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LETTER TO THE EDITOR

Emergence of the stromal vascular fraction and secretome in regenerative medicine

Ratan Kumar Choudhary, Shanti Choudhary, Abhishek Tripathi

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Abstract

Recently, we read a mini-review published by Jeyaraman *et al*. The article explored the optimal methods for isolating mesenchymal stromal cells from adipose tissue-derived stromal vascular fraction (SVF). Key factors include tissue source, processing techniques, cell viability assessment, and the advantages/disadvantages of autologous *vs* allogeneic use. The authors emphasized the need for standardized protocols for SVF isolation, ethical and regulatory standards for cell-based therapy, and safety to advance mesenchymal stromal cell-based therapies in human patients. This manuscript shares our perspective on SVF isolation in canines. We discussed future directions to potentiate effective regenerative medicine therapeutics in human and veterinary medicine.

Key Words: Stromal vascular fraction; Mesenchymal stem cells; Veterinary regenerative medicine; Isolation procedures, Canine model; Secretome

Core Tip: A recent mini-review highlighted critical steps for optimal stromal vascular fraction (SVF) isolation from adipose tissue, including liposuction refinement, tissue handling, enzymatic digestion, and rigorous quality control for cell viability and purity. This article expanded upon the review by examining the advantages and limitations of SVF isolation, exploring SVF isolation in canine patients, and discussing the future potential of SVF in regenerative medicine.

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TO THE EDITOR

Recently, we read a mini-review article entitled "Understanding and controlling the variables for stromal vascular fraction therapy" by Jeyaraman *et al*[1]. The article provided a comprehensive overview of the critical steps involved in mesenchymal stromal cell (MSC) isolation from stromal vascular fraction (SVF) harvested from adipose tissues. The authors highlighted the significance of each step in determining the quality and quantity of the final product. Furthermore, the authors emphasized standardization, quality control, safety, and ethical consideration before therapeutic application in treating diseases like osteoarthritis.

Including a section on adipose tissue biology, regenerative products, and comparison between autologous and allogeneic SVF sources offers valuable context for understanding the broader implications of MSC isolation. The discussion on anesthetic choices and aspiration steps adds another practical relevance to the article. While the article provided a solid foundation for the SVF isolation and standardization process, other areas could have been further elaborated to enhance the impact of this article.

The authors might have delved deeper into protocol standardization, including specific matrices and benchmarks for accessing MSC quality and quantity. The quantity of stem cells is estimated using stem cell surface markers, which are inaccurate because they identify more abundant committed progenitor cells in addition to stem cells. New technology, such as kinetic stem cell counting, utilizes a label-free technique to quantify specific fractions of stem cells, progenitor cells, and differentiated cells in a biological sample[2]. Precise quantification of stem cells is important in determining the dosage of therapeutic tissue stem cells like hematopoietic stem cells[3]. In a similar fashion, a specific fraction of tissue-specific MSCs can be quantified in SVF harvested from adipose tissue collected from various sites.

This mini-review primarily focused on technical aspects of MSCs isolation. Expanding the utility of MSCs derived from the SVF for clinical applications in other diseases would have strengthened the impact of the article. In addition, given the increasing interest in regenerative medicine, a brief discussion on the regulatory landscape of MSC-based therapy in India would have also been quite relevant.

PERSPECTIVE ON THE CANINE SVF AND SECRETOME

The focus of the article on human adipose tissue is commendable. Expanding the scope to include the isolation of SVF from model animal tissues like canine adipose tissue would have significantly enhanced the relevance to a broader audience. Canine models are frequently used in biomedical research and advancements in canine regenerative medicine. We have observed in the canine model that the adipose tissue harvested from different sites has different proportions of stem cells, of which the peri-ovarian region was the best site for adipose tissue harvest, consistent with the observation from the literature[4]. While human and canine MSCs share many core characteristics, there are also species-specific differences. For instance, canine MSCs exhibit a moderate expression of surface markers like CD90, CD73, and CD166 compared to their human counterparts[5]. Our unpublished data suggest that canine SVF has a faster osteogenic differentiation potential, reaching maturity in 16 days compared to 21 days for human SVF. While the immunomodulatory properties of human SVF, including modulation of T cells and B cells, are well-established, research on the immunomodulatory effects of canine SVF remains limited.

