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The Role of MSC-Derived Exosomes in Soft Tissue Remodelling via the PTEN and PI3K/AKT Pathway Following Wide Excision of Fibrosarcoma: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Fibrosarcoma is a neoplasm of fibroblast tissue with varying collagen production. Fibrosarcoma, an aggressive form of soft tissue cancer, is currently a major challenge in the field of oncology. Although its prevalence is relatively low compared to other cancers, fibrosarcoma's severity lies in its tendency to infiltrate and destroy healthy tissue quickly. Surgical excision is the mainstay of

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treatment for fibrosarcoma. This procedure is critical to optimizing patient outcomes while minimizing surgical risks and complications. MSCs show positive results in the regeneration of fibrous tissue through their ability to differentiate into tenocytes or fibroblasts and their paracrines. MSCs also have effects that promote healing and tissue remodeling increases the synthesis of extracellular matrix components and restores tissue structure and function. MSCs also release products in the form of growth factors and cytokines modulate inflammatory responses, and stimulate endogenous, enhancing angiogenesis repair mechanisms. Adipose tissue-derived MSCs can increase the production of type I and type III collagen via the PI3K/Akt signaling pathway in fibroblasts. Furthermore, exosomes from adipose tissue-derived MSCs have been found to prevent scarring, suggesting that cell-free therapy may be an effective strategy. Due to the limited research on the effects of MSC on soft tissue remodelling wide excision of fibrosarcoma, the author initiated the creation of this review article. In this literature review, we summarize the latest research which aims to provide an overview of the effect of mesenchymal stem cells in regenerating fibrous tissue in soft tissue damage after wide excision of fibrosarcoma, so that in the future research can be carried out on this matter with the aim of minimizing complications after surgery.

Keywords: Mesenchymal stem cells; PTEN pathway; P13K/Akt pathway; Soft Tissue Remodelling; firbrosarcoma wide excison.

1. INTRODUCTION

Fibrosarcoma is a neoplasm of fibroblast tissue with varying collagen production. Fibrosarcoma, an aggressive form of soft tissue cancer, is currently a major challenge in the field of oncology. Although its prevalence is relatively low compared to other cancers, fibrosarcoma's severity lies in its tendency to infiltrate and destroy healthy tissue quickly. This malignancy originates from connective tissue, such as muscles, tendons and ligaments, so early detection and appropriate treatment are very important to improve patient recovery outcomes. Surgical excision is the main of treatment for fibrosarcoma. This procedure is critical to optimizing patient outcomes while minimizing surgical risks and complications. And basic pathology is necessary to help determine an accurate diagnosis of each sarcomatous lesion and help guide appropriate treatment (Davis et al. 2023). Intramuscular tumors should undergo compartmental en-bloc excision. In these cases, no additional radiation therapy is indicated. If there is extracompartmental growth, or the tumor does not reach the origin or insertion of the muscle, a wide surgical resection is appropriate to obtain a tumor-free margin. A margin of two centimeters has been recommended for this wide excision. However, there is no definitive evidence for the best safety margin. Surrounding structures such as nerves and vascular structures must always be considered “(Davis et al. 2023).

MSCs show positive results in the regeneration of fibrous tissue through their ability to differentiate into tenocytes or fibroblasts and their paracrines. MSCs also have effects that promote healing and tissue remodeling increases the synthesis of extracellular matrix components and restores tissue structure and function. MSCs also release products in the form of growth factors and cytokines modulate inflammatory responses, and stimulate endogenous, enhancing angiogenesis repair mechanisms (Rehman et al. 2023).

