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# Cyclosporine A treatment for Ullrich congenital muscular dystrophy: a cellular study of mitochondrial dysfunction and its rescue.

Hicks D<sup>1</sup>, Lampe AK, Laval SH, Allamand V, Jimenez-Mallebrera C, Walter MC, Muntoni F, Quijano-Roy S, Richard P, Straub V, Lochmüller H, Bushby KM.

## Author information

### Abstract

Mutations in COL6A1, COL6A2 and COL6A3, the genes which encode the extra-cellular matrix component collagen VI, lead to Bethlem myopathy and **Ullrich congenital muscular dystrophy** (UCMD). Although the Col6a1(-/-) null mouse has an extremely mild neuromuscular phenotype, a **mitochondrial** defect has been demonstrated, linked to dysregulation of the **mitochondrial** permeability transition pore (PTP) opening. This finding has been replicated in UCMD muscle cells in culture, providing justification for a clinical trial using **cyclosporine** A, an inhibitor of PTP opening. We investigated whether PTP dysregulation could be detected in UCMD fibroblasts (the predominant source of muscle collagen VI), in myoblast cells from patients with other diseases and its response to **rescue** agents other than collagen VI. Although we confirm the presence of PTP dysregulation in muscle-derived cultures from two UCMD patients, fibroblasts from the same patients and the majority of fibroblasts from other well-characterized UCMD patients behave normally. PTP dysregulation is found in limb girdle **muscular dystrophy** (LGMD) type 2B myoblasts but not in myoblasts from patients with Bethlem myopathy, merosin-deficient **congenital muscular dystrophy**, LGMD2A, Duchenne **muscular dystrophy** and Leigh syndrome. In addition to **rescue** by **cyclosporine** A and collagen VI, this **cellular** phenotype was also rescued by other extra-cellular matrix constituents (laminin and collagen I). As the muscle derived cultures demonstrating PTP dysregulation shared poor growth in culture and lack of desmin labelling, we believe that PTP dysregulation may be a particular characteristic of the state of these cells in culture and is not specific to the collagen VI defect, and can in any case be rescued by a range of extra-cellular matrix components. Further work is needed on the relationship of PTP dysregulation

with UCMD pathology.

## Comment in

On the pathogenesis of collagen VI **muscular** dystrophies--comment on article of Hicks et al.  
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