Nicotinic stimulation induces Tristetraprolin over-production and attenuates inflammation in muscle.

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Abstract:

Cholinergic signaling suppresses inflammation in blood and brain and attenuates apoptosis in other tissues, but whether it blocks inflammation in skeletal muscle under toxicant exposure, injuries and diseases remained unexplored. Here, we report nicotinic attenuation of inflammation and alteration of apoptotic protein expression pattern in murine muscle tissue and cultured myotubes, involving the RNA-binding protein, Tristetraprolin, and the anti-apoptotic protein, Mcl-1. In muscles and C2C12 myotubes, cholinergic excitation by exposure to nicotine or the organophosphorous pesticide, Paraoxon, induced Tristetraprolin overproduction while reducing pro-inflammatory transcripts such as IL-6, CXCL1 (KC) and CCL2 (MCP-1). Furthermore, nicotinic excitation under exposure to the bacterial endotoxin LPS attenuated over-expression of the CCL2 and suppressed the transcriptional activity of NF-κB and AP-1. Tristetraprolin was essential for this anti-inflammatory effect of nicotine in basal conditions. However, its knockdown also impaired the pro-inflammatory response to LPS. Finally, in vivo administration of Paraoxon or recombinant Acetylcholinesterase, leading respectively to either gain or loss of cholinergic signaling, modified muscle expression of key mRNA processing factors and several of their apoptosis-related targets. Specifically, cholinergic imbalances enhanced the kinase activators of the Serine-Arginine splicing kinases, Clk1 and Clk3. Moreover, Paraoxon raised the levels of the anti-apoptotic protein, Mcl-1, through a previously unrecognized polyadenylation site selection mechanism, producing longer, less stable Mcl-1 mRNA transcripts. Together, our findings demonstrate that in addition to activating muscle function, acetylcholine regulates muscle inflammation and cell survival, and point to Tristetraprolin and the choice of Mcl-1 mRNA polyadenylation sites as potential key players in muscle reactions to insults.

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