2. MESENCHYMAL STEM CELLS CHARACTERISTICS

MSCs are a type of multipotent stem cells derived from various sources, such as umbilical cord (UC-MSC), bone marrow (BM-MSC), adipose tissue (AD-MSC), and dental pulp (DP-MSC)” (Rehman et al. 2023). These cells can be regenerative medicine due to their ability to renew themselves, differentiate into several cell lineages, and modulate immune responses. MSCs have the potential to differentiate into fibroblasts, osteoblasts, chondrocytes and adipocytes which aim for tissue repair and regeneration (Han et al. 2019). MSCs can be extracted by various methods depending on the tissue source. For example, BM-MSCs can be taken from bone marrow aspiration, followed by isolation and expansion in culture. AD-MSCs can be obtained through liposuction or surgical excision of adipose tissue, which is then extracted into MSCs. UC-MSCs come from umbilical cord tissue or blood, while DP-MSCs are obtained from dental pulp extracted for therapeutic or orthodontic purposes (Rehman et al. 2023). Each MSC source has its own

advantages and disadvantages in terms of cell yield, proliferation capacity, and differentiation potential. Fig. 1. shows a general scheme for the isolation and expansion of MSCs for clinical applications (Xiu et al. 2022, Wang et al. 2020).

2.1 The Role of the Mesenchymal Stem Cells Derived Exosome via PTEN and P13K/Akt Pathway

Exosomes are substances released by cells other than MSCs and are responsible for intercellular communication. Exosomes are granular substances with a diameter of 50–150 nm secreted by cells. Their surface contains lipids and proteins derived from the cell membrane, while the interior contains nucleic acids (microRNA, messenger RNA, and DNA), proteins, and other intracellular substances. Various MSCs derived from tissues secrete exosomes; however, the function of exosomes varies depending on the tissue of origin. In one case, bioinformatics analysis has revealed that exosomes from bone marrow-derived MSCs have high regenerative potential, exosomes from adipose tissue-derived MSCs have high immunomodulatory potential, and exosomes from umbilical cord-derived MSCs have high tissue damage repair potential (Wang et al. 2020). Exosomes from adipose tissue-derived MSCs have potential in skin injury healing, nerve regeneration, ischemia-reperfusion, parenchymal organ diseases, and obesity. Specifically, adipose tissue-derived MSCs can increase the production of type I and type III collagen via the PI3K/Akt signaling pathway in fibroblasts. Furthermore, exosomes from adipose tissue-derived MSCs have been found to prevent scarring, suggesting that cell-free therapy may be an effective strategy (Hong et al. 2019). The Research by cheng xiu and colleagues are using StarBase tool predicted that miR-150-5p might target PTEN (Xiu et al. 2022). In addition, PTEN expression was detected by RT-qPCR and western blot analyses in HaCaT cells treated with different concentrations of H_2O_2, which reported that PTEN level increased in a concentration-dependent manner. Moreover, by detecting the luciferase activities, we found that miR-150-5p mimic decreased the luciferase activity of HEK-293T cells transfected with WT-PTEN, but had no effect on the luciferase activity of HEK-293T cells transfected with MUT-PTEN. RIP assay further confirmed the interaction between miR-150-5p and PTEN. Moreover, the expression of miR-150-5p and PTEN and the phosphorylation of PI3K and AKT were detected by RT-qPCR and western blot analysis in HaCaT cells transfected with miR-150-5p mimic, miR-150-5p inhibitor, or miR-150-5p inhibitor＋sh-PTEN. The results showed that compared with the mimic NC group, the expression levels of miR-150-5p, p-PI3K, and p-AKT in the miR-150-5p mimic group increased significantly, while the PTEN mRNA and protein expression decreased significantly; the expression levels of miR-150-5p, p-PI3K and p-AKT substantially decreased, and the expression levels of PTEN mRNA and protein increased in the miR-150-5p inhibitor group, compared with the inhibitor NC group. Compared with the miR-150-5p inhibitor group, the expression of p-PI3K and p-AKT in the miR-150-5p inhibitor ＋ sh-PTEN group increased significantly, while the expression of PTEN mRNA and protein decreased substantially. These results suggest that miR-150-5p regulates PI3K/AKT pathway by regulating PTEN" (Xiu et al. 2022). Summary information on the derived exosome potential of mesenchymal stem cells can be seen in Fig. 2.

