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Mini Review

Therapeutic Implications of Stem Cell Secretome

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Abstract

The stem cell secretome is a collective mixture of soluble and insoluble factors released by stem cells during paracrine communication and/or autocrine signaling. In addition to intracellular communication, these paracrine factors play an integral role in tissue development and generation, acting as the primary driving force in the regenerative properties of stem cells. Despite such great potential of stem cell secretome in therapeutic applications, the lack of secretome-based treatments available for the public at the time of writing is odd and puzzling. Hence, this review aims to provide insights into recent advancements in understanding the stem cell secretome, as well as discuss future possibilities and current limitations that must be overcome for the proper development of secretome-based therapies. Through utilizing the MEDLINE database from the National Library of Medicine® (NLM), we found that while there is much evidence of the therapeutic effects of secretome-based therapy, flaws involving regulations and standardization hinder it from revolutionizing regenerative medicine at present. It is cardinal to emphasize that while secretome-based therapy may be the solution for many untreatable conditions, much research is still required before it is approved for clinical practice.

More Information

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Abbreviations: AFSC: Amniotic Fluid Stem Cell; AFSC-S: Amniotic Fluid Stem Cell Secretome; cfAF: Cell-free Amniotic Fluid; EVs: Extracellular Vesicles; FDA: Food and Drug Administration; GMP: Good Manufacturing Practice; HSCT: Hematopoietic Stem Cell Transplantation; IND: Investigational New Drug; MSC: Mesenchymal Stem Cell

Introduction

Stem cells are undifferentiated cells with unique abilities to self-renew or differentiate into various cell lineages. In recent decades, stem cells have been extensively studied for their therapeutic effects and clinical trials show promising prospects in revolutionizing medical treatments [1]. For instance, Hematopoietic Stem Cell Transplantation (HSCT) is a widely used treatment for diseases like leukemia, lymphoma, and immune deficiency syndromes due to its ability to augment bone marrow function [2]. Studies investigating the use of stem cells in therapy have also demonstrated the relevance and diversity of stem cells in treatments, ranging from wound healing to neurological disorders [3]. Despite that, HSCT remains the only U.S. Food and Drug Administration (FDA) approved stem cell therapy for public use [4].

The FDA's strict viewpoint stems from safety and efficacy concerns surrounding the use of unapproved stem cell therapies. Existing stem cell therapy studies find it a great challenge to meet the requirements for regulatory approval due to the incomplete understanding of available pathways and mechanisms of stem cells. Some of the risks associated with stem cell transplants (whether autologous or allogenic) reported include immune rejection and tumorigenicity [5]. These drawbacks pose significant challenges that need to be addressed for novel treatments to be safe and readily available clinically.

In search of alternatives, the stem cell secretome presented itself as a viable and promising cell-free option. The cell secretome is a collective mixture of soluble factors (cytokines, growth factors and chemokines) and insoluble factors (extracellular vesicles, exosomes) secreted or otherwise released by the cells for paracrine communication and autocrine signaling (Figure 1). Typically collected in the form of a conditioned medium, the factors that are found in the stem cell secretome were demonstrated to be the primary driving force in the regenerative properties of stem cells,

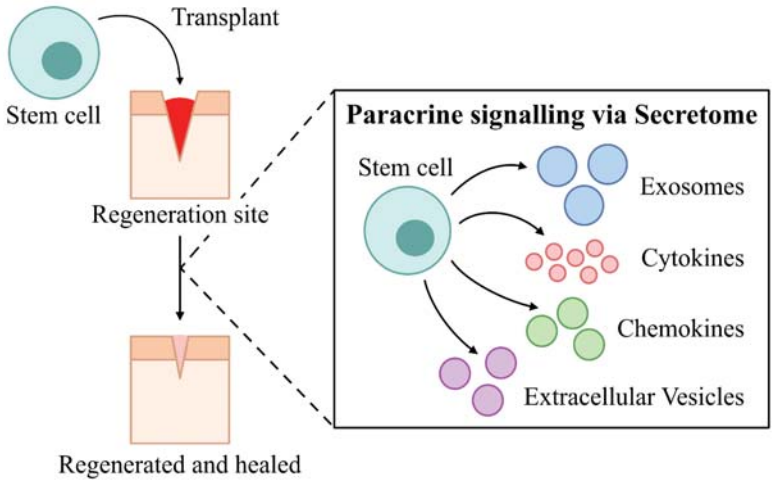

Figure 1: Schematic of stem cell secretome released by stem cells after transplantation, allowing regeneration of surrounding tissue at the stem cell transplantation site through paracrine signaling. Stem cell secretome consists of numerous components, including (but not limited to) exosomes, cytokines, growth factors, and extracellular vesicles this schematic was made with Affinity Designer 2.

rather than the differentiation of transplanted stem cells [6]. For instance, Extracellular Vesicles (EVs) and exosomes which are found in cell secretomes have demonstrated their therapeutic role in areas such as neuroprotection and immunomodulation [7].

The potential clinical applications of the stem cell secretome were elucidated by multiple studies investigating its therapeutic properties. In particular, the Mesenchymal Stem Cell (MSC) secretome is being studied extensively due to the abundance of MSC and its relative ease of collection. Preliminary studies have reported MSC paracrine effects aiding in accelerated functional recovery in myocardial infarctions and the regeneration of chronic non-healing wounds [8-10]. The concept of secretome-based therapy is a feasible and safe therapeutic approach if developed correctly, with several clinical trials reporting no adverse effects in patients [3].

