Regenerative Medicine

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Contributor: Vivian Alonso-Goulart

The use of biological templates for the suitable growth of adipose-derived mesenchymal stem cells (AD-MSC) and “neo-tissue” construction has exponentially increased over the last years. The bioengineered scaffolds still have a prominent and biocompatible framework playing a role in tissue regeneration. In order to supply AD-MSCs, biomaterials, as the stem cell niche, are more often supplemented by or stimulate molecular signals that allow differentiation events into several strains, besides their secretion of cytokines and effects of immunomodulation. This systematic review aims to highlight the details of the integration of several types of biomaterials used in association with AD-MSCs, collecting notorious and basic data of in vitro and in vivo assays, taking into account the relevance of the interference of the cell lineage origin and handling cell line protocols for both the replacement and repairing of damaged tissues or organs in clinical application. Our group analyzed the quality and results of the 98 articles selected from PubMed, Scopus and Web of Science. A total of 97% of the articles retrieved demonstrated the potential in clinical applications. The synthetic polymers were the most used biomaterials associated with AD-MSCs and almost half of the selected articles were applied on bone regeneration.

biomaterial stem cells tissue engineering

1. Introduction

1.1. Biomaterial: The Biological Generation Template

Biomaterials, natural or synthetic, composites, ceramics and metals alive or lifeless, are being defined as materials that interact with biological systems [1]. The fully interactive, biocompatible, biodegradable and non-cytotoxic biological system framework is still widely used in regenerative medicine to assist in treatments of wounds and diseases, also enabling the creation of substitutes for medical devices. Biomaterials are biosynthesized in micro/nanometric terms, with basic structural units, grains, particles, fibers or other constituent components, bigger/smaller than 200 nm, also in all sizes and shapes [2]. The affluent diversity of surface and characteristics defines all types of functions, designed to interact with cellular and molecular events well, interfering with their biological activities with no toxicity [3]. The wide variety of clinical applications favor the design of unique techniques, such as tissue engineering, drug delivery, bioimaging, gene therapy and 3D bioprinting [4]. In addition, the combination of different techniques to prepare compartmented scaffolds is a promising path to reveal not only sophistication in the translational studies, but a challenge to approach accordingly the volume of numerous scaffold designs and application methods, bringing reliable sources for repairing the tissue or organ.

Actually, supporting cells during the formation of new tissues is a quite amazing and promising ability of biomaterials; in addition, the fabricated scaffolds outweigh their advantages in supporting cell adhesion, proliferation and growth, by controlling the biochemical and mechanical properties of the microenvironment for successful cell delivery [5]. By decreasing the size of the material to the nanoscale with nanotechnology, the surface area is dramatically increased and the correlation between surface area and volume can create superior physicochemical properties [6].

1.2. Stem Cells: Origin, Design and Differentiation

One of the first records about stem cells came with Danchakoff V. (1916), who, in particular, took advantage of the differentiation of cells as a criterion for cell identification. Some time later, a model for differentiation of hematopoietic stem cells was shown by Wolf and Trentin (1970). “Mesenchymal Stem Cells” was shown a few years after by Caplan (1991). In 2019, the International Society for Cellular Therapy (ISCT) published a short communication about a new position statement on nomenclature and the affirmation was for the use of MSC for mesenchymal stromal cell [7].

Stem cells are described as cells with the capacity of differentiating into one or more types of cells and those are commonly called specialized cells. According to the origin of the cells, they can be classified as either embryonic or adult stem cells. Embryonic stem cells (ESCs), despite being pluripotent and able to be differentiated into any type of cells, face problems regarding their use because of ethical issues related to human embryos, which are used for obtaining the cells [8][9]. In addition, some studies have shown that samples of ESCs can have possible tumor-promoting cells, as demonstrated [10]. Adult stem cells have a limited growth potential, if compared with embryonic stem cells, but are most likely to fit ethical regulations for use in research. Mesenchymal stem cells (MSCs) are one of the groups of adult stem cells and they have important characteristics, such as the capability of differentiation into adipogenic, chondrogenic, osteogenic and even neurogenic cells. These cells can also show immunomodulatory properties, as well as secrete bioactive molecules, making them valuable for therapeutics in degenerative and autoimmune diseases [9][11]. MSCs are classified according to criteria established by the International Society for Cellular Therapy (ISCT) and some of the requirements to be met are adherence and fibroblastoid morphology, as well as surface markers, such as CD105, CD73 and CD45, for example. In addition, they must be able to differentiate into osteoblast, chondrocyte or adipocyte cell lineages in vitro [8][11].

