightest pixel. B: a histogram of the cohort divided into low (blue) and high (grey) subgroups according to the optimal cut-off value. C: relative risk plot, the red line is the optimal cut-point. D: provisional survival curve (high *DMD* expression in grey).

Methods

DMD patient-derived fibroblast cell lines harbouring distal *DMD* mutations affecting the expression of Dp71 were obtained from the MRC Centre for Neuromuscular Diseases Biobank, London. Cell migration was measured using scratch assays and proliferation measured based on metabolic activity using WST-1 reagent (Roche). Cancer genomics data sets were obtained from cBioPortal and based on data from the TCGA Research Network. X-tile was used for cut-point determination and preliminary statistical analysis.

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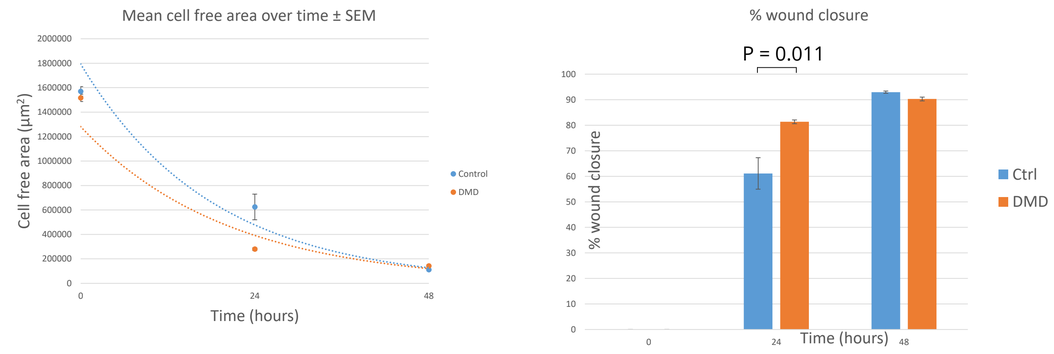
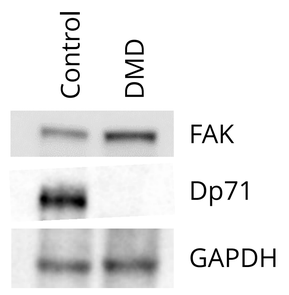
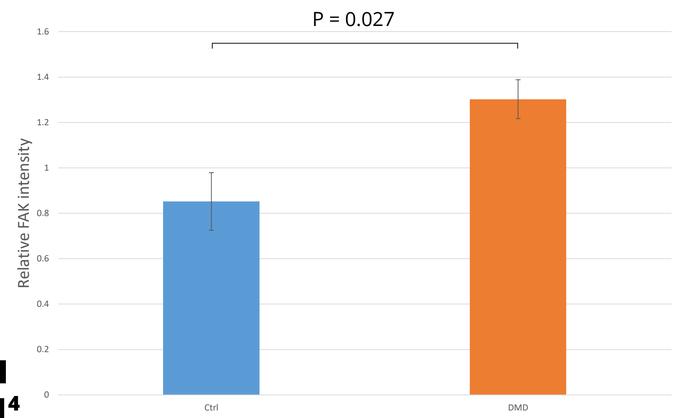
2. Ash et al (2018). Neuropathophysiology of Duchenne muscular dystrophy: involvement of the dystrophin isoform Dp71 in cell migration and proliferation. *Neuromuscular Disorders*, 28, S13–S14
3. Wang et al (2014). Dystrophin is a tumor suppressor in human cancers with myogenic programs. *Nature Genetics*, 46(6), 601–606
4. Tan et al (2017). Altered Biological Properties in Dp71 Over-Expressing HBE Cells. *Cellular Physiology and Biochemistry*, 43(5), 2022–2036.

DMD patient-derived fibroblast cell lines lacking Dp71 migrate faster than controls

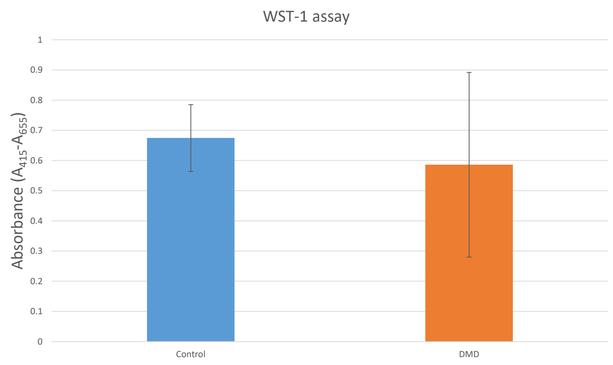


DMD patient-derived fibroblast cell lines lacking Dp71 express a higher level of Focal adhesion kinase (FAK) than controls





FAK is a key regulator of cell migration and binds to Dp71[4]



DMD patient-derived fibroblasts lacking Dp71 have lower metabolic activity than controls

Summary

- Alterations in cell migration and proliferation are directly linked to Duchenne comorbidities such as intellectual disability, autism, epilepsy and ADHD
- Cell migration could represent an innovative target for therapeutic intervention in DMD
- The *DMD* gene may represent a novel target for therapeutic intervention in various cancers
- We are developing RNA-based therapeutics to target *DMD* gene variants in the brain
- We actively seek collaboration in these areas

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