Ca^{2+} influx in Duchenne muscular dystrophy - membrane tears, SACs, SOCs, TRPC1, or TRPV2?

D.G. Allen,[1] E.W. Yeung,[2] O.L. Gervasio[3] and N.P. Whitehead,[4] [1]Bosch Institute, Sydney Medical School, University of Sydney, NSW 2006, Australia, [2]Department of Rehabilitation Sciences, Hong Kong Polytechnic University, Hong Kong, [3]Novartis, North Ryde, NSW 2113, Australia and [4]Department of Physiology and Biophysics, University of Washington, Seattle, WA, USA.

It is established that degenerating muscle fibres in Duchenne muscular dystrophy (DMD) are loaded with Ca^{2+} and it is widely believed that this elevated Ca^{2+} has an important role in the pathology of the disease through activation of proteases (calpains), damaging mitochondria and activating phospholipases leading to membrane damage. However the source of this additional Ca^{2+} is uncertain. Many authorities state that dystrophin is a cytoskeletal protein connecting the contractile machinery to the membrane and the extracellular matrix and that in its absence the membrane is more fragile and susceptible to "membrane tears". These tears would be an important source of Ca^{2+} influx and the membrane repair process would have a key role in limiting this source of Ca^{2+}. In our view the evidence for this mechanism is limited. Many studies have found evidence for increased activity of various channels in DMD, particularly stretch-activated channels (SACs) and store-operated channels (SOCs) which are Ca^{2+} permeable and could contribute to Ca^{2+} influx. Our work has focused on stretch-activated channels whose activity is enhanced by contractions in which the muscle is stretched. We show that blocking these channels with either streptomycin, Gd^{3+} or the spider venom peptide GsMTx-4 prevents the rise of Ca^{2+} and reduces many aspects of muscle damage. However the molecular basis of these channels remains uncertain with TRPC1 and TRPV2 current contenders. Establishing the molecular basis of the Ca^{2+} influx channels and the signaling pathways that regulate their activity are critical steps for understanding the early pathology of DMD.