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EDITORIAL OPEN ACCESS

Could multilineage-differentiating stress enduring (Muse) cell be a better alternative of mesenchymal stem cells-based treatment for central nervous system injuries?

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Friedenstein's original observations led to the discovery of a special cell population that possesses multipotent stem cell properties [1], and these bone marrow derived adult stem cells were commonly called mesenchymal stem cells (MSCs) later, though the appropriateness of this term is still fiercely debated, i.e., there are, currently, many different terms with slightly different definitions that try to define the similar population. Regardless, the presence of MSC-like cell population has been proven in almost all adult and embryonic tissues, however, their exact entity remains an enigma [2].

The translational potential of MSCs in regenerative medicine has been well recognized [2–4]. Since MSCs possess many highly desirable features, such as easy accessibility without ethic concern, excellent safety profile (non-tumorigenic and non-immunogenic), ability to exert trophic effects, self-renewal and at least multipotent differentiation, anti-apoptotic and immunomodulatory effects, capacity for migration to the injury site and participating in regeneration and integration in a variety of tissues.

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However, even though tremendous efforts have been devoted in the past decades to realize their potentials, MSCs are still facing daunting challenges [5], and many major practical and theoretical limitations that have bottlenecked the field so far are thought to be donor cell, i.e., MSC, related.

For example, MSCs have been normally cultured in basal medium (DMEM or alpha-MEM) with the addition of fetal bovine serum (FBS) as a source of growth factors, cytokines and mitogens, raising a general concern for public health due to the possible communicable diseases, i.e., prion-transmitted bovine spongiform encephalopathy (BSE). Therefore, producing clinical grade MSCs for human use, or MSCs as advanced therapy medicinal products (ATMP) according to Good Manufacturing Practice (GMP) guidelines [5, 6], still represents a major global challenge.

In addition, MSCs are usually harvested from mesenchymal tissues, such as the bone marrow, adipose tissue, and umbilical cord, and cultured as adherent cells. Therefore, MSCs are seen as crude cell populations comprising a heterogeneous population, comprising mesenchymal cells with different phenotype, origin, and differentiation state [6, 7], and also other minor populations, such as, fibroblasts, blood vessel-associated cells (endothelial cells and pericytes), even sensory nerve-related glial cells (Schwann cells), as well as several types of stem or progenitor cells, such as neural crest-derived stem cells and endothelial progenitors.

Nevertheless, it is worthy to point out that the real concern is the variations associated with the heterogeneity, not the heterogeneity itself. The variations of MSCs are normally manifested as variable marker content and expression ratios, variable differential potentials towards different lineages, and variations among different batches, or tissue origins, or lab origin. These variations greatly hinder the repeatability of the clinical applications. Furthermore, the reported unusual ability of broad spectrum of differentiation beyond the germ layer lineages was extremely controversial and confusing [8, 9].

For these reasons, investigators are seeking potential better alternatives of these heterogeneous MSCs, or

at least ways to address the variations, while still keep most of the desirable features of MSCs. Against this background, a novel type of pluripotent stem cell, Multilineage-differentiating stress enduring (Muse) cells, was recently discovered from mesenchymal tissues [10] and cultured MSCs [11]. It is now known that Muse is essentially a subpopulation of the heterogeneous MSCs, since Muse cells comprise about 0.03% of bone marrow mononuclear cells, and several percentage of cultured bone marrow MSCs [10].

Interestingly, Muse cells are positive for both MSC (CD105, CD90 and CD29) and pluripotency (SSEA-3) markers [10]. More importantly, unlike regular MSCs, Muse cells are able to robustly differentiate into all three germ layers, even at a single cell level [12, 13]. The Muse cells can also migrate to damaged sites in vivo, and spontaneously differentiate into any cells compatible with the targeted tissue, and contribute to tissue repair [14]. It is now thought that these Muse cells may account for the wide variety of differentiation abilities and tissue repair effects that have been originally observed in MSCs. On top of that, like MSCs, Muse cells also have excellent safety profile (non-tumorigenic and non-immunogenic).

For these reasons, many investigators now hold high expectation for these newly discovered cells for regenerative medicine, especially for treatment of CNS injuries, based mainly on the hypothesis that if the cells can robustly differentiate into neuronal lineage and can be integrated into the damaged CNS tissue, it would likely improve the efficiency of the existing MSC transplantation.

