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Modulation of Caspase Activity in Muscle Stem Cells Regulates Muscle Regeneration and Function

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Muscle homeostasis involves de novo myogenesis, as observed in conditions of acute or chronic muscle damage. Tumor Necrosis Factor (TNF) triggers skeletal muscle wasting and inhibits muscle regeneration. We show that intramuscular treatment with the myogenic factor Arg8-vasopressin (AVP) enhanced skeletal muscle regeneration and rescued the inhibitory effects of TNF on regeneration. The functional analysis of regenerating muscle performance following TNF or AVP treatments revealed that the two factors had opposite effects on muscle force and fatigue, and that AVP rescued TNF negative effects on muscle performance. Muscle regeneration is, at least in part, regulated by caspase activation in PW1 Interstitial Cells (PICs). The participation of these CD34+ Sca-1+ PW1+ cells to muscle regeneration is hampered by TNF and rescued by AVP. The contrasting effects of AVP and TNF in vivo are recapitulated in cultured myogenic cells, which express both PW1, a caspase activator, and Hsp70, a caspase inhibitor. Hsp70 and PW1 co-immunoprecipitated and co-localized in muscle cells. In vivo Hsp70 expression was upregulated by AVP, and Hsp70 overexpression per se counteracted the TNF block of muscle regeneration. In summary, AVP counteracts TNF effects through a cross-talk at the level of Hsp70, a pivotal regulator of caspase activity in myogenic cells. Diminishing caspase activity is important for a prompt morphological and functional recovery following injury.