The modifying network of spinal muscular atrophy

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F-actin bundling plastin 3 (PLS3) is a fully protective modifier of the neuromuscular disease spinal muscular atrophy (SMA), the most common genetic cause of infant death. The generation of a conditional *PLS3* over-expressing mouse and its breeding into an SMA background allowed us to decipher the exact biological mechanism underlying PLS3-mediated SMA protection. We show that PLS3 is a key regulator that restores main processes depending on actin dynamics in SMA motor neurons (MN). MN soma size significantly increased and a higher number of afferent proprioceptive inputs were counted in SMA_{PLS3} compared to SMA mice. PLS3 increased presynaptic F-actin amount, rescued synaptic vesicle and active zones content, restored the organization of readily releasable pool vesicles and increased quantal content at the neuromuscular junctions (NMJs). Most remarkably, stabilized axons by PLS3 over-expression delayed axon pruning, counteracting poor axonal connectivity at SMA NMJs. These findings together with the observation of increased endplate and muscle fiber size upon MN-specific PLS3 over-expression suggest that PLS3 significantly improves neurotransmission. Indeed, ubiquitous over-expression improves survival and motor function in SMA mice. As PLS3 seems to act independently of Smn, PLS3 might be a potential therapeutic target not only in SMA but also other MN diseases.