POLYMER THERAPEUTICS FOR THE TREATMENT OF CHRONIC SPINAL CORD INJURIES

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Abstract

The medical application of nanotechnology has enormous potential to improve human health, especially in serious chronic disease such as cancer and neurodegeneration.[1-3] In this sense, Polymer Therapeutics represents an outstanding approach for the treatment of several pathologies, being one of the first nanomedicines with more than 16 polymer-drug conjugates in advanced clinical trials and several already transferred to routine clinical use. Although considerable experimental improvements in neuronal activity in acute and subacute stages after Spinal Cord Injury (SCI) have been made in the last decade, little progress has been made in the chronic stage. In the chronic scenario, tissue degeneration and reactive scarring isolate the injured area from the potential re-growing axons.[4] However, there are currently no studies which cover all fundamental criteria: cell replacement, neuroprotection and axonal growth promotion strategies and even fewer in chronic stages. Considering all tissue degeneration and the massive cell loss that occurs, transplantation of spinal cord derived and functional compatible cells result mandatory for tissue repair. Based on the multifaceted lesion that occurs, a combinatory therapeutic approach is clearly required.[5] We aim to the design of a nanomedicine for neuroprotection and axonal growth promotion. The property of multivalency provided by the use of polymeric carriers allows the conjugation of several bioactive agents in the same polymer in such a way that for SCI, the combination of a neuroprotector with an axonal growth inductor and other active principle such as chondroitinase, for glial scar disruption could markedly enhance the therapeutic value of these macromolecules. In this communication we present a first approach for the combinatorial treatment of SCI, where an axonal growth inductor (Fasudil®) conjugated to a multifunctional and biodegradable polymer such as Poly-L-Glutamic acid (PGA) is evaluated for combination with stem cell transplantation.

The conjugation of Fasudil to PGA has been achieved through different biodegradable linkers (amide and carbamate) and the different release rate profiles and toxicities of the conjugates has been evaluated in vitro showing different release rates depending on the linkage and no associated toxicities. Furthermore, the conjugation of a fluorescent dye (Oregon Green) enabled the study of the cellular uptake on injury activated ependymal cells and points to an energy dependent endocytosis internalization mechanism. In vitro tests on ROCK inhibition activity and axonal elongation has been carried out. All these results are promising for a therapy towards the treatment of SCI based on the combination of polymer conjugates and stem cells transplantation.

References

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