Increased levels of TRPC1 and caveolin-3 in *mdx* mouse

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Duchenne Muscular Dystrophy (DMD) is an X-linked genetic disease caused by the absence of dystrophin, which links the cytoskeleton to the membrane-bound dystrophin-associated glycoproteins (DAG). Increased levels of intracellular calcium in muscle cells is one of the causes of muscle damage in DMD and we have proposed that the increased calcium influx enters through a class of stretch activated channels (SACs) (Yeung *et al.*, 2005) which are thought to be encoded by TRPC1 (Maroto *et al.*, 2005). The aim of the present investigation is to understand the link between dystrophin absence and increased activity of SACs. Caveolin-3 is a membrane-bound protein which locates DAG to the caveolae and whose overexpression also leads to a dystophic phenotype. In smooth muscle TRPC1 has been shown to interact with caveolin-1 (Lockwich *et al.*, 2000). Src kinase co-fractionates with caveolin-3 (Song *et al.*, 1996) and can also activate channels from the TRPC family (Kawasaki *et al.*, 2006). We therefore studied the levels of expression and interaction of caveolin-3, TRPC1 and Src kinase in *mdx* mice, a mouse model which also lacks dystrophin expression. Caveolin-3 was increased in *mdx* mouse (Western Blot). This increase was confirmed by immunohistochemistry using skeletal muscle cryosections, showing higher levels of caveolin-3 both at the sarcolemma region and in the cytoplasm. TRPC1 was also increased in *mdx* mouse (Western Blot, immunohistochemistry). Over 50% of caveolin and TRPC1 co-localized at the sarcolemma region and their interaction was confirmed using co-immunoprecipitation. pY418-Src, the active form of Src kinase, was increased in *mdx* mouse. These results suggest that that caveolin-3 links dystrophin to TRPC1 and raise the possibility that Src kinase might be involved in the overactivity of the channel encoded by TRPC1.

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