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Regulation of motor neuron degeneration in spinal muscular atrophy – A new pathogenic mechanism and treatment strategy

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Abstract

Spinal muscular atrophy (SMA), the leading genetic cause of infant mortality, is characterized by the loss of spinal motor neurons controlling locomotion. However, the pathogenic mechanism of SMA remains largely unknown. Using two SMA mouse models and induced pluripotent stem (iPS) cells from SMA patients' fibroblasts, we show here that the activity of cyclin-dependent kinase (Cdk) is specifically up-regulated in SMA spinal motor neurons, leading to the phosphorylation of histone deacetylase 5 (HDAC5) and its cytoplasmic accumulation in vivo. The up-regulation of HDAC5 phosphorylation occurs before detectable SMA pathology, suggesting it may be one of the early initiators of the disease. In SMA motor neurons, Cdk phosphorylates HDAC5 on a novel phosphorylation site, Serine 279 (S279), within the nuclear localization sequence. This phosphorylation event results in decreased nuclear localizations of HDAC5 and its associating pro-survival transcription factor Myocyte Enhancer Factor 2 (MEF2), leading to motor neuron death in SMA. Intriguingly, drug inhibition of the Cdk signaling pathway diminishes disease symptoms in human SMA iPS cell-derived motor neurons. Together, our results reveal a mechanism regulating motor neuron degeneration in SMA through phosphorylation-dependent nuclear export of a chromatin-remodeling enzyme, and suggest a new therapeutic strategy for treating SMA and other neurodegenerative disorders.