Title: **Immunomodulatory Layered Double Hydroxide Nanoparticles Enable Neurogenesis by Targeting TGFBR 2**

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Abstract:

Spinal cord injury (SCI) is a serious disease commonly happened in traffic, industrial, mining and sports accidents with no effective treatment method at present. One of the key problems for SCI recovery is the regulation of immune microenvironment to regenerate impaired neurons and reconstruct damaged neural circuits. Functional biomaterials have created promising SCI repair solutions for immune microenvironment amelioration and reconstruction. In this study, we used biodegradable Mg/Al layered double hydroxide nanoparticles (LDH) as a novel strategy for neural regeneration and immunoregulation. LDH achieved significant performance in accelerating neural stem cells (NSCs) migration and neural differentiation. In vivo, the behavioral and electrophysiological performance of SCI mice was significantly improved by LDH implantation, with BrdU+ endogenous NSCs and neurons clearly observed in the lesion sites. In addition, as a carrier, LDH loaded with NT3 (LDH-NT3) exhibited better recovery effects with regard to basso mouse scale (BMS) score, motor evoked potential (MEP) performance, synaptic transmission and neuron-neuron synaptic transmission. LDH/LDH-NT3 inhibited the inflammatory responses and accelerate the neural regeneration through key gene TGFBR2, by which LDH decreased the expression of M1 markers and increased the expression of M2 markers in both microglia and bone marrow-derived macrophages (BMDCs). Thus, we have developed Mg/Al-LDH that can be used to construct a suitable immune microenvironment for SCI recovery and have revealed the targeted receptor.