

Lack of TRPC1 channels impairs skeletal muscle regeneration.

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We have previously showed in vitro that Ca^{2+} entry through TRPC1 ion channels regulates myoblasts migration and differentiation by activating calpain, a Ca^{2+} -dependent protease which cleaves myristoylated alanine-rich C-kinase substrate (MARCKS) protein to allow myoblasts migration. To explore, in vivo, whether the absence of TRPC1 channel impairs skeletal muscle regeneration, we used cardiotoxin injections to induce muscle injury in adult TRPC1^{+/+} and TRPC1^{-/-} mice. Interestingly, we observed that regenerated TRPC1^{-/-} muscles had a smaller fibre size and a decreased specific force respectively after 10 and 14 days of regeneration. We also observed an increase of central nuclei at day 14 of regeneration in TRPC1^{-/-} whereas, at this stage, in TRPC1^{+/+} muscles, nuclei were essentially situated in the periphery of the fibres. These observations indicate a delay in muscle regeneration in TRPC1^{-/-} mice in comparison with their controls. To understand the molecular mechanisms which sustain this delayed regeneration in TRPC1^{-/-} mice, we investigated myogenic transcription factors implicated in the control of myogenesis. In comparison with TRPC1^{-/-}, TRPC1^{+/+} muscles showed an earlier increase of the mRNA level and of the protein expression of MyoD, Myf5 and myogenin. Interestingly, developmental Myosin Heavy Chain (MHCd), a well known downstream target of MyoD during muscle regeneration, was also expressed earlier in TRPC1^{+/+} than in TRPC1^{-/-} muscles. Finally, we also observed a more important and earlier phosphorylation of both Akt and P70S6k in TRPC1^{+/+} muscles than in TRPC1^{-/-} muscles, suggesting, as previously reported, an involvement of Akt / mTOR / P70S6k pathway in the control of protein synthesis, muscles fibres size and muscle regeneration in vivo. Altogether, our results demonstrate the importance of TRPC1 channels in skeletal muscles development both in vitro and in vivo and identify Akt / mTOR / P70S6K as the main pathway affected in TRPC1^{-/-} during muscle regeneration in vivo.