https://doi.org/10.1038/s44222-023-00064-2

Stem cell-derived exosome versus stem cell therapy

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Stem cell therapies are being explored for the treatment of various diseases, including haematological disease, immune disease, neurodegenerative disease, and tissue injuries. Alternatively, stem cell-derived exosomes may provide similar clinical benefits without the biosafety concerns associated with the transplantation of living cells. However, large-scale manufacturing and purification, batch-to-batch variation, and analysis of the complex cargos of exosomes will need to be addressed to enable their clinical translation.

Stem cell therapy

Stem cells, including embryonic stem (ES) cells, induced pluripotent stem (iPS) cells and adult stem cells, have the ability to self-renew and give rise to differentiated cells. Their potential to differentiate into cells of different tissues makes them particularly interesting for applications in regenerative medicine — for example, ES cell-derived cardiomyocyte transplantation is promising for myocardium regeneration. However, since the first therapy using stem cells has been developed in 1957, only few stem cell-based therapies have entered the clinic. According to data from the US National Institutes of Health (NIH), thousands of stem cell therapy-related clinical trials have been registered. At present, the only US Food and Drug Administration (FDA)-approved stem cell therapy is haematopoietic progenitor cell (HPC) transplantation for haematopoietic and immunological reconstitution in patients with disorders that affect the haematopoietic system. In addition, a few stem cell products derived from mesenchymal stem cells or tissue-specific stem cells have been approved for clinical use, such as Prochymal, approved in Canada for the treatment of acute graft-versus-host disease, and Holoclar, approved in Europe to repair injured cornea[1]. The lack of clinical translation may be due to some unavoidable drawbacks with regards to stem cell therapy. The large diameter of stem cells may lead to their accumulation in the lung after intravenous injection and thus, infusion toxicity. Furthermore, allogeneic stem cells carry antigens that may elicit an immune response. Moreover, stem cell injection may result in oncological complications, including haematological and non-haematological malignancies (teratoma and non-teratoma tumours, respectively)[2]. Some of the observed beneficial effects of stem cells may be partly due to their paracrine action rather than the long-term engraftment of transplanted stem cells[3].

Stem cell-derived exosomes

Stem cells, just like every other cell in the human body, release exosomes to communicate with each other. Exosomes are membrane-bound vesicles with a diameter of about 40–160 nm, which are released from cells by an endosomal pathway. The diverse components of exosomes in the form of nucleic acids, proteins, lipids and metabolites, not only reflect their cellular origin, but also endow them with potential therapeutic functions, similar to their donor cells, which may be exploited for cell-free therapy[4]. Therefore, therapeutic applications of stem cell-derived exosomes have been preclinically explored.

At least 150 clinical trials have been registered in ClinicalTrials.gov investigating exosome-based therapies for a variety of diseases, including respiratory diseases, infectious diseases, and cancer (using 'exosome therapy' as a keyword search on www.clinicaltrials.gov). Among those trials, 31 apply exosomes derived from stem cells, primarily mesenchymal stem cells from different tissues, which are tested as an alternative to mesenchymal stem cell therapy. These pre-clinical and clinical investigations suggest that exosomes released by stem cells may partially recapitulate the therapeutic effects of their donor cells without the drawbacks inherent to stem cell therapy (Table 1).

In contrast to stem cells, exosomes cannot self-replicate, eliminating concerns about potential tumour formation after stem cell transplantation. Exosomes are also stable enough for long-term frozen storage and storage at room temperature after lyophilization. Their small size further allows sterilization by filtration[5]. In addition, exosomes can be administered by several routes; for example, nebulized or lyophilized lung stem cell-derived exosomes can be administrated by inhalation to treat lung diseases[5,6]. Moreover, their hydrophilic lumen and phospholipid bilayer containing membrane proteins can be engineered and modified to display molecules or for drug loading; lung stem cell-derived exosomes were recently decorated with the receptor-binding domain of recombinant SARS-CoV-2 as an inhalable COVID-19 vaccine[7]. In 2020, the first clinical trial (NCT04592484) of an engineered exosome therapy (exoSTING[8]) was launched by Codiak Biosciences for the treatment of multiple solid tumours, indicating that engineering exosomes may be a future direction for therapeutic applications of stem cell-derived exosomes.

