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Advances in Cell Therapy Using Rabbit Models for Regenerative Medicine

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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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ABSTRACT

Cell therapy represents an innovative and promising approach to treating debilitating conditions, and animal testing on rabbits has played a crucial role in advancing this therapy. The objective of this manuscript aims to review the literature on the use of lagomorphs in cell therapy studies. The Pubmed and ScienceDirect databases were used, with the descriptors: Cell therapy and experimentation in rabbits; rabbits and cell therapy. After an initial retrieval of 1799 articles, those that did not specifically address the use of rabbits in cell therapy or were unrelated to the scope of

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this review were excluded. This resulted in a final selection of 21 articles. The present work presents a broad and distinct view of cell therapy and its different applicability, presenting a promising framework for animal experimentation in rabbits, and the advantages of using this animal model.

Keywords: Autologous therapy; allogeneic therapy; debilitating conditions; mesenchymal stem cells; tissue engineering.

1. INTRODUCTION

Cell therapy, a cornerstone of regenerative medicine, has revolutionized the treatment of numerous debilitating conditions by harnessing the body's ability to heal itself through the use of living cells [1]. Animal experimentation, particularly in rabbits, has been fundamental to the advancement of research in cell therapy due to their physiological and biological similarities to humans, especially in the cardiovascular and musculoskeletal systems [2]. Notable examples include its application in detrusor hypocontractility [3], the reduction of the inflammatory process associated with osteoarthritis [4], modulation of tissue repair in injured vocal folds [5], in tissue engineering for blood vessels [6], in the treatment of neurological sequelae resulting from distemper [7], in rare genetic disorders [8], in ligament reconstruction [9], in the treatment of spinal cord injuries [10], and in the management of multiple myeloma [11]. These interventions have the potential to significantly improve patients' quality of life, as damaged or dysfunctional cells can be replaced by healthy ones, thereby restoring the function of affected tissues and organs.

Additionally, cell therapy can be classified into two types based on the origin of the cells: autologous, when obtained from the patient themselves, and allogenic, when obtained from a donor [12]. Autologous cell therapy represents a remarkable advancement in the field of regenerative medicine, with the primary advantage of lesser due to immune rejection, as the implanted cells are genetically identical to those of the recipient. In contrast, allogenic therapy employs cells derived from a donor genetically distinct from the recipient, offering substantial advantages, particularly in situations where autologous cells are unfeasible for therapeutic purposes due to pathologies or genetic defects [13]. This procedure has paved the way for the development of treatments for various hematological and immunological diseases. However, allogenic therapy introduces an increased risk of immune rejection and complications, such as graft-versus-host disease (GVHD) [14].

Moreover, animal experimentation has demonstrated extremely promising potential and is continuously expanding. Investigations focused on rabbits have shown significant potential in regenerative medicine, as these animals exhibit physiological and biological characteristics that are similar to those of humans, thereby rendering them relevant as experimental models for tissue regeneration research [15]. This therapy represents an emerging frontier in biomedical research, with significant implications for regenerative medicine, addressing challenges such as the validity of data obtained when compared to other animals. Thus, rabbits emerge as an ideal model for investigating cell therapies, facilitating advancements in the understanding and application of these techniques in the treatment of various pathologies [16]. Although these animal models provide valuable insights for research, significant challenges remain in translating these findings into clinical practice.

The European rabbit (*Oryctolagus cuniculus*) has been widely used in studies of human pathologies, such as cancer, cardiovascular diseases, diabetes, and neurodegenerative diseases, and has served as a suitable experimental model for the treatment of various diseases since early 1900s, due to its similarity to humans in brain and neuronal development processes. Moreover, the cost of breeding and maintaining this animal is not high, which facilitates research development. In light of the advances and challenges in cell therapy, this manuscript aims to review the literature on the influence and effectiveness of cell based therapy in rabbits.

Additionally, the results of this review will contribute to a better understanding of the potential applications of cell therapy in clinical settings.

2. METHODOLOGY

This work is a literature review, which used PubMed and Science Direct as databases with the following descriptors: Cell therapy and experimentation in rabbits; rabbits and cell therapy. These descriptors were used in the databases to obtain a more precise number of articles for analysis. A total of 1,659 articles were found in the PubMed database and 140 articles in the Science Direct database. Inclusion criteria included articles in English and Portuguese published between 2019 and 2024. The time frame of 2019–2024 was selected to focus on the most current advancements in cell therapy, reflecting the latest experimental models and therapeutic approaches in regenerative medicine. The selection was based on the reading of titles, abstracts, and introductions; additionally, only articles involved rabbits were included. Fig. 1 shows the number of articles included and excluded. The criteria for selecting scientific records were applied by two independent authors, and discrepancies were resolved by consensus between them. The screening of articles was based on reading titles, abstracts, and introductions, and those classified as clinical trials, preclinical trials, and systematic reviews mentioning the use of rabbits in cell therapy were included. It is important to emphasize that the full-text articles were meticulously analyzed regarding relevance, quality, and study design, ensuring that they met the criteria of being either preclinical or clinical trials specifically related to cell therapy in rabbits.

