The "Salmon Spirit" of translational medical research

As a group of primitive cells characterized by self-renewal and multilineage differentiation, stem cells have awakened great interest in regenerative and translational medicine. Various stem cell types hold potential for use in clinical studies, with mesenchymal stem cells (MSCs) considered the most important cell type for regenerative medicine because of their qualities of easy isolation, multipotency, immunological naivety, and ethical advantages. The pleiotropic properties of MSCs, including immunomodulation, growth factor production, angiogenesis, anti-fibrosis, anti-oxidation, and anti-apoptosis, make them suitable for large-scale application in various disease therapies. Clinical trials using MSCs for a wide spectrum of conditions including diabetes mellitus (1), liver disease (2), cardiac disease (3), and kidney disease (4), are now underway. Notably, since February 2020, six registered clinical trials have been conducted in China to investigate the safety and efficiency of MSC therapy for pneumonia patients infected with 2019-nCoV (ClinicalTrials.gov Identifier: NCT04252118, NCT04288102, NCT04293692, NCT04273646, NCT04269525, and NCT04276987).

The number of MSC trials in progress has continued to expand. However, the majority of the current trials are still in the early phase I/II stage, suggesting that MSCs are not moving out of the clinical pipeline. Although the majority of the trials confirmed the safety of MSC infusion, the adverse effects such as headache, fever, and local pain could be easily overlooked, with clinical efficacy taking priority. In addition, MSC trials have frequently proved unsuccessful, such as the MSC trials for ischemic stroke (Manipal Acunova, India) and ARDS (China), which failed or were terminated (5). Of course, there are still many problems surrounding the use of MSCs in clinical trials.

Currently, no standardized protocols or guidelines exist for MSC clinical trials. The general lack of knowledge surrounding their *in vivo* outcomes and the mechanism of their activity is another obstacle for MSC transplantation. Various sources have been used to isolate and manufacture MSCs for clinical trials, irrespective of the very different natures of the MSC populations. The heterogeneity of the MSCs isolated from different origins and the route of administration should be critically addressed during the evaluation of the clinical data and the interpretation of clinical benefits. *In vitro* culture systems can add heterogeneity to the phenotype and genotype of MSCs, and improved culture strategies are therefore needed to mimic organ-specific microenvironments *in vitro*. The route of administration followed by the *in vivo* distribution is also an important and controversial topic surrounding MSCs. For instance, intra-arterial delivery may hold the advantage of increasing the deposition of MSCs at the injury site, especially the liver.

After intravenous administration, most MSCs succumb to apoptosis, with only a small fraction of cells able to survive (6). Inadequate amounts of cells, homing, long-term engraftment, and differentiation limit their therapeutic efficacy. To improve the low survival rates of transplanted stem cells, over the past decade, many innovative biomaterials, such as hydrogels, have been developed. Besides, pharmaceutical pre-activation, genetic engineering, or reprogramming of MSCs into the progenitor cells of targeted tissues have been used to enhance their therapeutic potency (7). This challenges the search for precise biomarkers to identify the progenitor cells before transplantation. Moreover, the trophic factors and extracellular vesicles secreted by MSCs could serve as an alternative, cell-free therapy to overcome the tumorigenic or immunogenic risk of stem cell transplantation.

To increase the chances of success in future clinical trials, larger-scale studies are needed to determine the appropriate cell source, delivery route, dosage, therapeutic window, and the intrinsic mechanisms of MSCs in tissue repair. Extending the biological and bioengineering approaches to manufacturing MSCs will certainly allow for safer and more effective therapeutic strategies to be developed, thus paving the way for progress in the field.

This series of *Annals of Translational Medicine* is dedicated to the topic of "Stem Cell and Clinical Application". We have attempted to shed light on some of the current clinical applications, strategies, mechanisms, and unsolved problems relating to stem cell therapy. Although there are still many challenges and questions that need to be addressed, we hope this series on the clinical application of stem cells will contribute to the growth of this field of study.

For me, translational medical research is just like the life cycle of a salmon. As we all know, every fall, thousands of salmon leave the Pacific Ocean and swim up the Fraser River in Canada to breed before they die. In this long and arduous process, they jump up and hit the riverbed time and time again, with reproduction as the only reward for their unremitting efforts. Clinicians are just like adult salmon in the ocean: they look imperturbable, but they face great unknown risks and challenges.

Both have to swim upstream: the salmon to breed, and the clinicians to seek the pathogenesis and new treatment for diseases. And the young salmon that hatch in the peaceful lake just like research scientists, who have to nobly endure loneliness as they continue to grow daily through repetitive experiments. Despite the extremely low survival rate of the salmon, each little fish has the innate conviction that it will find its way back to the ocean; just like scientists possess the firm conviction that they will one day find the path to the clinical application of a new technique or theory. So with the "salmon spirit" in mind, we can find the optimal application of MSCs in the near future.

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References

1. El-Badawy A, El-Badri N. Clinical Efficacy of Stem Cell Therapy for Diabetes Mellitus: A Meta-Analysis. PLoS One 2016;11:e0151938.
2. Suk KT, Yoon JH, Kim MY, et al. Transplantation with autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: Phase 2 trial. Hepatology 2016;64:2185-97.
3. Singh A, Singh A, Sen D. Mesenchymal stem cells in cardiac regeneration: a detailed progress report of the last 6 years (2010-2015). Stem Cell Res Ther 2016;7:82.
4. Peired AJ, Sisti A, Romagnani P. Mesenchymal Stem Cell-Based Therapy for Kidney Disease: A Review of Clinical Evidence. Stem Cells Int 2016;2016:4798639.
5. Trounson A, McDonald C. Stem Cell Therapies in Clinical Trials: Progress and Challenges. Cell Stem Cell 2015;17:11-22.
6. Galipeau J, Sensébé L. Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities. Cell Stem Cell 2018;22:824-33.
7. Dimmeler S, Ding S, Rando TA, et al. Translational strategies and challenges in regenerative medicine. Nat Med 2014;20:814-21.

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