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Adipose Derived Regenerative (Stem) Cells (ADRCs): The Scientific Revolution that Never Happened

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Introduction

Mesodermal stem cells with a multi-germline potential that could be derived from adipose tissue were described by Zuk et al. [1]. Stem cells which have a self-renewal capacity, a long-term viability and a multi-lineage potential have a vast array of applications. The first source of stem cells were the embryonic cells but, the most frequently source currently used in clinical applications is the bone marrow stroma, from which Mesenchymal Stem Cells (MSCs) can be obtained. Many authors debate that with some noticeable limitations, MSCs are not an ideal alternative. The clinical uses of such cells not only cause general pain and morbidity, but also upon bone marrow stroma harvest, a low yield (cell number) is acquired. Moreover, Adipose Derived (stem) Cells (ADRCs) derive from the adipose tissue stroma is widely available and is very easily isolated through liposuction [2]. The stem cells obtained from liposuction are also more in number than the obtained by bone marrow aspiration [3].

Furthermore, ADRCs are capable of multiple mesodermal lineage differentiation with an ectodermal potential. They can differentiate into a vast array of tissues including bone (osteogenic differentiation), cartilage (chondrogenic differentiation), fat (lipogenic differentiation) and muscle (myogenic differentiation). They have also shown neurogenic differentiation potential [1].

One noteworthy advantage of ADRCs is that the number of stem cells in fat remains constant with ageing and does not decrease (unlike MSCs) (Healio, 2020). ADRCs have also some other distinctive properties compared to other multipotent stem cell alternatives. They can be found in abundant quantities, they can easily be harvested with minimally invasive procedures, they can differentiate into various lineages in a controllable and reproducible manner, they can be safely and effectively transplanted to both an autologous and allogeneic host and they can also be processed in line with the current Good Manufacturing Practice guidelines [4].

Research has proven that ADRCs can be useful in the treatment of a vast array of conditions: diabetes mellitus, urinary incontinence, glioblastoma, Huntington's disease, multiple sclerosis, stroke, Crohn's disease, rheumatoid arthritis, perianal fistula and colitis. Additionally, ADRCs can heavily initiate and/or accelerate tissue repair in bone, cartilage, muscle, fat, neural tissue, laryngeal tissue, cardiovascular tissue, pancreatic tissue, hepatic tissue and epithelial tissue [5]. The healing capabilities of ADRCs are attributed to their anti-inflammatory effect, their support of tissue remodeling over scar formation, apoptosis inhibition, tissue differentiation (bone, cartilage, ligament, tendon, etc.) and the recruitment of cells such as endothelial progenitor cells that are required for tissue growth, around the damaged tissues [2].

Low risk allogeneic treatments are possible thanks to the low immunogenicity of ADRCs. This is due to the low number of Major Histocompatibility Complex (MHC) molecules on the cell surface paired with the secretion of chemokines that alter the immune response to promote tolerance of the new tissue [2]. Unlike induced Pluripotent Stem Cells (iPSCs) which are associated with substantial ethical issues, ADRCs do demonstrate the risk of tumorigenesis. In addition, the autologous use of the cells does not bear the risk of Human Leukocyte Antigen (HLA) mismatch associated with allogeneic cells [6].

Considering that these cells have very high plasticity, being capable of switching phenotypes at a late stage of development with the ability to cross germ layers and revolutionizing the world of regenerative medicine with such healing properties, the therapies using ADRCs never entered the realm of everyday medicine [1]. In this editorial, the reasons behind such phenomenon will be thoroughly discussed.

Initially, we emphasize the fact that the ethical implications of iPSCs and embryonic stem cells

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may not apply to this specific discussion as ADRCs are classified as adult stem cells [7]. We therefore aim to discuss potential factors that have led to a lack of treatment availability/options utilizing ADRCs.

Obtaining ADRCs (Isolation)

One of the chief reasons ADRCs treatments are not widely available is the cost and regulatory burden required in obtaining ARDCs for clinical application. The most common method through which ADRCs are currently isolated is enzymatic digestion [8]. However, this form of isolation qualifies ADRCs to be included in the same extensive regulatory pathways as a "drug". Moreover, the automated enzymatic digestion methods are expensive and might impact on safety and efficacy, other than potentially causing stem cell differentiation. For instance, collagenase, an enzyme commonly used in many procedures in ADRCs isolation is shown to induce a local inflammatory reaction by activating the human complement system [9].

Various other isolation methods have been suggested in the literature as alternatives to enzymatic digestion/isolation. Fraser et al. [10] describe the use of ultrasound energy, however an extremely poor efficiency of cell extraction was observed. Mechanical isolation could be an ideal option even when compared to an enzymatic isolation that can lead twelve times higher mean cell yield [10]. Augmenting non-enzymatically isolated ADRCs with Platelet Rich Plasma (PRP) could overcome the increased need for adipose tissue extraction but more research is needed with regards to this procedure [6].

One other method of using these cells that is investigated by researchers is the indirect use of ADRCs which bypasses the need for isolation. The exosomes of ADRCs can be of huge benefit as a 'cell-free' therapy alternative of using these cells but further research is required in this field [11-13].

