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HHS Vulnerability Disclosure

IMT504 blocks allodynia in rats with spared nerve injury by promoting the migration of mesenchymal stem cells and by favoring an anti-inflammatory milieu at the injured nerve

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Abstract

IMT504, a noncoding, non-CpG oligodeoxynucleotide, modulates pain-like behavior in rats undergoing peripheral nerve injury, through mechanisms that remain poorly characterized. Here, we chose the spared nerve injury model in rats to analyze the contribution of mesenchymal stem cells (MSCs) in the mechanisms of action of IMT504. We show that a single subcutaneous administration of IMT504 reverses mechanical and cold allodynia for at least 5 weeks posttreatment. This event correlated with long-lasting increases in the percentage of MSCs in peripheral blood and injured sciatic nerves, in a process seemingly influenced by modifications in the CXCL12-CXCR4 axis. Also, injured nerves presented with reduced tumor necrosis factor-α and interleukin-1β and increased transforming growth factor-β1 and interleukin-10 protein levels. In vitro analysis of IMT504-pretreated rat or human MSCs revealed internalized oligodeoxynucleotide and confirmed its promigratory effects. Moreover, IMT504-pretreatment induced transcript expression of Tgf-β1 and Il-10 in MSCs; the increase in Il-10 becoming more robust after exposure to injured nerves. Ex vivo exposure of injured nerves to IMT504-pretreated MSCs confirmed the proinflammatory to anti-inflammatory switch observed in vivo. Interestingly, the sole exposure of injured nerves to IMT504 also resulted in downregulated Tnf-α and Il-1β transcripts. Altogether, we reveal for the first time a direct association between the antiallodynic actions of IMT504, its promigratory and cytokine secretion modulating effects on MSCs, and further anti-inflammatory actions at injured nerves. The recapitulation of key outcomes in human MSCs supports the translational potential of IMT504 as a novel treatment for neuropathic pain with a unique mechanism of action involving the regulation of neuroimmune interactions.

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