Regeneration strategies in the Central Nervous System

Drug-loaded nanoparticles for spinal cord injury regeneration

SR Cerqueira, JM Oliveira, JF Mano, N Sousa, AJ Salgado, RL Reis

Unlike fish, amphibia and even mammalial peripheral nerves, human central nervous system (CNS) axons have a very limited regeneration capability and do not spontaneously re-grow if lesioned. After damage or disruption, for instance caused by brain/ spinal cord injury (SCI) or stroke, a cascade of cellular and biochemical reactions occurs around the lesion site that creates a harsh environment for axons to regenerate. Immune and glial cells around the injury are also responsible for the production of molecules that restrain the axon re-growth, such as myelin associated inhibitors and chondroitin sulfate proteoglycans. Additionally, astrocytes and fibroblasts contribute to the formation of a scar around the damaged tissue that physically blocks axon repair. Thus, and in view of the latest findings it is imperative to block these inhibitory reactions and induce a more adequate environment for tissue repair and regeneration.

In our lab, we are currently developing biomaterial-based strategies to repair the injured CNS, focusing on spinal cord. The absence of effective therapies in SCI repair is in part due to its extreme complexity, but also to the lack of efficiency and targeting of the existing drugs. In order to target the detrimental cellular responses that follow the injury in a more specific and sustained manner, we developed a nanoparticle-based drug delivery system intended to target glial cells and modulate the inflammatory processes in SCI. Poly/(amido)amine (PAMAM) dendrimer nanoparticles grafted with carboxymethylchitosan (CMCht) were loaded with the anti-inflammatory corticosteroid methylprednisolone. The nanoparticles were shown to be internalized by glial cells without affecting its metabolic viability, while releasing the drug in a sustained and prolonged manner. Nanoparticle administration in spinal cord injured rats induced improved recovery in these animals, suggesting that nanoparticles can limit the damage extent and contribute to nerve repair/ sparing.

We believe that strategies such as this, intending to minimize the secondary events that follow nervous injury can be an opportunity for successful treatments in CNS tissue repair.

[1] Kordower J, Tuszynski MH. CNS regeneration: basic science and clinical advances: Academic Press; 2011.
[2] Horner PJ, Gage FH. Regenerating the damaged central nervous system. Nature. 2000;407:963-70.
[3] Oliveira JM, Kotobuki N, Marques AP, Pirraco RP, Benesch J, Hirose M, et al. Surface Engineered Carboxymethylchitosan/Poly(amidoamine) Dendrimer Nanoparticles for Intracellular Targeting. Advanced Functional Materials. 2008;18:1840-53.
[4] Salgado AJ, Oliveira JM, Pirraco RP, Pereira VH, Fraga JS, Marques AP, et al. Carboxymethylchitosan/Poly(amidoamine) Dendrimer Nanoparticles in Central Nervous Systems-Regenerative Medicine: Effects on Neuron/Glial Cell Viability and Internalization Efficiency. Macromolecular Bioscience. 2010;10:1130-40.
[5] Cerqueira SR, Oliveira JM, Silva NA, Leite-Almeida H, Ribeiro-Samy S, Almeida A, et al. Microglia Response and In Vivo Therapeutic Potential of Methylprednisolone-Loaded Dendrimer Nanoparticles in Spinal Cord Injury. Small. 2013;9:738-49.