An issue that remains is the separation of ADRCs from differentiated cells. Many studies have attempted to characterize biological cell surface markers via flow cytometry analysis, but a unique single marker has yet to be identified [14,15]. What is imperative to bear in mind is that a final cell product must be characterized to ensure that a sufficient, safe and efficient product is being administered for treatment [16].

Therapeutical Costs and the Pharmaceutical Perspective

ADRC therapies that reduces the dependency on drugs or other medical appliances, have no incentive to the pharmaceutical industry and in terms of research for ADRC development, their own source of revenue will be hindered. Furthermore, the pharmaceutical companies might lose control of many drugs as ADRCs treatments would be developed in direct relationship with physicians not over the counter. Large pharmaceutical companies estimate around $5 billion per new medicine development, a business which is worth fighting for [17].

ADRCs will never be mass produced by pharmaceutical companies since they cannot be commercialized as they are intended for use at point of care, personalized with the patient's own DNA. Even though ADRCs derived from various donors would have similar morphologic, immunophenotypic, and differentiation properties, there may still be biologic and functional differences [16].

Furthermore, it is impossible to create ADRC "drugs" without risk of contamination. Lastly, a manufactured drug should be uniform in dose, strength and purity, which is also impossible with ADRCs. The latter is a major concern for market authorization and quality assurance. Considering that ADRCs yield varies based on the donor, ensuring comparability between ADRC batches and processes is currently very difficult, making quality, safety, efficacy and efficiency demonstration expensive. This reduces feasibility for patients and healthcare services [16].

According to the FDA, ADRCs enzymatic isolation is currently classified as a "drug". Therefore, they have to be manufactured and approved in a regulated manner as opposed to isolating those cells as a surgical procedure in an operating room where it comes under the domain of a surgical procedure [18].

However, the European Medicines Agency (EMA) categorized enzymatically isolated ADRCs as non-advanced therapy medicinal product [6]. This shows that different bodies have different and opposing classifications leading to a lack of clear standards. This may be a matter of definitions, while the cells themselves are not "drugs", the chemicals they produce once they have been transplanted to a damaged area for treatment could be seen as can cause these cells to be considered as drugs.

Broadly speaking, other than the fact that they are lengthy and expensive, clinical trials are not cost-effective. It takes a large amount of time for trials to be done which can negatively impact patient revenue for both private clinics and pharmaceutical firms [19].

The economics and the financial side of treatments must always be considered. Currently, ADRCs are expensive as they are relatively new and the cost of their development, testing and production has to be met. However, they will rapidly become cheaper as more patients are treated, as the manufacturing process becomes more efficient and as patents expire [20].

More and More Issues

It is quite evident that more interdisciplinary and international collaboration in research is required. This is due to the fact that many sources are currently controverting each other. A wide range of the literature highlight the utter safety of these cells in therapy, yet many others claim issues with safety and efficacy. In spite of the presence of many reports underlining the healing potential of ADRCs, there is a lack of evidence to support the efficacy of the usage of these cells; hence more research is required to "fill in" the lack of data for their effectiveness [19]. Nevertheless, there is no single test that can adequately measure product attributes that predict the potency or the clinical safety/efficacy for these cells [16].

Nonetheless, research in this field leads to a plethora of ethical issues [20]. A research in a controversial field where there are continuous fears of the usage of these cells for potentially malignant purposes. Perhaps one of the other main reasons research in this domain is hindered is our fear of the unknown and failures in treatment [21]. However, many treatments fail and result in unwanted results everyday around the world and these risks are the realities of modern medicine. But maybe the reason failures in stem cell therapies hit the news and go viral is that the whole concept of stem cells is new and is basically a "hot topic" and not necessarily these cells being not fit for purpose.

Other noteworthy problems in the implementation of ADRCs treatments are the lack of reputation and the many misconceptions

in the science of regenerative medicine with stem cells. Across the world, these cells have been unfortunately marketed and publicized by unregulated private providers as a "miracle treatment" without concrete evidence to support the claims [22]. Hence the stem cells are being used as a sophisticated advertisement for private services, while the unapproved treatments are being delivered to desperate patients [23]. When a treatment is unreliable and not covered by insurance plans or healthcare services, patients may need a traditional treatment later, making the stem cell therapy not only pointless but also damaging its reputation and validity [3].

Montague refers to some cases where patients got practically "scammed" as they were being given treatments that did not help their condition and were not based on any evidence, under the name of stem cell therapies [24]. Some other reports were also given regarding stem cell therapies that were found to have no stem cells whatsoever. In other words, more realism is required [22].

These misconceptions that were partly formed in the first place by unnecessary hysteria to attract funding for research can harm the funding and the progress of its research [25].

A Simple Future as it should be

Admittedly, most of the research at the moment is focused on maximizing efficiency and efficacy alongside safety. It may seem that our non uniform approach and maybe avaricious behavior has actually prevented us from achieving ADRCs therapies. Perhaps focusing our attention on profits, maximizing efficiency and yield has allowed arguments from opponents of regenerative medicine to emphasize on our lack of standards or even to label the science as a "hoax". Obviously there is a need for safety, but what is equally important is a cost-effective treatment that is compliant with the regulations, with large amounts of data and evidence that support and justify it. We believe that this can only be achieved with better and extremely affordable mechanical separation devices, providing us to understand the minimal viable dosage and treat as many patients as possible.

This could be the path to adding this revolutionizing therapy to the tools of modern medicine.

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