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Review

Modulatory effects of mesenchymal stem cells on leucocytes and leukemic cells: A double-edged sword?

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ABSTRACT

Mesenchymal stem cells (MSCs) have drawn much attention amongst stem cell researchers in the past few decades. The ability of the MSC to differentiate into cells of mesodermal and non-mesodermal origins has made them an attractive approach for cell-based therapy and regenerative medicine. The MSCs have immunosuppressive activities that may have considerable therapeutic values in autoimmune diseases. However, despite the many beneficial effects reported, there is a growing body of evidence, which suggests that MSCs could be a culprit of enhanced tumour growth, metastasis and drug resistance in leukaemia, via some modulatory effects. Many controversies regarding the interactions between MSCs and leukaemia still exist. Furthermore, the role of MSCs in leukemogenesis and its progression remain largely unknown. Hence it is important to understand how the MSCs modulate leukaemia before these cells could be safely used in the treatment of leukaemia patients.

Contents

1. Introduction

Haematopoietic stem cells (HSCs) are multi-potent cells with the ability to differentiate into many types of blood cells based on the stimuli provided. These cells are usually found in abundance in the bone marrow [1] and cord blood [2,3]. In the bone marrow, there is also another type of multi-potent stem cells known as the mesenchymal stem cells (MSCs) [4,5]. These cells are distinct from the HSCs and are referred to as non-haematopoietic cells. When the MSCs were discovered, it was proposed that these multi-potent cells could play an important role in cell-based therapies and regenerative medicine [6,7].

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Research on MSCs has truly evolved; coming a long way in revolutionizing and bringing new hopes to the treatment of many fatal and debilitating conditions [8,9]. This is because these multi-potent cells can be easily isolated and expanded using cell culture conditions and also be induced to terminally differentiate into other cell types such as adipocytes, chondrocytes, osteoblasts, neural cells and haematopoietic-supporting stromal cells. In addition to their multipotent differentiation capacity, the MSCs have been reported to have modulatory effects on various types of cells, which can sometimes turn out to be a "double-edged sword". For instance, the MSCs were found to alleviate adverse immune reactions in certain circumstances such as autoimmune diseases and in graft-versus-host disease (GVHD) whilst in other conditions, the MSCs have been shown to support growth of solid and haematological malignancies, especially leukaemia. The present article looks at some important past discoveries in MSC research to provide an overview of the modulatory effects and the interactions between MSCs and leukemic cells.

2. Leukaemia

Leukaemia belongs to a group of haematological malignancies that are characteristically marked by abnormal and dysregulated proliferation of leucocytes. Today, much of what we know about leukaemia originated from the work of two renowned scientists, John Hughes Bennett and Rudolph Virchow, who first described the disease in 1845 [10]. Leukaemia remains the commonest cancer in children, making up of about 34% of all childhood cancer cases [11]. In contrast, this disease is less common in adults. Globally, leukaemia ranks the 9th and 10th most common cancer for men and women, respectively. While the aetiology of leukaemia is largely unknown for most leukemic patients, several risk factors such as radiation, alkylating drugs [12], viruses [13] and some chromosomal disorders [14] involving genetic instability have been thought to play a role in its pathogenesis.

3. Mesenchymal stem cells

Stem cells belong to a group of biological cells, which possess the ability to self-renew, to extensively proliferate and to give rise to daughter cells. These daughter cells have limited proliferative potential but are capable of differentiating to become many types of cells depending on the stimuli received. Stem cells can be broadly classified as embryonic, adult or induced pluripotent stem cells. The existence of stem cells was first described in the year 1908 by Alexander Maximov, a prominent Russian histologist [15]. The cells were found to possess self-renewing properties [16] as well as other major biological properties [17].

The mesenchymal stem cells (MSCs) were discovered by Friedenstein and co-workers in 1968 [18]. These authors described these cells as a special type of self-renewing cells found in the bone marrow, which could be precursors for osteogenic and haematopoietic tissues. However, interest in studying the properties and utility of these stem cells only gained momentum in the 1980s [19–23].

