An Autophagy-Sensitive Nanoplatform via Chirality-Selective Modulation for Functional Peripheral Nerve Repair and Target Organ Homeostasis

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Abstract

Introduction: Peripheral nerve injury (PNI) and diabetic peripheral neuropathy (DPN) are prevalent and destructive problems in clinical practice; however, there is currently no precise strategy for them despite a wide range of attempts due to the ambiguous neuromodulation effects. Accumulating evidence indicates the opposite functions of chiral enantiomers in various diseases, suggesting that chirality-selective modulation should be investigated.

Methods: We fabricated levorotatory (L), dextrorotatory (D) and racemic (R) Fe_3O_4 enantiomers by L-/D-/R-aspartate-induced nanoparticle self-assembly. Then, the effects of Fe_3O_4 nanoparticle enantiomers on Schwann cells (SCs) were examinated through RNA sequencing and SCs phenotype detection, followed by mechanism investigation. The male rats were employed to establish PNI and DPN models, the therapautic outcomes by Fe_3O_4 nanoparticle enantiomers were detected.

Results: Fe_3O_4 nanoparticle enantiomers were synthesized to clarify the concept of chirality-selective neuromodulation. Transcriptomic and experimental analyses indicated that D-Fe_3O_4 were endocytosed by Schwann cells, promoting their proliferation,

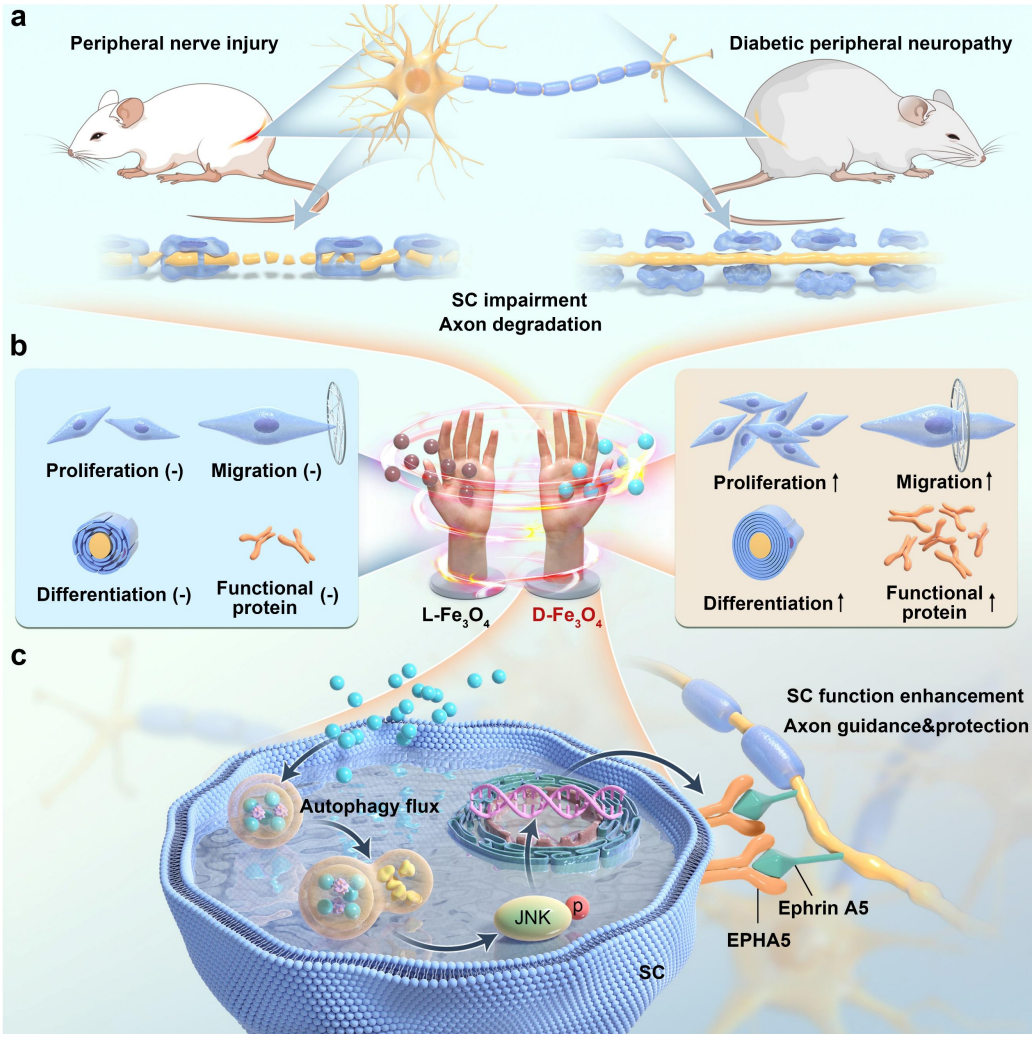
migration, and differentiation into the remyelinated phenotype through the autophagy-driven p-JNK/EPHA5 pathway. Furthermore, implants loaded with D-Fe_3O_4 exhibited more rapid structural reconstruction along with better sensory and locomotive restoration in the PNI and DPN models. The functional neural repair achieved through D-Fe_3O_4 led to the maintenance of the morphology of target organs and limb health homeostasis.

Discussion: Previous nerve impants exhibited less great performance at the early stage of neural regeneration due to unmanageable SCs function and axonal collapse. In addition, immunological cascades-induced microenvironment imbalance led to SCs and axon degradation in diabetes-related chronic neuropathy. It demonstrated that microenvironment control was vital for functional nerve repair, whereas many attempts by bioactive nanoparticles failed to achieve satisfactory outcomes. The present study discovered that the autophagy flux retardation within SCs contributed to peripheral nerve dysfunction. Furthermore, we first screened the D-Fe_3O_4 displayed enhanced capacities of autophagy restoration, cell survival and remyelination, by which a chiral Fe_3O_4-based tissue engineering strategy was designed to confirm its therapeutic outcomes in neurotrauma and diabetic neuropathy models. This study makes a significant contribution to the literature because it is the first to establish chirality-driven neuromodulation as a viable and mechanistically supported approach to nerve tissue engineering. Our findings bridge nanomaterial science and neural regeneration and suggest a new avenue for the development of targeted regenerative therapies.

Significance/Clinical Relevance: This study broadens our understanding of chirality-selective neuromodulation of chiral enantiomers and offers a promising approach with significant translational potential for functional nerve tissue repair and target organ homeostasis.

Keywords

Neurotrauma, Neuropathy, Schwann cell, Chirality, Autophagy



Schematic illustration of chirality-selective modulation by dextral Fe_3O_4 enantiomer for nerve tissue repair. a) The pathphysiological phenotype of PNI and DPN. b) Differentiated effects induced by Fe_3O_4 enantiomers. c) Mechanism of D-Fe_3O_4 modulating SCs activities.