Nanoformulation and multitarget therapy for early spinal cord injury

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Traumatic spinal cord injury (SCI) is an important cause of disability and death. Despite advancements in the medical and surgical treatments, and the preclinical evidence on cellular and molecular mechanisms occurring during the very early phase of the lesion, SCI is considered an incurable condition. The complex pathophysiology of SCI includes a primary phase characterized by the ischemic damage which reflects the trauma, and a secondary phase sustained by the inflammatory cell cascade that is characterized by the progression of demyelination, scar formation, neurodegeneration and central cavitation. Our lab is committed in development of therapeutic strategies to interfere with secondary degeneration, counteracting inflammation and improving endogenous regeneration (i.e. remyelination). In this study we tested, in the rat model of T8 contusion spinal cord injury, a multi-drug treatment with ibuprofen (antinflammatory), murine Nerve Growth Factor (mNGF, neuroprotector) and triiodothyronine (T3, promyelinating agent) conjugated to PLGA nanoparticles. mNGF and T3-conjugated nanoparticles were subdurally administered immediately after traumatic lesion induction, while Ibuprofen was chronically administered via subcutaneous osmotic minipump. This delivery schema ensured a controlled and prolonged release rate of the drugs. Animals were evaluated at 8 and 60 days after the lesion to study the biodistribution of nanoparticles and the treatment effects on glutamate release, tissue inflammation and astroglial reaction, morphological indices of myelination and axonal injury and, finally, the long-term locomotor outcome. All these parameters significantly improved in treated animal. Moreover, T3-conjugated nanoparticles, when tested in vitro, were able to enter neurons, astrocyte and oligodendrocyte precursor cells (OPC), also favoring the full OPC maturation into myelinating oligodendrocytes.