ORAI1 downregulation ameliorates the multi-systemic signs of Tubular aggregate myopathy (TAM) and Stormorken Syndrome (STRMK)

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Résumé

Tubular aggregate myopathy (TAM) and Stormorken syndrome (STRMK) are clinically overlapping diseases affecting skeletal muscle, bones, spleen and platelets. They are caused by gain-of-function mutations in the Ca2+ sensor STIM1 or the Ca2+ channel ORAI1, both regulating Ca2+ balance through the ubiquitous store-operated Ca2+ entry (SOCE) mechanism. Functional investigations have shown that the TAM/STRMK mutations induce overactive SOCE, resulting in excessive influx of extracellular Ca2+. We previously generated a mouse model (*Stim1R304W/+*), recapitulating the main clinical signs of TAM/STRMK patients, and representing a unique tool to assess therapeutic strategies.
Currently, no therapies have been approved for TAM/STRMK. However, SOCE is amenable to manipulation. We aimed to rebalance Ca2+ homeostasis in *Stim1R304W/+* mice through shRNA-mediated downregulation of *Orai1*. Intravenous injections of AAV9 carrying *Orai1*-specific shRNAs significantly reduced *Orai1* expression by 80%. Compared with non-injected controls, treated *Stim1R304W/+* mice manifested increased body size and improved muscle force production and relaxation kinetics 3 months post injection. Moreover, histological analyses of muscle samples evidenced a normalization of fiber size and shape, and we also noted a partial restoration of spleen size, architecture and the number and distribution of megakaryocytes, the platelet precursor cells.
In conclusion, shRNA-mediated downregulation of *Orai1* improved the multi-systemic signs of TAM/STRMK. The treatment efficiently corrected the muscle, bone and spleen phenotypes in *Stim1R304W/+* mice, but had no measurable effect on platelet numbers and bleeding diathesis. In view of the high conservation of the targeted *Orai1* sequences in mouse and human, this approach represents a viable strategy for prospective clinical trials.

Mots-Clés: Tubular aggregate myopathy, Stormorken syndrome, ORAI1, Calcium, shRNA, ASO

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