Bone marrow (BM) is a widely known and used source of MSC, but it can be obtained from several adult tissues. For instance, adipose tissue (AT) is another great source of MSC and also dental tissues, extra-embryonic tissues (such as amniotic fluid, amniotic membrane, fetal membrane and placenta), endometrium and Wharton’s jelly [12][13]. The procedure to obtain stem cells from BM is very invasive and painful. On the other hand, the harvesting process of adipose-derived stem cells (AD-MSCs) is fairly simple, considering that liposuction and bichectomy surgery waste material contain these cells [13]. Buccal fat pad (BFP), which can be obtained from bichectomy surgery, are cells phenotypically similar to AD-MSCs obtained from liposuction surgery [14]. Moreover, this source has drawn attention for being very accessible. It is also known that the concentration of AD-MSCs in adipose tissue is almost five hundred times the concentration of BM-MSC in bone marrow [15]. In conclusion, AD-MSC and BFP

are promising sources of MSC, due to their easy harvest and for being a source of stem cells of great value [13][14]. In addition, they have prominent implications in tissue regeneration due to their ability to differentiate into multiple lineages and to secrete various cytokines, as well as having immunomodulatory effects [16].

2. General Findings (Flow Diagram Results)

The electronic search process in the databases output 1436 studies. Among them, 98 articles published in 2010–2020 met all inclusion criteria (**Figure 2**).

