

Original Article

Evaluation of mesenchymal stem cells in the healing of anastomosed carotid arteries

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Abstract: Cell therapies could be the future of medicine. Many centers worldwide consider the use of stem cells to treat certain conditions. Well, proper homing remains the challenge, which means the ability to target the cells to the targeted site. Intraoperative transplantation of stem cells can overcome the homing challenge. However, it could be a double-edged sword, if a proper technique was not conducted. In this comment, a practical example of that is presented, where the use of stem cells in the vascular and neurovascular surgeries shows a promising potential, but the way in which the cells are processed and introduced is a critical step that should be given a lot of attention.

Keywords: Mesenchymal stem cells, regenerative therapy, vascular anastomosis, neurovascular surgery

MSCs are multipotent stem cells that can differentiate into various cell types, giving a tremendous regenerative potential. However, these cells have proven a great ability to modulate various types of inflammatory and immune reactions, so that they are used to attenuate the immunity in graft versus host reactions following bone marrow transplantation [1].

MSCs secrete many immune-modulatory factors such as interleukin (IL) 10, transforming growth factor β (TGF- β), prostaglandin E2 (PGE2) and vascular endothelial growth factor (VEGF). IL10 is one of the major anti-inflammatory cytokines that down regulates the expression of the cytokines in the T helper-1 cells, and the major histocompatibility class-II antigens and the costimulatory molecules on the surface of the macrophages. Moreover, IL10 is capable of suppressing the production of IL8 in a dose dependent manner [1, 2].

While the endothelial adhesiveness increases significantly in response to IL1 β , TNF α , IFN γ , and lipopolysaccharide stimulation, which increases the leukocytic (macrophages and lymphocytes) migration into the site of inflammation, TGF- β , secreted by MSCs, has the ability to block these effects in a dose dependent manner [3]. Nevertheless, PGE2 functions

towards the inhibition of the proliferation, differentiation and function of the antigen presenting and cytotoxic cells, including the dendritic cells, macrophages and natural killer (NK) cells [4]. Moreover, VEGF has neuro-protective effects, where it enhances the survival of schwann cells and cerebellar granule neurons, and protects against the degeneration of the motor neurons [Duffy AM, Bouchier-Hayes DJ and Harmey JH. Vascular Endothelial Growth Factor (VEGF) and Its Role in Non-Endothelial Cells: Autocrine Signalling by VEGF. In: Madame Curie Bioscience Database (Internet). Austin (TX): Landes Bioscience; 2000-2013. <https://www.ncbi.nlm.nih.gov/books/NBK6482/>]. Hence, MSCs are expected to improve healing at sites of surgical anastomoses and improve tissue regeneration and re-vascularization.

While many studies are being conducted to establish the clinical application of MSCs, the work done by Joseph Touma & colleagues [5] and Adnan Altun & colleagues [6], for instance, showed contradictory results regarding the benefits of MSCs in the vascular surgeries. The aim of the study by Adnan Altun & colleagues was to evaluate the ability of MSCs to improve the clinical and histopathological healing of vascular anastomosis in carotid arteries [6]. The study concluded, however, that the local admin-

istration of MSCs didn't show a positive influence on the success of the vascular anastomosis. In their work, the local MSCs inoculation was followed by wrapping with an 8 mm sheet of Surgicel and soaking with BioGlue [6]. On the other side, Joseph Touma & colleagues experimentally proved a positive value of MSCs in solid occlusion of arteriovenous malformations, promoting cellular regeneration rather than thrombus formation. In their experimental work, the MSCs were supported with hyaluronic acid hydrogel, and injected through a catheter into the rete mirabile [5].

The process of healing is a dynamic process that includes angiogenesis (neovascularization), inflammation (inflammatory cell infiltration), fibroplasia and restoration of the connective tissue matrix (collagen deposition), wound contraction and remodeling, epithelialization, and differentiation. If the inflammatory phase persists without timely and orderly progression, wound healing may become delayed or severe scarring may occur, resulting in clinical problems such as chronicity or anastomosis stenosis [7]. Thus, the addition of an extra-inflammatory load to the tissue injury is expected to hinder the healing process and the beneficial actions of MSCs.

Surgicel is a hemostatic agent made of an oxidized cellulose polymer (polyanhydroglucuronic acid) and is used to control post-surgical bleeding. It provides physical matrix for clotting initiation and an antimicrobial effect through its low pH. Nevertheless, Surgicel can disturb proper healing by inducing foreign body reaction and lowering the pH, which can trigger strong inflammation and delay wound healing [8].

BioGlue is produced by Cryolife Inc, Kennesaw, GA. It contains bovine serum albumin 25% and glutaraldehyde 10%. In addition to eliciting a foreign body reaction, its application as an adjunct to sutures in vascular surgery triggers granulomatous inflammation and provokes eosinophilic, lymphocytic and plasma cells infiltrations [9].

Thus, the step of wrapping at the anastomosis site in the study by Adnan Altun & colleagues [7] added an extra challenge to the surgical insult and the locally transplanted MSCs, rendering the presented results unreliable to evaluate a potential role of MSCs in the healing of

anastomosed carotid arteries. On the contrary, the use of hyaluronic acid hydrogel by Joseph Touma & colleagues [6], which resembles a favorable extracellular matrix, provided good support for the cells as well as the implantation process itself, thus, the presented results were positive.

In conclusion, the use of stem cells in the vascular and neurovascular surgeries have a promising potential, however the way in which the cells are processed and introduced is a critical step that should be given a lot of attention.

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