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Exosomes from adipose tissue-derived stem/stromal cells: A key to future regenerative medicine

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Abstract: Advances in regenerative medicine correlate strongly with progress in the use of adipose tissue-derived mesenchymal stem/stromal cells. The range of therapeutic indications has also expanded over recent years. Numerous recent studies have highlighted the primary importance of paracrine secretion by these cells. Though it is interesting to compare the different types of such secretions, we believe that exosomes (extra-cellular vesicles possessing the same properties as their source cells) will likely be the main key in tomorrow's cell therapy. Exosomes also have many advantages compared to the direct use of cells, making these particles a major target in fundamental and translational research.

Background

Mesenchymal stem/stromal cells (MSCs) have an extremely broad therapeutic potential and numerous applications have already emerged over the last decade. Correlated with improvements in extraction and isolation techniques for these cells, the clinical indications for their use have become more precise and more numerous. As adipose tissue constitutes a very important reservoir for MSCs (Zuk *et al.*, 2002) and allows an easy extraction of MSCs, adipose tissue-derived (AD)-MSCs are considered as the cell of choice for regenerative medicine (Laloze *et al.*, 2021). Indeed, they have similar anti-inflammatory properties than their counterparts from other tissues (such as bone marrow-derived- or umbilical cord-derived-MSCs) (Puissant *et al.*, 2005; Yoo *et al.*, 2009) making them the best candidate to treat diseases such as rheumatoid arthritis or systemic lupus erythematosus (Lipsky, 2001). They are also known for their high angiogenic potential which allows their use in various ischemic diseases such as diabetic foot (da Silva *et al.*, 2017; da Silva *et al.*, 2019).

In addition to their capacity to differentiate into mesodermal cells and their self-renewal, which are the main characteristics of these cells, they have paracrine properties which would be beneficial in wound healing, for example, but also in tissue bioengineering. Studies in the 2000s already showed the paracrine action of AD-MSCs which by secreting in particular interleukin-10 (IL-10), hepatocyte growth factor (HGF) and transforming growth factor (TGF)-beta inhibit the proliferation and secretion of pro-inflammatory cytokines by T lymphocytes (Puissant *et al.*, 2005; Wolf and Wolf, 2008; Yañez *et al.*, 2010) and induce a transition from the pro-inflammatory macrophage phenotype to an anti-inflammatory macrophage phenotype (Kim and Hematti, 2009; Manning *et al.*, 2015).

The paracrine functions of AD-MSCs are exerted in a variety of ways: cell to cell contact, secretion of soluble factors into the interstitium or secretion of extracellular vesicles. This last mechanism includes microvesicles (>150 nm) and exosomes (<150 nm) (Galipeau and Sensébé, 2018). The latter particles have gained more and more attention in translational research over recent years as they have many advantages for clinical use (Hu *et al.*, 2016).

Viewpoint

Exosomes are ubiquitous structures that reproduce most of the functional effects of the cells from which they are derived (Le Lay *et al.*, 2018) (Fig. 1). The main superiority of these particles is delivering higher levels of biomolecules leading to prolonged desired effect. In addition, exosomes show better homing to target tissue compared with parental cells. However, for optimal mass production of exosomes, it is necessary to have a reliable cell source (Mendt *et al.*, 2019). Due to the advantages described above, AD-MSCs currently represent the most promising cell source

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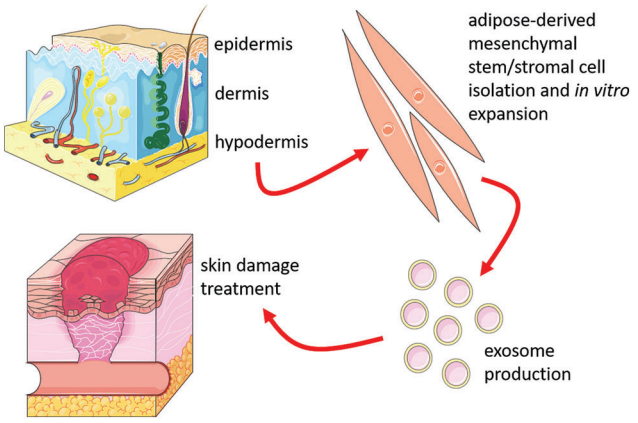

FIGURE 1. Exosomes obtained from adipose tissue-derived mesenchymal stem/stromal cells (AD-MSCs) for cutaneous wound treatment. AD-MSCs are easy to isolate and they produce significant quantities of exosomes, permitting their allogeneic use and the creation of exosome banks (realized by using in part Servier Medical ART, https://smart.servier.com/).

(Yeo *et al.*, 2013). Moreover, their small size avoids the problems of venous or arterial thrombosis (Cho *et al.*, 2018).

Vizoso *et al.* (2017) has also demonstrated the possibility of modifying exosomes before their use in order to obtain specific desired effects on targeted cells according to the required effect or therapy (Vizoso *et al.*, 2017). Additionally, it has been shown that the use of stem-cell-cultured conditioned media or exosomes was more economical and convenient than using cells since it avoids invasive cell transplantation procedures (Osugi *et al.*, 2012; Bian *et al.*, 2022). Thus, for all of the above-mentioned reasons, exosomes from AD-MSCs deserve the attention of researchers.