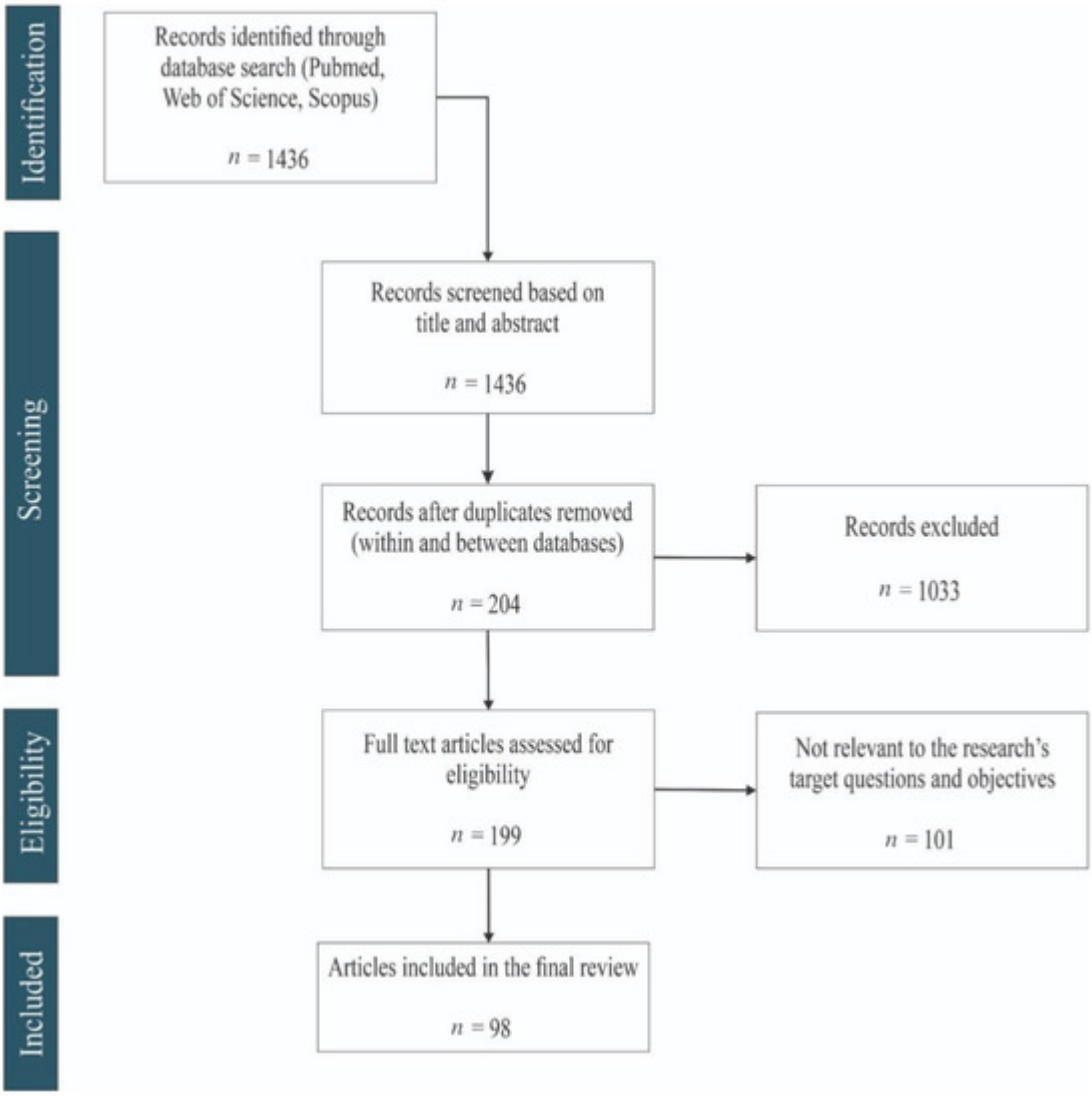

Figure 2. PRISMA chart showing the screening process for the selection of eligible studies.

3. Quality of the Selected Articles

More than three quarters of the questions about the quality of the selected articles were answered positively, showing the good quality of the retrieved articles. Only 7% of the questions got an unclear answer and 14% a negative answer to the established criteria (**Figure 3**A).