The International Society for Cellular Therapy (ISCT) has proposed some minimal criteria that could be used to define the multi-potent MSCs (Table 1) [24]. However, it must be stressed here that the proposed properties for the identification of MSCs by the ISCT may not be definitive as there are reports in the literature, which have found some MSCs may not fulfil some of the criteria listed in Table 1. For instance, Wan and co-workers [19] reported that a non-adherent population of cells from the bone marrow may be a source of MSCs. Despite this, the proposed guidelines by the ISCT still remain an essential benchmark for the identification of MSCs and are generally accepted as properties that can be used to identify MSCs.

The ability to successfully harvest MSCs from the bone marrow relies predominantly on the adherent properties of these cells. Several factors have been shown to contribute to the enrichment of MSCs from fresh bone marrow culture, including cell surface antigen Stro-1 [25], CD106 [20], and antibodies to cell surface molecules such as CD105 (SH2), CD73 (SH3/SH4) [21], W8B2, 57D2, W4A5 [22] as well as CD271 [23].

Table 1
Properties that define mesenchymal stem cells[a].

Properties that must be present
➢ Adhere to plastic culture vessels used in standard tissue culture conditions
➢ Express cell surface molecules such as $CD105^+$, $CD73^+$, $CD90^+$
➢ Multi-potent: Can differentiate along the mesodermal lineage into osteoblasts, adipocytes and chrondroblasts when specific cell-culture conditions are employed
Properties that must not be present
➢ Lack expression of surface markers such as CD45, CD34, CD14/11b, CD79α/19 and HLA-DR

[a] Adapted from the International Society for Cellular Therapy[28].

Currently in the literature, there are many studies, which show that the MSCs can differentiate into specialized cells of the mesodermal lineage as well as into lineages that usually arise from the endodermal and ectodermal origins. For example, MSCs have been shown to have the ability to differentiate into hepatocytes [26], neuronal cells [27], endothelial cells [28] as well as insulin-producing cells with beta-cell phenotype [29]. The multi-potent capacities of the MSCs and their therapeutic potential in tissue repair and regeneration have made these cells popular amongst stem cell researchers [5]. Several studies have demonstrated that MSCs were capable of regenerating cardiac tissues [30–35] and lung tissues [36] and may also play a regenerative role in musculoskeletal disorders [37–40]. However, it should be noted that the ability of MSC to differentiate into many of the above-mentioned tissues is not robust as there are some results that have been controversial.

The MSCs were also found to possess immunomodulatory properties such as T-cell suppression [41,42], which can favour allogeneic [43] and syngeneic [44] tumour growth in animals. On the one hand, the immunomodulatory properties of the MSCs cells may be beneficial to patients who experience rejections or adverse immune reactions such as those occurring in graft-versus-host disease (GVHD) [45–49] and autoimmune diseases [50,51]. Whilst on the other hand, the modulatory properties of these cells have been shown to induce tumour growth [44,52,53], metastasis [28,54] as well as drug resistance [55] in various types of cancers. Such tumour modulation has also been demonstrated in haematological malignancies, especially leukaemia [55,56]. The MSCs can also play a role in various healing processes [57,58].

4. Immunomodulatory effects of mesenchymal stem cells

The MSCs have been found to have immunomodulatory effects on T- and B-lymphocytes as well as monocytes. A summary of the effects of MSCs on immune cells is illustrated in Fig. 1. To date, most of these studies have demonstrated the effects of the MSCs on the maturation and function of immune cells using cell-based models. It is worth mentioning that there are also a few animal model-based studies that have confirmed some of the immunomodulatory properties of the MSCs especially in relation to the inhibiting proliferation of activated T-cells. However, some of these studies also reported conflicting findings in relation to the tolerogenic properties of MSCs. Such discrepancies may be attributed to the origin, isolation and expansion techniques used to culture MSCs. Hence further in vivo exploration is necessary before conclusive remarks on the immunomodulatory properties of MSCs can be made.

4.1. Effects of mesenchymal stem cells on T-lymphocytes

The interactions between MSCs and various types of immune cells are complex but interesting. In several studies, MSCs have been shown to suppress T-lymphocyte activation and proliferation induced by