One recent report [15] directly evaluated the therapeutic effects of human Muse cells in treating infarct brain injury of mice, therefore directly tested the above-mentioned hypothesis. To our best knowledge, this is the first study that directly tested the therapeutic potential of Muse cells in clinically relevant central nervous system (CNS) injury model.

Specifically, the authors separated human bone marrow MSCs into Muse and non-Muse cells, and transplanted each of them, in parallel with regular MSC, into focal cerebral ischemia model to analyze their contribution to tissue regeneration and functional recovery.

As expected, the authors found that Muse cells and non-Muse cells contributed differently to tissue regeneration. Specifically, Muse cells were more responsible for replacement of the lost neurons through their integration into the peri-infarct cortex and spontaneous differentiation into neurons, while non-Muse cells or regular MSC did not remain in the host brain for long-term.

However, the surprising data came from the function recovery tests. Even though Muse cells showed much better integration efficiency, the motor function recovery of Muse cell-treated animals started to recover significantly later (not earlier) than non-Muse cell-treated animals and did not even catch up at the end the experiment (42 days after the transplantation), and both subgroups (Muse and non-Muse) performed worse than the regular MSC group in this function recovery test. Consistently, similar trend was also found in another function recovery test, i.e., the test of spatial memory.

The only other available clinical relevant report that treating diabetic skin ulcers with adipose Muse cells, however, found that not only Muse-rich cells showed much better integration efficiency histologically, but also significantly accelerated wound healing functionally, compared with Muse-poor cells [16].

At this point, we believe that the consensus has far from been established yet, because there are clearly multiple ways to reconcile these two [15, 16] seemly conflicting available reports, and one of the key unanswered questions is whether the finding in CNS injury model is unique to this specific setting. Future endeavors along the same conceptual line will be certainly needed to clarify the issue. Nevertheless, the sharp contrast between Muse cells and non-Muse cells in functional and histological analysis in the CNS model [15] may have multifold immediate implications:

(1) This study indicated that high integration efficiency of transplanted therapeutic donor cells does not automatically translated directly into better functional recovery. Even this may sound a little counterintuitive, in light of the complexity of functional recovery of CNS injury, it is not completely implausible. Regardless, this is a blow to the original unrealistic assumption that essentially equals the histological repair with functional recovery.

(2) Functional recovery of CNS injury is certainly a multifaceted process that may dependent on the pleiotropic effects of MSCs, including inflammation modulation and production of neurotrophic factors, as well as replacement of lost neuronal cells by neuronal differentiation of MSCs. Such pleiotropic effects may be dependent on different subpopulations of MSCs. If that is the case, we may end up in an uncomfortable dilemma: if we want to keep all key subpopulations, we will have to deal with the frustrating issue of variations associated with heterogeneity. On the other hand, if we want to reduce the variations by over-purifying the MSCs, we may arbitrarily throw away key subpopulations.

(3) It is reasonable to speculate that different subpopulations may work interdependently or even synergistically through different ways and at different time points. Therefore, overemphasizing the purification process may not be wise. The right approach seems to be: selecting the key subpopulations and optimizing their overall

ratios, based on deep understanding the function of different subpopulations in MSCs.

(4) The future focus of research may have to be shift according to the current understanding (if it is proved to be true), since the geometry and composition of MSCs is still very much obscure, and the specific cells that responsible for each effect have not been clarified.

For decades, numerous studies have indicated that the transplanted regular MSCs enhance motor function recovery and ameliorate cognitive dysfunction after the insults in animal models or clinical trials of various neurological disorders, including cerebral infarct. It is worthy to stress that we almost always hold unfavorable view about the many well-known variables, such as donor cell factors, patient factors, and other treatment factors that could negatively influence the repeatability of final outcomes, and forget that some of the variables actually showed us valuable insights for regenerative medicine in the long-term.

Overall, among others, the studies of Muse cells highlighted that we still know very little about this mysterious MSC population almost half century after its discovery, and there will probably be a long way before we have a fairly complete understanding of the population, and can consistently and confidently harness the therapeutic potentials of MSCs.

Keywords: Central nervous system injuries, Multilineage-differentiating stress enduring (Muse), Regenerative medicine

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Yuyun Li – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Guarantor

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Conflict of Interest

Authors declare no conflict of interest.

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