Early pathways to muscle damage in muscular dystrophy

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Duchenne muscular dystrophy is a severe degenerative disease of muscle caused by a mutation in the gene for dystrophin. As a consequence the muscle is completely lacking the cytoskeletal protein dystrophin. The early manifestations of the disease include muscle weakness and raised serum creatine kinase while the later manifestations include muscle atrophy combined with inflammation and fibrosis. In addition to loss of dystrophin, the dystrophin-associated proteins in the membrane are all reduced in expression. Conversely a number of proteins show increased expression including TRPC1 (a membrane channel with permeability to cations), caveolin-3 (the scaffolding protein for caveolae), src kinase (a ubiquitous tyrosine kinase) and various subunits of NADPH oxidase (which produces superoxide). In the *mdx* mouse, which also lacks dystrophin, we have shown that contractions in which the muscle is stretched (eccentric contractions) produce a long lasting increase in intracellular calcium (Yeung *et al.*, 2005). This rise in intracellular calcium can be prevented by drugs which block stretch-activated channels (SACs), which may be encoded or regulated by TRPC1. Subsequently we showed that SACs can be activated by reactive oxygen species (ROS), which in the *mdx* mouse appear to arise from NADPH oxidase (Whitehead *et al.*, 2010). One possible pathway by which ROS activate SACs is through the src kinase, which is activated by ROS, and might then phosphorylate and activate SACs (Gervasio *et al.*, 2008). A recent proposal is that NADPH oxidase may be stimulated to produce ROS by stretch *via* attached cytoskeletal elements (X-ROS signalling) (Prosser, Ward & Lederer, 2011). These early pathways lead to elevated intracellular calcium and ROS in the dystrophic muscle and may be the triggers to the later pathology.

Gervasio OL, Whitehead NP, Yeung EW, Phillips WD, & Allen DG (2008). *Journal of Cell Science* **121**: 2246-2255.

Prosser BL, Ward CW, & Lederer WJ (2011). *Science* **333**, 1440-1445.

Whitehead NP, Yeung EW, Froehner SC, & Allen DG (2010). *PLoS ONE* **5**: e15354.

Yeung EW, Whitehead NP, Suchyna TM, Gottlieb PA, Sachs F, & Allen DG (2005). *Journal of Physiology* **562**: 367-380.