Modulation of myelin phagocytosis by means of anti-inflammatory treatment as a therapy of spinal injury

IMPACT

Spinal cord injury (SCI) is a neurological condition which severely affects the quality of life of the patients and constitutes a heavy financial burden for the individual and society. Current medical treatment focuses exclusively on rehabilitation. Anti-inflammatory treatment of SCI with corticosteroids was introduced in the 1980s, but due to side effects, and limited benefits and the need to initiate this treatment within eight hours after injury, it is no longer recommended [1]. No curative, disease-modifying treatment of SCI is presently available. The experiments reported in the present thesis addressed this important medical need.

Myelin is an insulating sheath that forms around nerves. After SCI, myelin breakdown and accumulation can trigger inflammatory responses in the lesion site and be an obstacle for axon regeneration. This thesis found two compounds, retinoic acid (RA) and bile acid, as anti-inflammatory treatments that could improve myelin clearance by macrophage in vitro experiments. Retinoic acid, as a potential pharmacotherapy for SCI, has several advantages. Compared with other signaling proteins, RA has a much lower molecular weight of approximately 300 Da. Considering its molecular structures, RA is highly oil-soluble and able to diffuse across the cell membrane. Bile acids obtained from forty-four different animals (including human bile) have been used as a host of maladies in traditional Chinese medicine for centuries. Its roots can be traced back to the Zhou dynasty (c. 1046-256 BCE) [2]. With the development of times, the composition of various animal biles was based on rigorous separatory and advanced chemical identification techniques. Bile acids can easily cross the blood-brain barrier, based on their presently known principal chemical components. Therefore, they are also very interesting therapeutic tools for SCI treatments. Our data support that RA and bile acid have an anti-inflammatory effect on the myelin clearance

process. However, additional research is needed to establish their clinical utility.

Plenty of preclinical and clinical studies with various stem cells suggest their use as a promising strategy for the treatment of SCI. Mesenchymal stem cells (MSCs) are so far the best candidates for use in regenerative medicine. MSC are easily harvested and can be isolated from different types of tissues (including bone marrow, umbilical cord, adipose tissue, and placenta). However, the main shortcomings of MSC therapies lie in their unsatisfactory translation from small animal experimental models (mice and rats) into human clinical practice. This thesis tested a new human bone marrow-derived stromal cell (bmSC) as a therapy in animal SCI models. Our results showed that human bmSC has neuroprotective properties after SCI at molecular and tissue level, but was not sufficient to induce motor function recovery at individual level. For the clinical trial, Neuro-Cells is an autologous fresh stem cells containing product which modulates the secondary inflammation following a TSCI, reduces apoptosis (cell death) in the injured spinal cord, reduces scar tissue formation in the damaged spinal cord and creates a cell regenerative environment in the injured spinal cord. Human bmSC, which we used in this thesis, was prepared the same way as neuro-cells in the clinical trial. Phase I clinical study is an open clinical trial to investigate the safety of the intrathecal application of Neuro-Cells in the treatment of end stage (chronic), traumatic complete (AIS grade A) and incomplete (AIS grade B/C) SCI patients. As the clinical trial is still in progress, the final conclusion is not yet known.

The societal impact of the present thesis derives primarily from potential clinical applications that may lead to successful treatments of SCI. On a second level, the commercial exploitation of these therapies is likely to confer an economical benefit.

In chapter II we identified retinoic acid as a regulator of myelin clearance by macrophages, and the results in chapter III indicate that the bile acid TLCA rescues phagocytosis activity under inflammatory conditions. Therefore, clinical strategies may be developed based on these molecular targets that benefit not only SCI but also other neuropathologies where the accumulation of myelin and cellular debris is involved. A new preparation of bmSC was investigated, whose effective mechanism of action most

likely depends on their anti-inflammatory effects. Based on the data reported in chapter IV, a phase I clinical trial was initiated to test the safety of a new bmSC preparation in SCI patients (Protocol A2019SCI04, EudraCT 2019-003366-40). Following a successful completion of this study at the Hospital Nacional de Parapléjicos, Toledo, Spain, a phase II/III multi-center RCT has been applied for in 2021 (Protocol A2017SCI03, EudraCT 2018-000805-22). The results of chapter V revealed the limitations of TUDCA in a preclinical setting of SCI. Since this bile acid is currently being explored in several other neuropathologies, these findings are as important as a positive therapeutic effect would have been.

The bmSC preparation investigated in chapters IV and V is intellectual property of Neuroplast BV, Geleen, Netherlands (patent WO2015/059300A1). A successful outcome of the intended clinical trial will lead to a commercial exploitation of this product with possible benefits to local employment and tax revenue.

In conclusion, the current thesis is a significant step forward to a more comprehensive and creative therapy for spinal cord injury.

1. Short DJ, El Masry WS, Jones PW. High dose methylprednisolone in the management of acute spinal cord injury – a systematic review from a clinical perspective. Spinal Cord 38 (2000): 273-286.

2.Wang DQH, Carey MC. Therapeutic uses of animal biles in traditional Chinese medicine: An ethnopharmacological, biophysical chemical and medicinal review. World J Gastroenterol 2014; 20(29): 9952-997