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Mini Review

Stem Cell- and Stem Cell-Free-Based Therapies: Pros and Cons

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Abstract

The efficiency of stem cell (SC)-based therapies has been proven in numerous animal and human studies. Along with the differentiation into several lineages, it is quite evident that SCs convey significant therapeutic effects in a paracrine manner via releasing various nano-sized extracellular vesicles (EVs) containing cytokines and bioactive factors. Notably, recent trials have stated the lack of stability and durability of the transplanted SCs at the site of injury for long periods, leading to the restrictions of SC in regenerative outcomes. Thus, EVs especially exosomes (Exos) gained much attention for therapeutic purposes and delivery purposes to the injury site. In contrast to whole-SC-based therapies, Exos can be used with fewer side effects. However, it should not be forgotten that both whole-SC- and cell-free-based options possess inherent pros and cons that necessitate being carefully evaluated before application in the clinical setting. Here, the effectiveness and limitations associated with whole-SC- and SC-free-based therapies in the clinical setting are briefly discussed.

Keywords: stem cell transplantation, cell-free system, exosomes, regenerative medicine, immune evasion

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1. Introduction

The need to explore and admit novel, developed, and alternative treatments for various pathological conditions has persuaded scientists and clinicians to focus on new therapeutic modalities [1]. Over the past two decades, researchers have concentrated on developing and improving cell-based therapies using varied stem cell (SC) types from different tissues. It is believed that SCs have unique properties such as self-renewability, and commitment into target cell lineages while these cells can produce a large number of their copies. Upon injection into the target sites, SCs can relatively control the activity of allo-reactive immune cells [1–3]. The aim of this review is to critically assess

the advantages and limitations of stem cell-based therapies and cell-free approaches, particularly focusing on exosomes, in the context of regenerative medicine, highlighting their potential clinical implications and challenges.

2. Challenges of Direct Stem Cell Transplantation and Microenvironment Influence

Recent decades have witnessed the emergence of data about the existence of other therapeutic tools in SCs after being transplanted *in vivo*. These cells can produce and release numerous signaling molecules and substances affecting the cell's dynamic growth [4– 6]. Despite the existence of magnificent therapeutic properties, the direct transplantation of SCs can face the risk of unwanted outcomes [7, 8]. For instance, most fractions of transplanted SCs disappeared a few weeks post-transplantation. This would be because of direct mechanical stress that can distort the membrane cell integrity. Besides, the activation and recall of resident immune-privileged cells in the periphery of the target organ can lead to the inactivation and elimination of transplanted SCs.

Compared to mature cell types, SCs are equipped with immune escaping mechanisms while differentiation into the target cells and the elevation of MHC molecules increase the possibility of SC rejection [9]. In terms of SC type and immuno-rejection properties, embryonic stem cells (ESCs) can likely provoke the activity of immune cells and the formation of anaplastic foci which restrict their application in clinical settings [10]. It should not be neglected that SCs can produce a large number of their offspring and undergo aberrant differentiation, resulting in the formation of anaplastic foci and even malfunctioned cells [11]. The introduction of SCs into the specific microenvironment can also influence their dynamic activity and regenerative outcomes. For instance, some studies have illustrated the tumorigenic and angiogenesis capacity of SCs in terms of tumor development and progression [12]. The balance between the cytokines and types of surrounding cells can educate SCs to behave differentially in tissues. For example, cancerous tissue-derived SCs tend to participate in cancer development, and healthy tissue-derived SCs show the property of suppressing cancer growth [13, 14]. Of course, there are few clinical trials related to the application of SCs in cancer patients, and thus any interpretation should be done carefully. SCs are usually trapped in the small-sized capillaries and vascular beds of hepatic and pulmonary tissues a few minutes after intravenous injection [15]. These features can increase the possibility of off-target effects and in some cases lead to the formation of intravascular thrombi and ischemic changes [16]. Allogeneic SCs are captured and cleared from the systemic circulation via

the activity of splenic and hepatic immune cells about 7–10 days post-administration [17]. Along with these statements, more standardized cell-based approaches with the minimum side effects are mandatory in clinical settings. This short review provides a brief discussion of the advantages and disadvantages of using whole-SC- and SC-free-based therapies in regenerative medicine (Figure **1**).

