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Review article

Bisphenol a and mesenchymal stem cells: Recent insights

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ABSTRACT

Mesenchymal stem cells (MSCs) are found in all adult mesenchymal tissues. They play a role in the maintenance of tissue homeostasis and repair by allowing renewal of the cellular stock. MSCs can be isolated from both human and animal sources. These cells are important in regenerative medicine and cell therapy, thus adipose tissue is a rich and promising source of these cells. Adipose-derived stem cells (ASCs) are often effective and safe, and have been used in preclinical and clinical studies for both autologous and allogeneic transplantation. The potential use of stem cell-based therapies for the repair and regeneration of various tissues and organs provides an important alternative therapeutic solution for the treatment of many diseases. However, it is necessary to have control of the cell manipulation process prior to their use. Exposure of humans to the endocrine disruptor bisphenol A (BPA) has been associated with increased weight and obesity, but the mechanisms by which BPA increases adipose tissue in humans remains to be determined. BPA has been classified as a potent endocrine-disrupting chemical that interferes with adipogenesis. Currently, few studies have reported the effect of BPA on the integrity and capacity for differentiation of MSCs. Thus, this review aims to present, for the first time, a current survey and a discussion of the effects of BPA action on MSCs.

1. Introduction

1.1. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are a heterogeneous cell population that comprises different progenitor cells possessing the ability to repair tissues, support hematopoiesis, and regulate immune and inflammatory responses [1]. These precursors can give rise to a variety of cell types, including adipocytes, osteoblasts, chondrocytes, myocytes, β-pancreatic islets cells, and, potentially, neuronal cells [2–4]. They can be found in virtually all tissues [5]. This population was first identified and isolated from bone marrow > 40 years ago [6]. In 2006, the International Society of Cellular Therapy established three minimum biological parameters to better identify these kind of cells, namely: (i) plastic adherence under standard *in vitro* culture conditions; (ii) expression of cluster of differentiation (CD) surface markers CD105, CD73, and CD90 with no expression of CD45, CD34, CD14 or CD11b, CD79a, or CD19 and HLA-DR (human leukocyte antigen–antigen D related); (iii) *in vitro* differentiation to osteoblasts, adipocytes, and chondrocytes [7–9]. MSCs can be expanded *in vitro* through consecutive passaging without significant changes to their major properties [10]. MSCs can also release chemokines and cytokines exerting paracrine effects [1]. For these reasons, this population has been extensively studied and analyzed, with the ultimate goal being to use them as cellular tools for the treatment of many types of diseases.

1.2. Adipose derived stem cells

As previously stated, MSCs can be found in practically all tissues [11]. However, up until 2000, adult stem cell lines appeared to derive exclusively from hematopoietic tissues [12], mesenchymal tissues [11], neural stem cells [13,14], and muscle satellite cells [15–17]. In 2001, a group from the University of California in Los Angeles (UCLA) discovered a stem cell population derived from the adipose tissue. Due to their isolation from human lipoaspirates, they were first termed “processed lipoaspirate cells”, but they are now referred to as “adipose-derived stem cells” (ASCs) [18]. The current term is more descriptive, as ASCs are a multi-lineage stem cell population that can be isolated from the stromo-vascular fraction of adipose tissue. In addition, in order to prove the ability of ASCs to be a multi-lineage cell population, Zuk and co-authors [18] utilized additional approaches such as the expression of multiple lineage-specific genes and functional biochemical

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assays to confirm that both differentiation capacity and clonogenicity are important requirements for identifying ASCs. When considering this issue, one of the main challenges in the identification of adult stem cells is the heterogeneity of their tissue of origin. The observed multi-lineage differentiation by ASCs may simply be due to the presence of multiple precursor populations, each completing their own developmental program [19]. Zuk's group found a way to circumvent this problem by isolating a single stem cell and obtaining proof of the cell's multi-potency. Employing this approach, they demonstrated its differentiation capacity and clonogenicity, and as a result proposed a new adult stem cell population [18]. Since 2002, many groups have confirmed the existence of these ASCs in both humans and animals [19]. Additionally, these cells also have the ability to differentiate into neuronal-like cells, and this has been confirmed by numerous studies since their first discovery [13,14,20,21].

For this reason, the use of adipose tissue-derived precursors as a therapeutic tool has grown considerably over the past years, and has triggered the growth of a new research field worldwide [22]. Regenerative medicine has evolved tremendously with these recent advances in stem cell research. The last decade has shown flashes of the astonishing potential of these cells in tissue regeneration [23]. Despite these advances, the availability of stem cells remains a challenge for both scientists and clinicians interested in regenerative medicine [24]. The main advantage of ASCs over mesenchymal stem cells derived from other sources, *e.g.* from bone marrow, is that they can be repeatedly harvested using minimally invasive techniques that have a low risk of morbidity [25]. Nonetheless, the ideal stem cell population should be easily accessible through a non-invasive procedure, provide an abundance of cells, be able to differentiate into a variety of cell lineages, able to be easily transplanted into an autologous or allogeneic host, and able to be manufactured in accordance with the currently accepted good manufacturing practice guidelines set by the FDA [26].