3. RESULTS AND DISCUSSION

The advances in cell therapy in this species have sparked growing interest, not only due to its direct applicability in the treatment of debilitating conditions, but also for its contribution to the understanding of the cellular mechanisms underlying tissue repair. With the potential to significantly impact regenerative medicine, this line of research continues to explore new clinical and scientific frontiers, aiming to improve patients' quality of life by replacing dysfunctional cells with healthy ones, thus restoring the function of affected tissues [4].

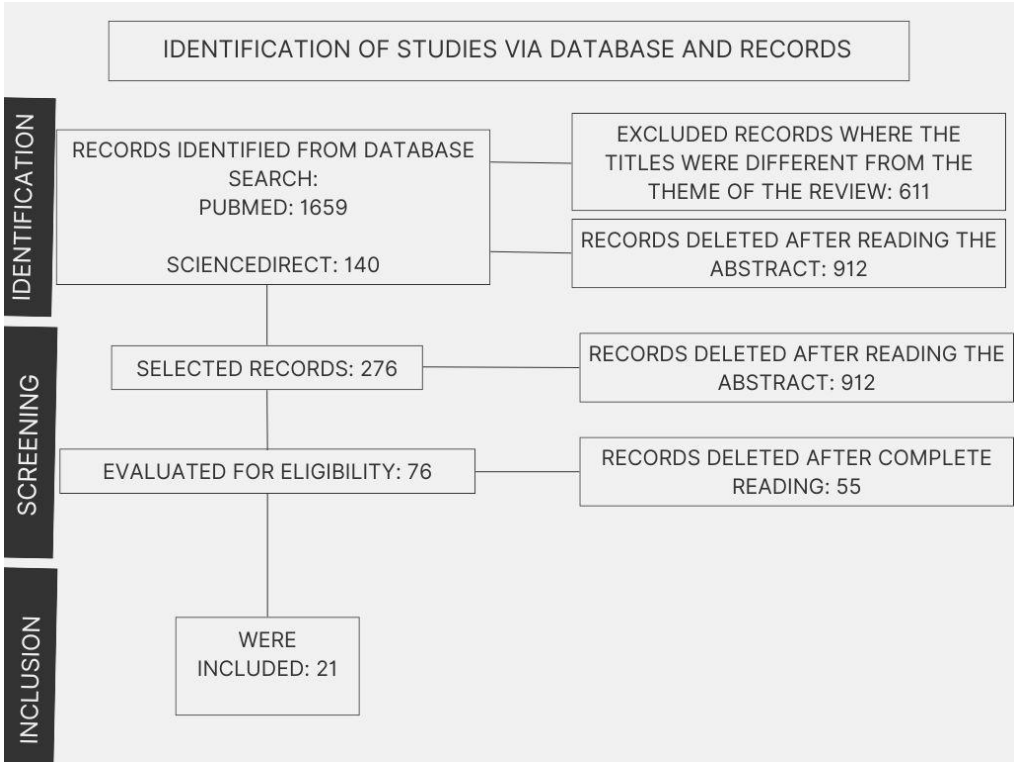

Fig. 1. Flowchart demonstrating the classification of included and excluded articles during the review: Authors, 2024

A study conducted by Zolocinska [17] in 2020 compared animal models for research with adipose tissue-derived mesenchymal stem cells. The investigation indicated that the adipose tissue mass of rabbits was significantly greater than that collected from rats. In addition to this advantage, rabbits are larger, which allows for more complex surgeries. In summary, they present low maintenance costs, ease of handling and housing, allowing for a greater number of surgical procedures, especially in orthopedic, cardiovascular, and neurological experiments. Recent research has shown a promising future in regenerative and based therapy involving mesenchymal stem cells (MSCs) and cellular engineering, including tissue-engineered blood vessels (TEBVs). Rodrigues [6] improved TEBV techniques by differentiating adipose tissue-derived mesenchymal stem cells into endothelium and smooth muscle in both an animal model and *in vitro*, demonstrating good cell colonization and differentiation, as confirmed by morphological characterization. This points to a promising future for the use of TEBV in *in vivo* models. In the continued study of stem cells, Khanmohammadi [18] indicated that the use of menstrual blood-derived stem cells (MenSCs) encapsulated in fibrin glue (FG) in the healing of osteochondral defects shows adequate *in vivo* regenerative capacity, suggesting they could be used in future clinical trial applications.

Liu [4], in their study, demonstrated that piezoelectric stimulation induced by exercise could promote chondrogenesis and cartilage regeneration in cases of osteoarthritis. The authors suggest that this treatment approach may be potentially applicable to the regeneration of other injured tissues.