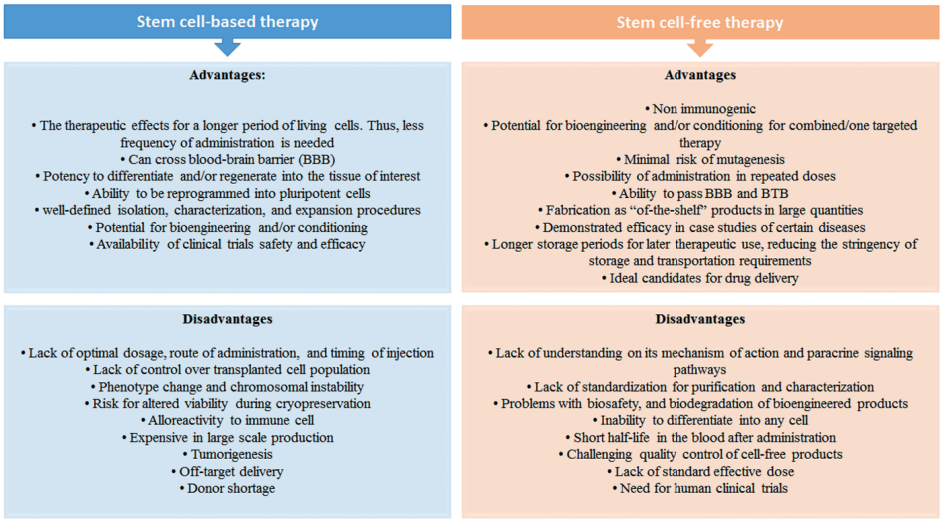

Figure 1: Advantages and disadvantages of cell-based and cell-free therapies [2, 3, 14, 18 – 21].

3. Cell-Free Therapies and Exosomes (Exos)

In recent years, wide ranges of evidence showed that SC-derived secretomes contain heterogeneous extracellular vesicles (EVs), Exos, and microvesicles, with various growth factors, cytokines, lipids, nucleotides, and proteins to alleviate the pathological conditions and alter the healing process [22–24]. To this end, cell-free therapies have become a novel approach in regenerative medicine [2–4, 18, 24–26]. Among different EV types, Exos have received the most attention in the treatment and repair of damaged cells and tissues. Exos use several uptake mechanisms to enter the host cells and can easily pass normal and pathological barriers such as the Blood-Brain Barrier (BBB), and the blood tumor barrier (BTB). Regarding the wide biodistribution rate, Exos can transfer bioactive metabolites between cells, and even interchange genetic information between the cells. From a molecular aspect, Exos mimic the proteomic and genomic status of parent SCs, making them an alternative therapeutic instead of SCs [14]. Drug-loading capacity is one of the most fascinating properties of Exos in regenerative medicine compared to formulated synthetic nanoparticles with comparable sizes such as liposomes [27, 28]. Using various internalization mechanisms, ligand-based endocytosis, direct fusion,

macropinocytosis, etc. facilitates the entry of cargo-loaded Exos into the target cells such as cancer cells [14, 22–24]. It is postulated that SC EVs are relatively safe as they are unable to replicate and differentiate unintendedly after administration in the body [14]. Despite the superiority of EV application compared to whole SC transplantation, there are several challenges yet to be addressed.

The lack of standard purification and enrichment protocol, quantification, and coordination, makes it difficult to evaluate the efficiency of Exos and other EVs in existing studies. Measurement of EV concentration, which is mostly based on EV total protein concentration, is not similar within parallel studies, whereas the particle number per milliliter is not practiced as an accurate method of EV quantification [14, 21, 29]. The non-target properties of transplanted EVs can lead to less therapeutic outcomes. To increase the on-target properties of EVs and Exos, bioengineering tools have been developed in the past years. Even, to reduce the side effects of chemo/therapeutics Exos are suitable bioshuttles in cancer patients [20, 23]. Besides, therapeutic purposes, the engineering tools enable us to load specific cargo types such as non-coding RNAs, recombinant proteins, immunological modulators, and antisense oligonucleotides to regulate certain signaling pathways inside the cells for analytical and basic research [30, 31]. Recent results of preclinical application have indicated that Exos and other EV types are superior to SCs in terms of therapeutic purposes [32]. Despite these properties, the lack of standard isolation and characterization protocols, quality of isolated Exos, transfer of insidious infections, etc. limit the bulk application of Exos in clinical settings. It seems that complete preclinical pharmacodynamics and pharmacokinetic assessments should be performed before using EV-based therapies in the clinic.

4. Conclusion

In conclusion, the field of regenerative medicine has seen significant advancements in both stem cell-based and cell-free therapies. While stem cells offer promise, they come with challenges related to transplantation and immune rejection. Cell-free therapies, particularly using exosomes, have emerged as a promising alternative, offering unique properties and delivery mechanisms. However, standardization and quality control remain critical concerns. Future research should focus on addressing these challenges to harness the full potential of these therapies in clinical settings.

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