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The pharmacological inhibition of JNK-pathway reduces severity of Spinal Muscular Atrophy in mice

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Spinal muscular atrophy (SMA) is a recessive autosomal neuromuscular disease, characterized by motor impairment, muscle atrophy and premature death following motor neuron (MN) degeneration, due to the lack of SMN (survival motor neuron) protein. Currently, the cellular and molecular mechanisms underlying MN death are only partly known [1], although recently it has been shown that the JNK-signalling pathway might be involved in the SMA pathogenesis. After confirming the activation of JNK in our SMA mouse model (SMN2+/+; SMNΔ7+/+; Smn-/-), we tested on these mice a synthetic JNK-inhibitor peptide (D-JNKI), by chronic administration from postnatal day 1 (P1) to P10; then, at age P12, we analyzed their spinal cords and quadriceps muscles. We observed that D-JNKI administration delayed MN death and decreased neuroinflammation in the spinal cord. Moreover, by inhibiting JNK pathway, the muscular fibers and the neuromuscular junctions appeared respectively more trophic and mature. The histological/molecular results positively correlated with improved motor performances and hindlimb muscular tone. Finally, the treatment slightly, but significantly increased lifespan in SMA mice. Overall, our results identify JNK as a promising target to reduce MN cell death and progressive skeletal muscle atrophy, providing insight into the role of JNK-pathway for developing alternative pharmacological strategies for the treatment of SMA.This work was supported by grants from CRT Foundation, Girotondo/ONLUS and SMArathon-ONLUS foundations.

References

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Key words

Motor neuron disease, apoptosis, innervation, neurodegeneration, therapy.

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