2.2 Firbrosarcoma Wide Excison Indications for which Mesenchymal Stem Cells Derived Exosome can be Administered

The indications for administering MSC exosomes to fibrosarcoma after wide excision surgery are Primary, low-grade, superficial and Primary, low-grade, deep and ≤5 cm fibrosarcoma and are less effective in cases of fibrosarcoma with positive and recurrent margins (Min et al. 2016, Grimer et al. 2010). The primary goal of wide excision surgery is to remove the entire tumor with a margin of normal tissue. An acceptable margin of normal tissue is defined as 1 cm of soft tissue or its equivalent (eg, fascial layer). However, in these surgical procedures, anatomical constraints mean that a truly wide resection is not possible without compromising critical anatomical structures such as nerves or blood vessels. In these situations, it may be acceptable to leave the planned microscopically positive surgical margin, after considering the risk of recurrence and morbidity of more radical surgery (Grimer et al. 2010).

3. CLINICAL AND EXPERIMENTAL TRIALS

In the experiments described in the literature, in vitro, exosomes are often expressed from MSC sources. One difference is that some exosomes have a predetermined content before expression.

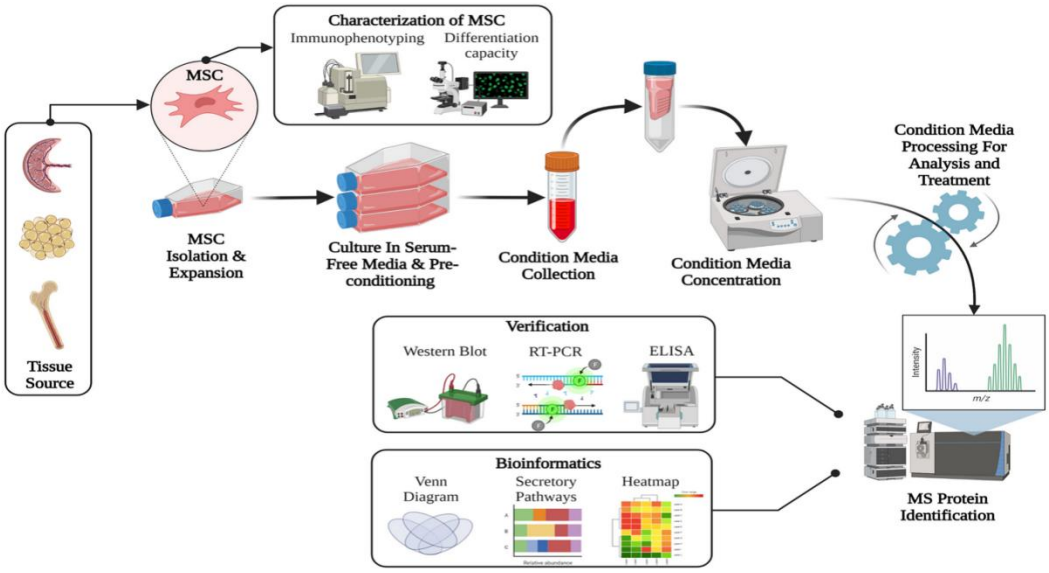

Fig. 1. General scheme for the isolation and expansion of MSCs for clinical applications (Rehman et al. 2023)