Clinical translation of stem cell-derived exosomes

The market prospects for stem cell and exosome therapy are promising. According to global market reports, the global stem cell market is projected to reach US$31.6 billion by 2030, and the global exosome market is anticipated to reach 1.03 billion by 2030. The NIH issued the National Institutes of Health Guidelines for Human Stem Cell Research in 2009, which mainly includes regulatory standards and ethical issues with regards to human ES and iPS cells. In addition, some international associations, including the International Society for Stem

Table 1 | Exosome versus stem cell therapy

Therapy	Number of clinical trials	Advantages	Disadvantages
Exosome therapy	158 studies	Small size Minimal risk of immune response and tumour formation Stable for long-term storage and transportation No ethical issues Multiple delivery routes Can be engineered to deliver drug cargos	Difficult to upscale manufacturing and purification Batch-to-batch variation No compatible GMP facility No established regulations and standards
Stem cell therapy	7,018 studies	Easy to isolate and expand at a large scale Multilineage differentiation potential Long-term engraftment Extensive pre-clinical and clinical study results Well established FDA guidelines	Oncological complications Fusion toxicity Immunogenicity Harsh storage and transportation conditions Ethical issues

Data obtained from ClinicalTrials.gov using 'exosome therapy' and 'stem cell therapy' as keywords, as of 28 February 2023.

Cell Research and the International Society for Extracellular Vesicles, have proposed guidelines to address divisive issues in stem cell and exosome research[9,10]. These guidelines provide resources for stem cell and exosome research; however, a global consensus on their clinical translation and manufacturing remains elusive. Of note, the FDA had to issue several public safety notifications on stem cell and exosome products. Therefore, comprehensive standards and regulations for stem cell and exosome therapy are needed. Encouragingly, the first stem cell-related international standard (ISO 24603) was published in August 2022, which may also be referred to for exosome research to standardize upstream steps of exosome production for exosome therapy.

The clinical translation of stem cell and exosome therapies relies on the large-scale manufacturing of stem cells and exosomes in good manufacturing practice (GMP) facilities. The development of HPC transplantation and chimeric antigen receptor (CAR)-T cells facilitated the establishment of GMP facilities for cell therapy products. However, GMP facilities for the generation, isolation and quality control of exosomes remain limited. Flask-based culture systems and ultracentrifugation methods that are used for the laboratory-scale isolation of exosomes are slow, laborious, and not compatible with large-scale manufacturing of GMP-grade exosomes. Alternatively, bioreactor systems and hollow-fibre membranes are being explored for cell culture and filtration, respectively, for the large-scale production of exosomes. Moreover, thorough quality control is needed to minimize batch-to-batch variance of exosomes. Thus, approaches are required that can accurately and reproducibly characterize exosomes, including concentration, particle size, zeta potential and exosomal markers. Instruments, such as ZetaView, Amnis, ImageStream and ONI Nanoimager, enable the characterization of the physicochemical properties of exosomes and may replace conventional approaches such as nanoparticle-tracking analysis, dynamic light scattering, western blotting and flow cytometry. Exosome quality control should also consider the heterogeneity of exosomes, which is affected by the status of donor cells and isolation methods. Therefore, standardized operating procedures are required, which could be based on the manufacturing of adeno-associated viruses, which is similar to the production and purification of exosomes. A streamlined closed operation system should be established to integrate large-scale manufacturing of exosomes with a fileable quality control testing program. Such a digital and automated system could further reduce the costs of exosome products by reducing manual operation and by implementing batch uniformity.

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Published online: 12 April 2023

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Acknowledgements

This work was supported by grants from the National Institutes of Health and the American Heart Association.

Author contributions

K.Z. researched data and wrote the article. K.C. revised the manuscript before submission. All authors made substantial contributions to discussion of content.

Competing interests

K.C. is a co-founder and equity holder of Xsome Biotech Inc. Xsome Biotech Inc. is a licensee of the intellectual property covering exosome delivery technologies and antiviral therapies from North Carolina State University. The other author declares no competing interests.

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