De Melo [10] reported preliminary results indicating that the developed orthosis significantly improves patients' mobility and autonomy, facilitating activities such as feeding and personal hygiene. This advancement is crucial, as the ability to perform such activities independently positively impacts the quality of life and self-esteem of individuals with spinal cord injuries. Despite the promising findings, the study identifies certain limitations, such as the small sample size and the need for an extended evaluation period to validate the long-term efficacy of the orthosis. Furthermore, Coelho [3] conducted a study demonstrating that the administration of mesenchymal stem cells (MSCs) in patients with detrusor underactivity resulted in a significant improvement in the contractile function of the detrusor muscle. However, despite the promising results, the study has some limitations that should be considered. Firstly, the sample size was relatively small, which may limit the generalizability of the findings. Future studies with larger samples are needed to validate these results. Secondly, the follow-up period for the patients was relatively short. Long-term evaluations are essential to determine the durability of the therapeutic effects of MSCs and to monitor for potential late adverse effects. MSCs may reduce neurological sequelae resulting from distemper. Villalba-Briones [7] addressed the host-parasite relationship and how stem cells improved the immune system of rabbits, which responded positively to treatment.

Additionally, Barbosa [11] introduced innovative CAR-T therapy for the treatment of multiple myeloma as a personalized cell therapy for cancer in rabbits. However, challenges such as associated toxicities and the need to improve CAR-T production and administration remain significant. Future research should explore ethical therapeutic combinations and resistance mechanisms to expand the clinical use in humans effectively.

Mesenchymal stromal cells (MSCs) have gained attention due to their immunomodulatory effects, evidenced both *in vitro* and *in vivo*. Nagubothu [5] aimed to determine whether local injection of these cells could modulate the inflammatory response. The study demonstrated that MSCs were able to positively modulate the early wound healing response by resolving the inflammatory phase and promoting tissue repair. However, a low level of injected MSCs persisted in the VF tissue.

Additionally, a study evaluated the effect of hyperbaric oxygen therapy (HBOT) on graft healing after anterior cruciate ligament (ACL) reconstruction, suggesting that the adjuvant use of HBOT may improve graft maturity and integration, along with knee stability, providing better healing outcomes after ACL reconstruction [9]. However, the study presented limitations regarding the ligamentization phase, which is a more prolonged process, making it impossible to assess late events related to the healing process. Furthermore, specific biological mechanisms related to the effects of HBOT on graft healing after ACL reconstruction were not explored. Nevertheless, the study provides relevant insights into the adjuvant use of hyperbaric oxygen in ACL reconstruction, showing therapeutic potential.

In the context of rare genetic diseases, gene editing techniques such as CRISPR-Cas9 represent a significant breakthrough. However, technical challenges persist, such as efficient delivery and safety, as well as ethical and accessibility concerns, which need to be addressed. The implementation of strict regulations and international collaboration are essential to ensure the safety and efficacy of these therapies. As highlighted by Azevedo [8], it is imperative to increase investments in technology to enable the application of these therapies in rabbits.

Rabbit models are essential for regenerative medicine research, especially in areas such as tissue engineering and organ regeneration [6]. They allow us to assess the biocompatibility of new biomaterials, ensuring their safety and efficacy before they are tested in humans. In addition, studies on wound healing in rabbits show promising results that can be quickly applied to clinical treatments. With regard to cartilage and bone regeneration, these recovery models provide excellent insights that could help patients with arthritis, for example [4,9]. Stem cell research in rabbits also helps us better understand the efficacy of these therapies before we proceed to clinical trials [18,3,6].

4. CONCLUSION

The present study offers a promising perspective on animal experimentation in rabbits, particularly highlighting its reduced applicability in terms of invasiveness, simplicity, and low cost, as evidenced by the authors. The reviewed articles and theses provided a comprehensive and diverse analysis of cell therapy and its various applications. Most studies demonstrated significant efficacy when rabbits were subjected to cell therapies, whether autologous or allogeneic. Therefore, further investigations are needed to elucidate scientific advancements in the treatment and management of diseases made possible through the ethical and safe use of these animal models.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology

Details of the AI usage are given below:

1. The generative AI technology used was ChatGPT, which is based on large language models (LLMs) developed by OpenAI. The applied version is the most recent in the series, belonging to the GPT-4 (Generative Pre-trained Transformer 4) family. All of the generative artificial intelligence behind ChatGPT was developed and trained by OpenAI.

2. The technology was used strictly to assist in the translation of the manuscript from Brazilian Portuguese to English for the purpose of publication in the current journal. After the translation, the text was reviewed again by team members to identify and correct any potential translation errors.

3. The input prompt used was: "Translate the text from Portuguese to English, without altering the meaning of the sentences."

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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