RGD inhibition of itgb1 ameliorates laminin-a2 deficient zebrafish fibre pathology.

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Abstract

Deficiency of muscle basement membrane (MBM) component laminin-α2, leads to muscular dystrophy congenital type 1a MDC1a, a currently untreatable myopathy. Laminin-α2 has two main binding partners within the MBM, dystroglycan and integrin. Integrins co-ordinate both cell adhesion and signalling, however there is little mechanistic insight into integrin's function at the MBM. In order to study integrin's role in basement membrane development and how this relates to the MBM's capacity to handle force, an itgβ1.b-/- zebrafish line was created. Histological examination revealed increased extracellular matrix (ECM) deposition at the MBM in the itgβ1.b-/- fish, when compared to controls. Surprisingly, both laminin and collagen proteins were found to be increased in expression at the MBM of the itgβ1.b-/--larvae, when compared to controls. This increase in extracellular matrix components resulted in a decrease in myotomal elasticity as determined by novel passive force analyses. To determine if it was possible to control ECM deposition at the MBM by manipulating integrin activity, RGD peptide, a potent inhibitor of integrin-β1, was injected into a zebrafish model of MDC1a. As postulated an increase in laminin and collagen was observed in the lama2-/- mutant MBM. Importantly, there was also an improvement in fibre stability at the MBM, judged by a reduction in fibre pathology. These results therefore show that, blocking ITGβ1 signalling increases ECM deposition at the MBM, a process that could be potentially exploited for treatment of MDC1a.

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