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Stem Cell Applications in Preventing Flap Rejection: A Call for More Clinical Research

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Dear Editor,

The field of flap surgery has experienced significant advancements in recent years; however, the challenge of flap rejection remains a critical hurdle. Cell-based therapies, particularly those involving stem cells, offer new hope for patients facing difficult-to-treat conditions (1). The potential of stem cell therapy in enhancing flap survival and preventing necrosis represents a promising frontier (2). While preclinical studies have shown encouraging results, the translation of these findings into clinical practice is still in its infancy (2-7). This editorial highlights the current state of research in this burgeoning field and calls for further clinical investigations to unlock its full potential.

Current Insights from Preclinical Studies

Almost all studies reviewed were conducted on rats and mice, using flaps obtained from the healthy tissues of these animals (4, 6, 8, 9). Most of the studies examined focused on random skin flaps (4, 9, 10). A few studies explored the use of perforator flaps and pectoral skin flaps (6, 8). While random skin flaps are the most commonly used type, the reviews indicate that stem cell applications have been employed to enhance the survival rates of axial, cranial uni-pedicled, and epigastric flaps (7, 10).

Bone Marrow Mesenchymal Stem Cells

Recently, a study by Bazgir et al. demonstrated the ability of bone marrow mesenchymal stem cells (BM-MSCs) to accelerate wound healing and improve the survival of perforator flaps in animal models (8). The mechanisms underlying this improvement include hemostasis, antioxidant activity, enhanced oxygen delivery, and exosome transport. These findings suggest that BM-MSCs hold significant promise in reconstructive surgery, but further exploration is needed to understand their full impact on flap survival and the molecular mechanisms involved.

Angiogenesis Promotion and Vascular Endothelial Growth Factor Upregulation

Systematic reviews of preclinical evidence emphasize that stem cell-based therapy promotes early angiogenesis by upregulating vascular endothelial growth factor (VEGF) (10). Techniques such as intra-arterial injection and the use of adipose-derived stem cells (ASCs) or xenogenic stem cells from humans have been particularly effective in improving the survival rate of small-area skin flaps (7). This highlights the versatility of stem cell therapy in preventing necrosis.

Adipose-Derived Stem Cells and Interleukin-6

Another exciting discovery is the role of ADSCs and their secretory factor, interleukin-6 (IL-6), in enhancing flap recovery and angiogenesis after ischemia-reperfusion injury. Adipose-derived stem cells (ADSCs) not only differentiate into endothelial cells but also secrete IL-6, which plays a crucial role in flap survival (6). These findings open avenues for clinical applications, emphasizing the need to delve deeper into the molecular pathways involved.

Composite Tissue Allografts and Immunosuppression

In cases of composite tissue allografts, stem cells have shown the potential to reduce systemic toxicity associated with immunosuppressants (9, 11). By modulating T-cell subsets and promoting anti-inflammatory cytokine production, MSCs and ASCs can enhance allograft survival and induce immunological

tolerance. This approach, combining temporary immunosuppression with stem cell infusion, has yielded promising results in extending transplant survival.

Administration and Estimated Mechanisms of Action

Almost all of the stem cells were injected subcutaneously in the flap area, while in some studies, stem cells were administered as sheets placed onto the sarcolemma (4, 9). Although it has been stated that cell tracking technology is insufficient for accurately following stem cells within skin flaps, important changes that enhance skin flap survival have been observed. Research has highlighted that stem cells play a crucial role in promoting neovascularization by increasing levels of VEGF, IL-6, and CD31, all of which contribute to greater blood vessel density. Additionally, it has been determined that these stem cells are involved in angiogenesis and the formation of capillary networks under higher magnification. It is believed that these mechanisms significantly improve the success rate by enhancing the survival of skin flaps (4, 6, 8-10).

Challenges and Considerations

While preclinical data are promising, several challenges need to be addressed to pave the way for clinical adoption:

Safety Concerns

The long-term fate of transplanted stem cells, potential tumorigenesis, and genetic modifications during ex vivo manipulations require rigorous evaluation. Tumorigenicity remains a key concern in pluripotent stem cell therapies due to the risk of residual undifferentiated or transformed cells forming tumors. While differentiation protocols aim for purity, rigorous preclinical evaluation is essential. Current in vivo and in vitro testing methods have limitations, and the lack of standardized guidelines necessitates a case-by-case regulatory approach. Establishing internationally harmonized tumorigenicity assessments is critical for ensuring the safety of these therapies. Good manufacturing practices (GMP) facilities are also essential for the safe collection, testing, and cryopreservation of cells.

Optimization of Therapy

Key questions remain unanswered:

1. What is the minimum number of stem cells required for effective tissue regeneration?

2. How long do replacement cells remain functional?

3. Which chemoattractants effectively direct stem cells to the site of injury?

Ethical and Practical Barriers

The accessibility and scalability of stem cell therapies must be improved. Additionally, understanding the underlying mechanisms of the stem cells' differentiation pathways is critical to ensure the success of stem cell-based interventions.

Clinical Applications and Future Directions

The integration of stem cell therapy into reconstructive surgery offers significant advantages, particularly for elderly patients or those with complex health profiles. Unlike traditional flap surgeries that rely on donor sites, stem cell-based approaches minimize morbidity and reduce surgical risks. For instance, mesenchymal stem cells could play a pivotal role in addressing tissue loss due to infection, trauma, tumors, and congenital abnormalities. However, robust clinical trials are necessary to establish stem cell therapy as a standard of care. Key focus areas should include:

- Understanding the mechanisms of stem cell differentiation and immunomodulation.

- Assessing the long-term outcomes and safety of stem cell-based interventions.

- Investigating the interplay between stem cells and their microenvironment during proliferation and differentiation.

A Call to Action

The potential of stem cell therapy to revolutionize reconstructive surgery cannot be overstated. However, to bridge the gap between promising preclinical findings and clinical application, we must invest in well-designed clinical trials. Researchers and clinicians must collaborate to explore the vast possibilities of stem cells while addressing the associated challenges and risks. Stem cell therapy holds the promise of treating diseases and conditions once considered untreatable. It is time to harness this potential and redefine the future of flap surgery and transplantation. Let this editorial serve as a rallying cry for the scientific community to prioritize this transformative area of research.

Footnotes

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