Transgenic expression of cardiac α-actin rescues the lethal phenotype of skeletal α-actin knockout mice

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Over 130 different mutations have been identified to date in the skeletal muscle α-actin gene (*ACTA1*). These mutations manifest as histologically distinct congenital myopathies, though most patients have clinically severe early onset disease. During skeletal muscle development, the cardiac α-actin isoform is the predominant actin isoform, but it is downregulated by birth (Ilkovski *et al.*, 2005). The cardiac and skeletal actin isoforms differ by 4 of 375 amino acids, with the differences consistent in all species that have these two proteins (Vandekerckhove *et al.*, 1986). Recently it has been shown that certain patients have recessive *ACTA1* disease caused by an absence of skeletal muscle α-actin. These patients all retained expression of cardiac α-actin in their skeletal muscles, with the disease severity correlating inversely with the level of cardiac α-actin expression (Nowak *et al.*, 2007). It was hypothesised that expression of cardiac α-actin could serve as a functional replacement for skeletal muscle α-actin. Transgenic mice expressing cardiac α-actin in postnatal skeletal muscle were generated and crossed with heterozygous skeletal muscle α-actin knock-out mice, producing mice with only cardiac α-actin in their skeletal muscle (rescued nulls). Muscle morphology of the rescued nulls was examined via light and electron microscopy. The contractile properties of single skeletal muscle fibres from rescued null mice were investigated using the skinned fibre technique. Homozygous skeletal α-actin knock-out mice all die by postnatal day 9 (Crawford *et al.*, 2002). This lethal phenotype was rescued by the transgenic expression of cardiac α-actin, allowing survival into adulthood and procreation (mice we term "rescued nulls"). 94 % of the rescued null mice survived until at least 3 months and the oldest are over 15 months old. The skeletal muscle from the rescued null mice was morphologically similar to controls. However, the rescued null skinned EDL fibres did display a 25 % reduction in normalised maximum force production (p = 0.001). Alterations in the Ca^{2+} sensitivity of the contractile apparatus were also observed as indicated by significant differences in the slopes of the pCa-force curves (p = 0.013) and the pCa10 values (p = 0.004) compared with controls. This small force deficit may not be of major significance, as the rescued null mice were found to be functionally normal, as measured by a grip strength test (p = 0.777) and Rota-rod testing (p = 0.472). These studies show that cardiac α-actin can functionally replace skeletal muscle α-actin in adult skeletal muscle, thus offering a potential treatment for the skeletal muscle α-actin myopathies.

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