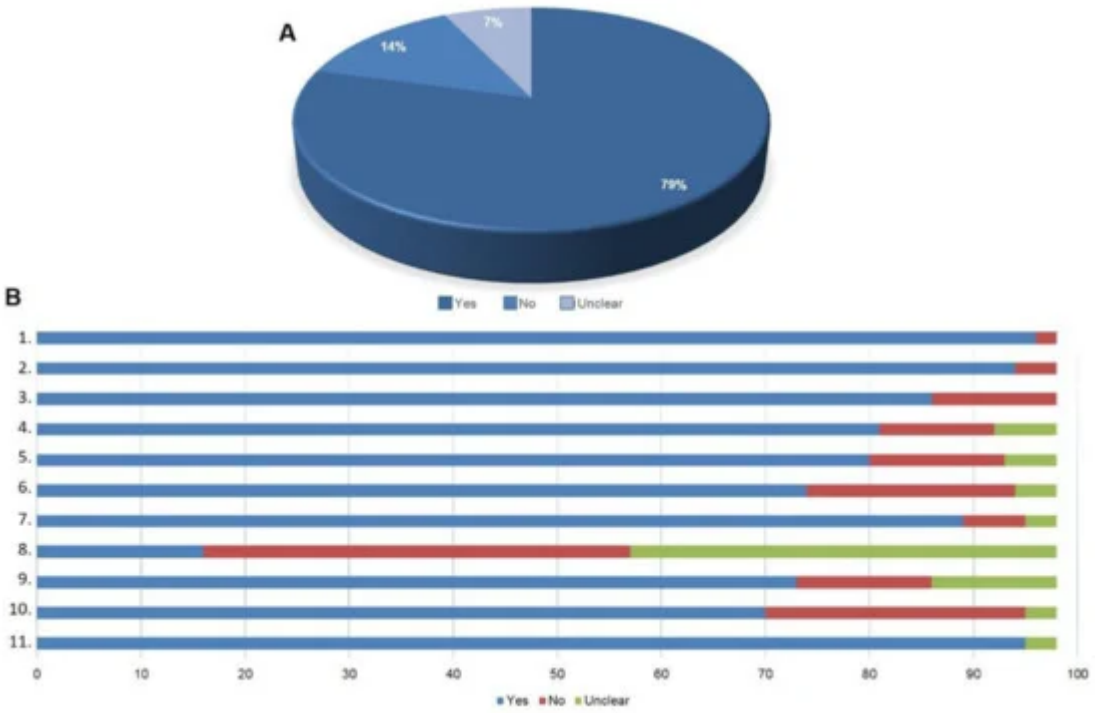

Figure 3. Analysis of the quality of the selected articles. (**A**) Overall retrieved articles. (**B**) Quality of the selected studies according to the eleven pre-defined assessment questions: 1. Was there a clear statement of the aims of the research? 2. Was the research design appropriate to address the aims of the research? 3. Was the execution of the methodologies described in sufficient detail to permit replication of the experiments? 4. Did the study provide a clear definition of what was considered to be a positive and negative control? 5. Have ethical issues been taken into consideration? 6. Was the data analysis sufficiently rigorous? 7. Was the study free of commercial funding? 8. Has the characterization of MSC been done according to ISCT criteria? 9. Were MSC used from the 2nd to the 5th passage in experiments? 10. Did MSCs demonstrate the potential for osteogenic, chondrogenic or adipogenic differentiation? 11. Did the research results show the potential of MSC in clinical applications? Yes (blue), No (red) and Unclear (green).

Only two selected articles did not state clearly the aims of the research, but most of the articles (95.9%) showed an appropriate experimental design. Most of the articles described the methodologies in sufficient detail to make room for the replication of the experiments. Less than 12% of the studies did not provide a clear definition for positive and negative controls. When biological samples were used, more than 80% considered ethical issues. We considered that around 75% of the articles reported sufficiently rigorous analyses of their data and only 20% of the results sections were poorly described.

However, more than 6.1% of the articles were funded by companies being susceptible to potential conflict of interests. The majority of MSC used in the retrieved articles did not inform that the characterization of the cells had been performed according to ISCT (International Society of Cellular Therapy). More than 74% of the selected articles used the cells from 2nd and 5th passages in experiments; 71.4% of the retrieved articles demonstrated the potential of cell differentiation and almost 97% showed the potential in clinical application (**Figure 3**B).

4. Publication Overview between 2010 and 2020

The search was limited to the papers with dates of publication between 2010 and 2020. The years 2014, 2015 and 2017 had the highest concentration of paper publications, as it is shown in **Figure 4**A. During these years, there were publications in twenty-five different countries and highlights with the greatest number of submissions in the United States and China (**Figure 4**B).

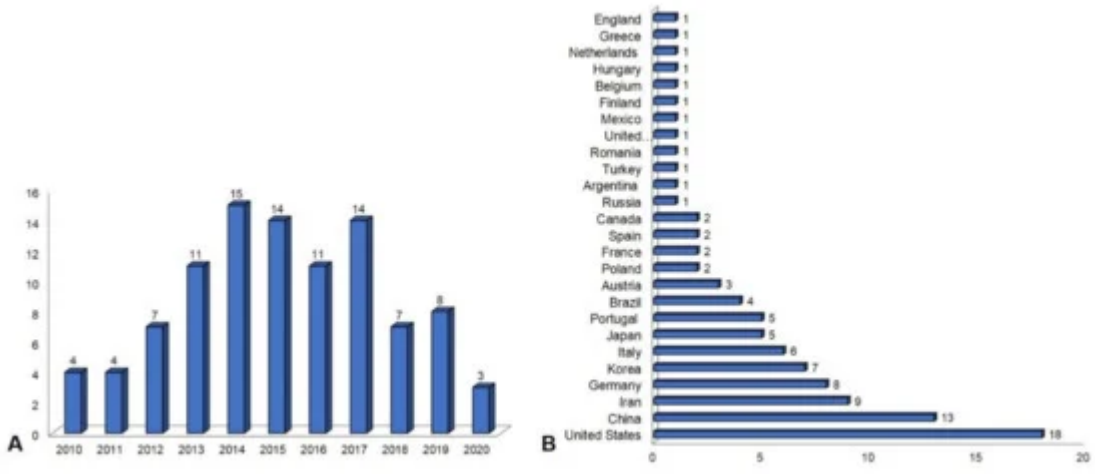

Figure 4. Overview of the numbers of publications about biomaterials and AD-MSCs for regenerative medicine worldwide. (**A**) Numbers of publications between 2010 and 2020. (**B**) Numbers of publication per country.

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