The future of SVF therapy holds immense promise. While currently utilized as a heterogeneous cell population, the potential to optimize its therapeutic efficacy lies in further understanding and manipulating its constituent cells by expansion. One exciting avenue of research involves culturing SVF in the presence of specific compounds to increase the stem cell fraction. Nucleoside analogs, such as xanthosine, promote the proliferation of stem cells from diverse tissues, including canine SVF (unpublished data), rat liver stem cells[6], and bovine and goat mammary stem cells[7,8]. However, the precise molecular mechanisms underlying their actions remain to be fully elucidated.

By identifying and utilizing growth factors, cytokines, or other bioactive molecules, it may be possible to expand the stem cell component within SVF selectively. This could lead to the development of more potent and targeted cell therapies. SVF may present several potential risks and challenges; firstly, the isolation and processing of SVF can introduce microbial contamination or damage to the cells, affecting their viability and function. Secondly, there is a risk of immune reactions, especially allogeneic administration, though MSCs are less immunogenic and safe for therapeutic applications in humans and canines. Additionally, the long-term safety and efficacy of canine SVF therapy remain unknown. Furthermore, the standardization and quality control of canine SVF preparations can be challenging, as the composition and characteristics of SVF can vary widely depending on the source and isolation method.

Another key aspect that needs to be determined is the regulatory and ethical issues. The differences in regulatory and ethical issues between canine SVF and human SVF should be carefully considered when formulating future treatment strategies. The use of human SVF is subject to stricter regulations and ethical guidelines. The National Guidelines for Stem Cell Research in India, as of today, prohibit stem cell therapy, except hematopoietic stem cell therapy for blood

disorders. All other stem cell therapies, including SVF, remain limited to investigational and clinical trial levels after obtaining necessary permissions. Canine SVF, on the other hand, may have less stringent regulations, mainly when used in veterinary medicine. Rules for the use of canine stem cells are yet to come. Ethical considerations, such as the welfare of animals and the potential for unintended consequences, should be carefully addressed while working with canine SVF.

The extraction and quality assessment of canine and human SVF requires careful consideration due to inherent species-specific differences. While both canine and human SVF are derived from adipose tissue, the anatomical location and quality of the tissue can vary between species, potentially affecting the yield and composition of the SVF. The optimal isolation methods for canine and human SVF may differ due to variations in cell surface markers, adhesion properties, and other cellular characteristics. Finally, the norms of the International Society for Cellular Therapy outline general guidelines for the ethical and scientific conduct of stem cell research and clinical applications and apply to both species. In addition to general standards, species-specific guidelines may apply to the production and use of canine SVF. Adherence to good manufacturing practices and principles remained essential for ensuring the quality and safety of SVF products for clinical use.

Another promising strategy involves harnessing the power of the stem cell secretome. This complex mixture of soluble factors, including growth factors, cytokines, and extracellular vesicles, is secreted by stem cells and may play a vital role in tissue repair and regeneration[9], cancer[10], and many other disease conditions. Generating a secretome for novel therapeutic agents would mitigate the challenges associated with allogeneic cell transplantation. Moreover, the secretome provides: (1) Direct administration at the site of injury to promote tissue repair and reduce inflammation; (2) The ability to encapsulate into biocompatible carriers to improve its stability and target delivery; and (3) The development of the synthetic or recombinant version of these molecules for therapeutic use by characterizing components of the secretome.

CONCLUSION

The standardization of SVF isolation is essential for improving the effectiveness of stem cell therapy. Cell-based treatment outcomes may differ due to the differences in tissue-harvesting site isolation protocols, including enzymatic digestion time, centrifugation speed, and many other variables. Harnessing the potential of the stem cell secretome and investigating canine models offer promising avenues for future advancements in SVF-based therapies.

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FOOTNOTES

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