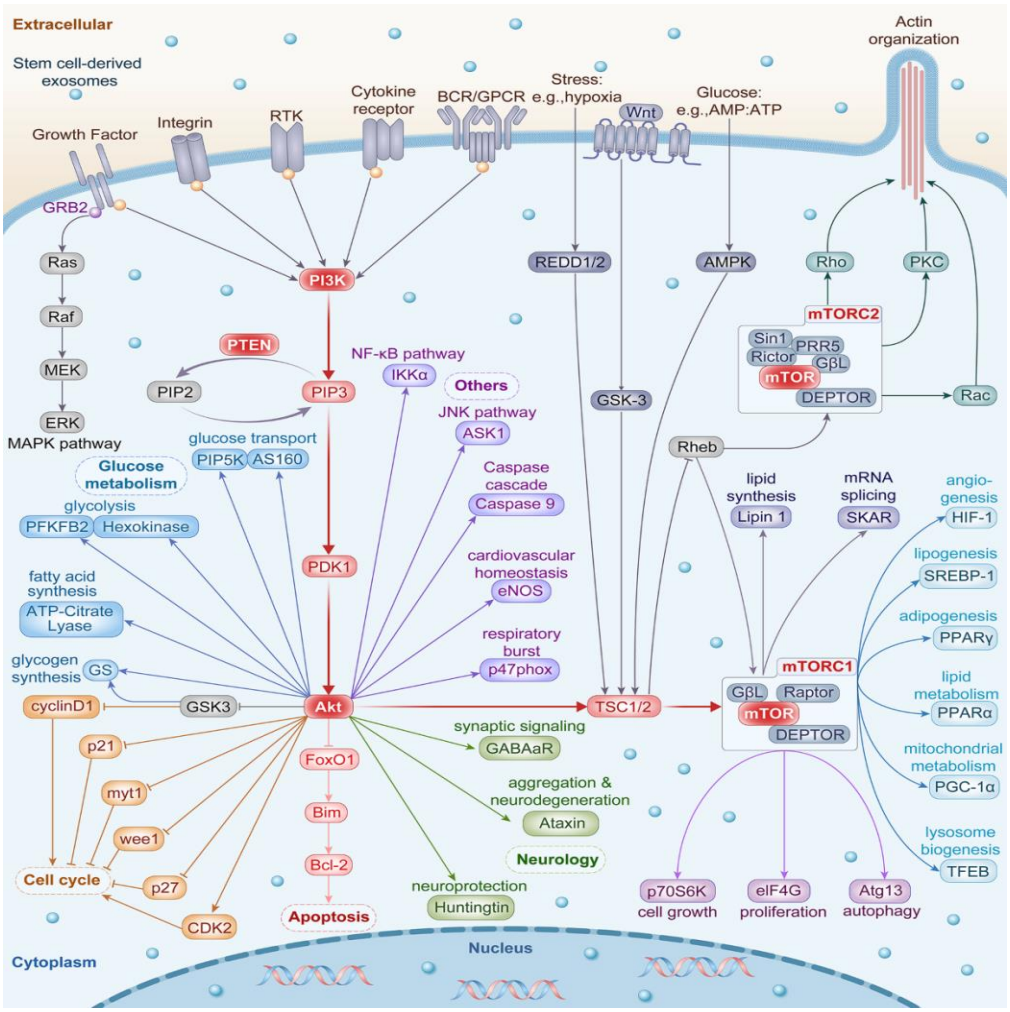

Fig. 2. The regulation of the mesenchymal stem cells derived exosome via PTEN and P13K/Akt pathway (Li et al. 2024)

In vitro, experiments typically use human umbilical vein endothelial cells (HUVEC), and human dermal fibroblasts (HDF) to observe changes in proliferation, migration, and other cellular functions after exosome treatment. In vivo, experiments involve injecting exosomes into experimental animals such as mice and rats to evaluate the regenerative effects on wound healing by assessing changes in endothelial proliferation, macrophage phenotype, fibroblast migration, vascular remodeling, collagen deposition, and other wound healing processes (Jing et al. 2023).

4. FUTURE DIRECTION

Currently, MSC exosomes have shown promising regenerative effects on soft tissue repair and regeneration (Zang et al. 2015). These nanoparticles and their mimics can provide similar regenerative effects as those achieved by cell therapy. It is encouraging that the majority of experimental evidence from MSC exosomes shows the effectiveness and safety of exosome use (Hade et al. 2021). However, research has only been conducted on preclinical models. As we can see from this review, the development of exosomal treatments is still in the early stages of research and is still limited in the clinical applications that have been achieved. The author hopes that this review can be useful as an idea for subsequent pre-clinical or even clinical research.

5. CONCLUSION

Exosomes secreted by MSCs have been widely utilized to develop novel regenerative therapies for various diseases because they possess most of the therapeutic properties of MSCs (Phinney et al. 2017). Exosomes offer a possibility of cell-free therapy, which minimizes the safety concerns associated with administering viable cells (Wan et al. 2022). In the case of MSC exosome administration on damaged soft tissue after wide excision for fibrosarcoma indication, MSC exosomes can be a regenerative agent in this condition. Many studies have stated that MSC exosomes has regenerative potential in tissue damage (Zanotti et al. 2018). The author hopes that there will be further preclinical and clinical studies on MSC exosomes administration on soft tissue damage after wide excision surgery, to develop insights into MSC-based regenerative therapy.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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