It is very well-known that our environment is contaminated with numerous chemical substances that can intrinsically alter the homeostasis and physiology of biological systems, resulting in a negative impact on human and animal health [27,28]. Concerning adipose-derived stem cells, some of these contaminating organic compounds are obesogenic but also possess the capacity to bind to hormone receptors and accumulate in fat tissue in different organisms [29]. Such molecules could well impact stem cell biology, impairing their differentiation efficiency and compromising their therapeutic use, as it has recently been reviewed for MSCs [30]. In this review, we will focus our attention on the effects of bisphenol A (BPA) on MSCs.

1.3. Obesogens

Obesogens are chemical compounds that can boost weight-gain by altering the number of adipocytes, increasing their ability to store fat, or by modifying several homeostatic processes [29] such as decreasing the amount of calories burned at rest, shifting the energy balance to favor the storage of calories, and modulating the mechanisms through which the body manages appetite and satiety [31]. The obesogen hypothesis has gained visibility in recent years due to the identification of obesogenic chemicals that promote adipogenesis and obesity in animals and humans [31–34]. Some of these compounds are referred to as endocrine disruptors since they interfere 'with the synthesis, secretion, transport, binding, or elimination of natural hormones' like estrogens, testosterone, and thyroid hormone, among others [35].

1.4. Endocrine disrupting chemicals

Endocrine disrupting chemicals (EDCs) are compounds present in our environment, food, and consumer products that interfere with the biosynthesis, metabolism, and action of hormones, resulting in alterations in the normal homeostatic or reproductive processes [36]. EDCs are produced as pesticides, plasticizers, or solvents. It was initially found that when they are absorbed into the body, they can either mimic or block hormones and disrupt the normal functions of the organism [37]. As a result, they were initially thought to exert their actions solely through nuclear hormone receptors, including estrogen receptors (ERs), androgen receptors (ARs), progesterone receptors, thyroid receptors (TRs), and retinoid receptors [36].

These substances are typically hydrophobic and lipophilic, which means that they work best in an environment that has a low concentration of water and an abundance of fatty acids. In aquatic systems and soil, EDCs are easily decanted in solids, whereas in organisms, they are partitioned into lipids. As a result, the EDCs are able to avoid being metabolized in the aqueous phase, allowing them to accumulate first in cells and fatty tissues, and then in the food chain [38].

1.5. Bisphenol A

Bisphenol A (BPA) is a synthetic chemical that, because of its structure, is multifaceted. The BPA (4, 4′-dihydroxy-2, 2-diphenylpropane) molecule consists of two phenol rings connected by a methyl bridge, with two methyl groups bound to the bridge [39]. BPA is classified as an endocrine disruptor, resulting in the relatively weak activation of estrogen receptor a (ERa) and b (ERb) [40–44]. BPA can also act as an antagonist of ERb [45]. This compound is used in the fabrication of polycarbonate plastic and epoxy resins, which can be used in impact-resistant safety equipment and baby bottles, as a protective coating inside metal food containers, or as a composite and sealant in dentistry [46]. This is one of the highest-volume chemicals produced globally, with 5.2 million metric tons estimated to have been produced in 2008 [47]. Because of its mass production and widespread adoption, the probability of environmental contamination with BPA has increased. Environmental contamination is possible *via* industrial wastewater treatment systems or sewage treatment plants that receive this compound. Other possible sources of BPA are also found in the environment, such as waste plastics in landfills and sewage sludge from wastewater treatment facilities. There is a considerable amount of monitoring of BPA levels in Europe, the United States, and Japan, and BPA has been detected in many different biological samples [48,49], for example, in human blood (< 0.5–22.3 ng/mL) [50,51], the serum of pregnant women (< 0.1–154 ng/mL) [52,53], urine (< 0.1–822 ng/mL) [46,54], saliva (0.1 ng/mL), amniotic fluid (2.80–5.62 ng/mL), umbilical cord (< 0.05–52 ng/mL), follicular fluid (1–2 ng/mL) [55], breast milk (< 0.04–11 ng/mL) [56], and adipose tissue (1.80 to 12.01 ng/g) [57] with BPA being principally stored in milk and adipose tissue. It has also been shown that > 90% of people tested for BPA in urine and blood tested positive [58], and that infants and children are the most affected [46].

Data from multiple sources have shown that the amount of BPA that humans are exposed to may cause adverse health effects, such as diabetes, obesity, abnormal neuronal behavior, developmental effects, and thyroid and reproductive disorders [58–61]. This has raised concerns among regulatory agencies all over the world [57]. Based on this, the United States Environmental Protection Agency (EPA) has determined a reference dose for BPA of 50 μg/kg body weight/day whereas the European Food Safety Authority (EFSA) have determined a reference dose of 4 μg/kg body weight/day [62]. *In vitro*, BPA has been found to cause mutagenicity in human RSa cells (a human embryonic clonal cell line established by double infection with Rous sarcoma virus and Simian virus 40) and HeLa cells [63] within the range of 100 nM to 10 μM [64]. Even though a direct genotoxic effect of BPA at low doses has not been reported, exposure to BPA at environmentally relevant doses, primarily during the developmental stages, represents a risk for carcinogenesis [62]. This compound has therefore become an environmental contaminant of considerable interest [49].

Perhaps due to BPA's shared structural homology with estrogen, it appears to be able to upregulate the expression of downstream targets, including peroxisome proliferator-activated receptor gamma (PPAR γ)