Moreover, numerous studies have already shown the efficacy of exosomes in pre-clinical models. Exosomes from AD-MSCs can stimulate cell migration, proliferation and collagen synthesis in fibroblasts, leading to accelerated wound healing *in vivo* (Hu *et al.*, 2016). Thus, there seem to be several mechanisms through which they could potentially enhance wound repair. They can also improve lipofilling by increasing angiogenesis and the rate of fat resorption. Indeed, they are similar to AD-MSCs in terms of fat resorption, up-regulating early inflammation and angiogenesis (Chen *et al.*, 2019). Recently, exosomes derived from hypoxia-treated AD-MSCs have shown great capacity to promote angiogenesis in lipofilling (Han *et al.*, 2019). Li *et al.* (2018) recently showed *in vitro* that exosomes secreted by AD-MSCs induced endothelial progenitor cell proliferation and the overexpression of nuclear factor erythroid 2 related factor (Nrf2), showing protective effects in a rat model of diabetic foot ulcer (Li *et al.*, 2018). They also promote increased collagen deposition in the late stage of wound healing in diabetic mice (Wang *et al.*, 2020).

Lastly, they have been shown to be therapeutically effective in animal disease models, for example by exhibiting immunosuppressive activity against atopic dermatitis (Cho *et al.*, 2018).

Discussion

Exosomes derived from AD-MSCs possess all the characteristics to be one of the main therapeutic tools in regenerative medicine in the coming years. We therefore encourage the scientific community to concentrate their efforts on this subject. Indeed, some important aspects remain to be investigated.

One of the advantages of AD-MSCs is their heterogeneity, coming from multiple sources. They thus have different characteristics depending on their region of origin or even depending on the tissue layer from which they are collected (Vijay *et al.*, 2020; Raajendiran *et al.*, 2019). It therefore seems obvious that exosomes will not all possess the same properties and advantages. Comparative studies would therefore allow targeting their use according to the pathology.

It will also be important to compare the efficacy of exosomes to soluble secreted factors. It is known that trophic factors produced by these stem cells can promote growth and viability of adjacent cells. Exosomes are also able to support angiogenesis by secreting factors such as vascular endothelial growth factor (VEGF) and angiopoietin 1 (Sacchetti *et al.*, 2007; Lin *et al.*, 2012; Watt *et al.*, 2013; Bortolotti *et al.*, 2015). C-X-C motif chemokine ligand 12 (CXCL12) also named stromal cell-derived factor 1 (SDF-1) is also secreted by MSCs and allows the recruitment of other immune cells and progenitors to the site of injury (Oswald *et al.*, 2004). The use of these soluble factors would be faster, easier and more cost effective; however, we believe that exosomes contain all the necessary materials to reproduce the same effects as the source cell.

The concept of tissue engineering in regenerative medicine integrates all the technologies using living cells or biomaterials (synthetic or natural), in order to reconstruct or regenerate human tissues and organs. MSC-based therapy combined with artificial scaffolds offers a promising strategy to promote wound healing or complete reconstruction of full-thickness skin. In this context, exosomes can be considered as a combined carrier and scaffold. Their natural biocompatibility and cell-targeting characteristics allow exosomes to transport drugs (Taverna *et al.*, 2017). As Vizoso and his colleagues have previously shown (Vizoso *et al.*, 2017), many recent studies have also revealed that some characteristics and contents of exosomes can be modified by other substances. Under particular culture conditions, exosomes can serve as stable and efficient vehicles to be loaded with specific proteins, lipids, and genetic material, including mRNAs, miRNAs, other small non-coding RNAs, and DNA (Bunggulawa *et al.*, 2018). Recently, Shafei *et al.* (2020) used exosomes loaded in alginate gel as a bioactive scaffold in an *in vivo* study. They showed that this active dressing technique could significantly promote wound healing, collagen synthesis and local angiogenesis (Shafei *et al.*, 2020).

Finally, despite the reservations expressed by some (Rezabakhsh *et al.*, 2021), the increasing number of clinical trials using exosomes (ClinicalTrials.gov) illustrates the safety and the potential efficacy of this type of treatment for treating diseases (Table 1).

Thus, we can conclude that exosomes represent a real challenge in basic research in order to benefit from their full potential. Numerous studies are still necessary to compare them to other actors but we see that exosomes are now a major key in regenerative medicine future.

TABLE 1

Clinical trials using exosomes from adipose tissue-derived stem/stromal cells

Clinical trials	Application
NCT04276987	Use for treat severe novel coronavirus pneumonia
NCT04270006	Treatment of periodontitis
NCT04544215	Treatment of pulmonary infection
NCT04388982	Treatment of Alzheimer's disease
NCT05259449	Diabetes
NCT03971955	Characterization of adult onset autoimmune diabetes
NCT04998058	Enhancement of bone formation in bone grafting

Availability of Data and Materials: No data are included within this viewpoint.

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