As more studies are conducted, researchers are looking to further understand pathways and mechanisms involved in the regenerative abilities of stem cell secretomes. Considerations such as dosage, formulation, efficacy, and biosafety are unknowns that require intense optimization for stem cell secretomes to be used effectively in clinical practice. Thus, this review aims to provide insights into recent advancements in understanding stem cell secretome and the future of secretome-based treatment will be discussed, including the distinct advantages and certain limitations presented by stem cell secretome.

Materials and methods

An electronic literature review was done utilizing the MEDLINE database from the National Library of Medicine® (NLM). MEDLINE is a premier bibliographic database containing more than 31 million references to journal articles in life sciences with a concentration on biomedicine. Studies of interest were searched with the following keyword combinations and Boolean operators: “stem cell” AND “secretome”; “stem cell” AND “conditioned media”; “stem cell” AND “extracellular vesicle”; “stem cell secretome” AND “clinical therapy”; “stem cell” AND “amniotic fluid”; “amniotic fluid” AND “clinical therapy”. Papers reviewed were limited to within 5 years of the date of the search, which was performed in February 2024.

Discussion

Recent advancements

Cell-free Amniotic Fluid-derived secretome (cfAF) is one of the current therapeutic options proposed for several diseases [11]. Using perinatal sources, Zeo Scientifics is developing a biological agent known as Zofin™. This acellular biologic contains over 300 naturally occurring cytokines, chemokines, growth factors, and exosomes, many of which play a role in anti-inflammation and tissue regeneration [12]. Zofin™ is currently undergoing Phase I/II clinical trials with FDA-approved Investigational New Drug (IND) applications for the treatment of COVID-19, and preliminary results currently show no adverse side effects while improving the symptoms of severe COVID-19 infections [12,13]. With such considerable advancements in the field, studies are investigating ways to expand on these findings and improve their practicality and accessibility.

A study reported that several bioactive factors of the Amniotic Fluid Stem Cell (AFSC) Secretome (AFSC-S) increased in concentration when generated under hypoxic conditions, highlighting the possibility of tailoring bioactive factor composition in the secretome for more effective and consistent therapeutic properties. The study also approached secretome collection from an *in vitro* angle, through expanding AFSC isolated from prenatal sources [14].

Although prenatal sources remain necessary for harvesting AFSC, this method presents a more sustainable and scalable alternative to existing practices.

While studies of secretome-based treatments are still in the early stages, these recent advancements demonstrate that secretome-based treatments could be viable in the future. Findings on the effects of varying secretome composition highlight the prospect that secretome-based treatments could be tailored to target various diseases, providing a more nuanced approach to developing medical treatments.

The future of stem cell secretome-based therapy

The regenerative potential of stem cell secretome offers distinct advantages over stem cell transplants. Firstly, the therapeutic use of secretome overcomes concerns about stem cell survival and degradation post-transplantation. The cell-free nature of the secretome greatly reduces the risk of immunogenicity and tumorigenicity compared to stem cell transplants. Secretome production has also been shown as an efficient and modulatory alternative for clinical applications by addressing issues such as invasive cell collection procedures, storage, and transportation [3,15,16]. Therefore, effectively harnessing the stem cell secretome is a viable alternative for discovering novel therapies without the risks associated with stem cell transplantation.

However, despite considerable advancements in the field, there are currently no FDA-approved therapies for the public that utilize a secretome-based approach. Similar to stem cell therapies, unknowns surrounding its mechanism of action lead to a lack of standardization on production and formulation techniques, which remain a key hurdle to overcome in the research phase. Formulation standards are heavily influenced by batch-to-batch variation, as minute variations in cell culture conditions could lead to differences in the cell secretory profile [16]. This implies that the cultivation of stem cells must adhere to strictly defined and stringent Good Manufacturing Practice (GMP) conditions to ensure that their secretome is reproducible, scalable, and viable for clinical use. In addition, standardization of dosage levels is cardinal in ensuring safety and efficacy. A study reported that treatment with secretome generated from earlier cell culture passages and applied in lower dosages per body weight demonstrated regenerative properties. In contrast, secretome generated from late cell culture passages and applied in high dosages per body weight showed detrimental effects, emphasizing the need to establish the optimal therapeutic window for these secretome-based treatments [17]. It is imperative to take a facilitative approach to data collection for proper formulation and production standardization before being approved for clinical practice [6].

It is also believed and stated by the FDA that while breakthroughs of stem cell products hold great potential, there are no scientific reasons to justify any different regulations on the efficacy and safety of stem cell products from other biological products. All products should still be tested according to the proper drug development pathways which involve systematic and rigorous structure. It should be facilitated *in vitro*, *in vivo* and in clinical research trials to assemble the necessary clinical data for licensure of any clinical therapies involving the stem cell secretome.

Conclusion

In conclusion, advancements and understanding of the stem cell secretome, such as with AFSC-S, show that research is actively moving towards increasing knowledge in the mechanisms and formulations of stem cell secretome, both *in vitro* and *in vivo*. However, in their current state, secretome-based treatments will still require much development and standardization. When clear and indisputable regulations have been optimized for consistent, safe, and effective incorporation of stem cell secretome in clinical applications, the field of regenerative medicine will undoubtedly take a revolutionary step forward, providing novel treatments for the general population.

Author contributions

JH and CC are the principal authors and were responsible for the first draft of the review. JH and CC were also responsible for the concept of the review. JH, CC, MK, and AJR were responsible for revising the article. AJR provided the direction of the review. All authors read and approved the final manuscript.

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