



## Cover Story

## Functional recovery in spinal cord injury using mesenchymal stem cells



The therapeutic potential of stem cells in treating nervous system disorders, such as spinal cord injury (SCI), Parkinson's disease, and multiple sclerosis, has been demonstrated in experimental animal models, but its translation to clinical study still requires overcoming several limitations. A crucial aspect is the preservation of stem cell viability and optimal delivery of therapeutic factors in the injured site. Stem cells in SCI are thought to act through multiple mechanisms combining immunomodulation, trophic support, tissue protection and axon regeneration. We need to understand the molecular mechanisms by which specific transplanted stem cells ameliorate SCI outcome. To date, engineered scaffolds have been used as a promising approach to sustain a long-lasting cell viability of stem cells in the injured site. The localized stem cells offer the opportunity to deliver factors optimizing the therapeutic effect of the treatment and exploiting their full therapeutic potential for reliable treatment for SCI. However, few attempts have been made for understanding how hydrogel contributes to the delivery of factors secreted from stem cells and what factors are released.

In this issue, Professor Veglianesse and his colleagues demonstrated that carbomer-agarose based hydrogel (CAH) offers the possibility to load and sustain human mesenchymal stem cells (hMSCs). CAH provides hMSCs with an optimal place close to the injured site and protects them from the hostile tissue [1]. The work by the Veglianesse team demonstrated for the first time that MSC loaded into CAH could deliver potential immunomodulating and neuroprotective factors that could recapitulate the efficacy of hMSCs *in vitro* and *in vivo*. Specifically, CCL2 protein has been validated to play a key role in recruiting peripheral macrophages and switching them to anti-inflammatory M2 like phenotype in the damaged site. The substantial pro-regenerative environment found after CCL2 treatment was also demonstrated by behavioral tests which showed significant motor recovery. The immune response after SCI has always been considered largely harmful, because of the production of toxic factors. However, some studies have reported a detrimental neurological outcome after anti-inflammatory treatment suggesting that some inflammatory responses are beneficial.

The Veglianesse team also found for the first time a new therapeutic role for CCL2 protein released by MSC-loaded hydrogel. CCL2 protein preserved motor neurons and increased neurite outgrowth showing neuroprotective mechanisms *in vitro* and *in vivo*. These results indicate that a pro-regenerative inflammatory modulation together with neuroprotection promoted by the CCL2 protein are fundamental for the efficacy of MSCs. This work provides an initial understanding of the

therapeutic complexity of these cells for acute traumatic lesions of the spinal cord. However, the authors have not excluded that other factors are also involved and released by hMSCs, or other protective mechanisms involving different agent/or cells are mediated by CCL2.

This study also provides an important therapeutic opportunity for controlling the migration of beneficial macrophages in the lesioned site through a single factor repairing the damaged spinal cord and preventing degeneration of motor neurons in SCI. Interestingly, the specific *in situ* recruitment of immune and stem cells after the damage makes the cellular delivery system a good candidate for delivering therapeutic agents into the injured site through cell migration such as demonstrated by Ho et al. for tumor therapy in this issue [2]. Alternatively, isolated potential factors can be loaded in biomaterials for a more controlled delivery with several advantages over cell delivery, such as removal of the variability of cell survival, optimized reproducibility of delivery in response to specific therapeutic needs. Indeed, these findings offer promising indications for future treatments with therapeutic factors that can be isolated and maximized for a successful clinical outcome. There is no doubt that many questions and challenges remain for clinical applications [3]. However, the success achieved with novel cell transplantation protocols by biopolymeric hydrogel scaffolds, together with a more knowledge of the mechanisms underlying stem cells efficacy, offers a promising foothold for future treatments with positive clinical outcome in humans.

## References

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