Immunosuppressive Properties of HLA-G Molecules Produced by Mesenchymal Stromal Cells

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Abstract

The main interest in human mesenchymal stromal cells (hMSCs) is correlated with their ability to suppress the proliferation of immune cells and to regulate the transplantation rejection. The mechanisms at the basis of MSCs activity need cell-cell interaction and the expression of molecules induced by the micro-environment. The inhibitory functions of MSCs involve several molecules as hepatocyte growth factor, transforming growth factor-beta (TGF-beta), interleukin-10 and -2 (IL-10, IL-2), tumor necrosis factor-alpha (TNF-alpha), prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), and HLA-G antigens. A large consensus has been obtained on the immuno-modulatory role of HLA-G molecules produced by hMSCs.

Keywords: Mesenchymal stromal cells; HLA-G; Immunosuppression

Human multipotent mesenchymal stromal cells (hMSCs), first described by Friedenstein in 70 years [1] as non-hematopoietic cell precursors with osteogenic potential, represent stem cells for non-hematopoietic tissues [2]. The functional and immunophenotypic characteristics of stromal cells have been recently reviewed and redefined by International Society for Cellular Therapy (ISCT) [3]: they must be defined as hMSCs, which are a plastic adherent cell population with multipotent differentiation capacity. To distinguish them from CD34+ hematopoietic progenitors, they must express a set of specific markers, as CD73, CD90 and CD105, which are the most frequently used. However, these criteria are not fully specific and some cell populations express them, such as fibroblasts, osteoblasts and skeletal muscle cells. In addition, although most hMSCs express low levels of MHC class I antigens, the importance of this expression is still a matter of debate. In fact, some reports suggest that the low MHC expression of hMSCs may be a major factor involved in their immunosuppressive properties.

In the last years several studies have demonstrated the peculiar immunological characteristics of hMSCs, as low antigenicity and high immunomodulatory ability, suggesting their clinical use to counteract rejection in regenerative medicine and tissue transplantation. Cultured allogeneic hMSCs are widely used in clinical trials in hematopoietic stem cell infusion [4-6], in solid-organ transplantation [7] and for treating autoimmune diseases [8,9]. However, the in vivo data are still controversial and a specific marker for hMSCs selection is needed. The low antigenicity of hMSCs is mainly caused by the low expression of classical HLA (human leukocyte antigen) class I molecules and the complete absence of HLA class II antigens and co-stimulatory molecules as CD80 (B7-1), CD86 (B7-2) and CD40 [10]. The main interest in hMSCs is correlated with their ability to suppress the proliferation of T lymphocytes induced by mitogenic agents and alloantigens which regulate the transplantation rejection [11]. Moreover, hMSCs are resistant to the CD8+ T lymphocyte cytotoxicity, they are able to inhibit the differentiation of dendritic cells responsible for the antigen presentation, the proliferation and antibody production of B lymphocytes and they stimulate the formation of regulatory T cells. The mechanisms at the basis of hMSCs activity need cell-cell interaction and the production of molecules induced by the micro-environment. The inhibitory functions of hMSCs involve several molecules as hepatocyte growth factor, transforming growth factor-beta (TGF-beta), interleukin-10 and -2 (IL-10, IL-2), tumour necrosis factor-alpha (TNF-alpha), prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO) [12] and HLA-G antigens [13]. A large consensus has been obtained on the immuno-modulatory role of HLA-G molecules.

HLA-G antigen is a non-classical HLA class I molecule characterized by 7 mRNA splicing isoforms, 4 membrane-bound (HLA-G1, G2, G3, G4) and 3 soluble (HLA-G5, G6, G7). Both soluble and membrane-bound isoforms are able to inhibit several immune functions as lytic and cytotoxic activity of Natural Killer (NK) cells and T CD8+ lymphocytes, the maturation of dendritic cells, and the alloproliferation of CD4+ T lymphocytes and to induce the formation of regulatory T cells. HLA-G molecules differ from classical HLA antigens for their lower allelic polymorphism (50 alleles, http://hla.alleles.org/class1.html) and the limited tissue distribution. HLA-G expression is induced in pathological conditions, as tumours and viral infections [14]. Taking into consideration the tolerogenic functions of HLA-G molecules, they could be a good candidate as a factor for hMSCs immuno-modulatory activity. Götherström et al. [15] have demonstrated the presence of HLA-G mRNA in both fetal and adult hMSCs. The modulation of HLA-G has been documented on the surface of hMSCs [16] and in their culture supernatants [17]. Several studies have confirmed that the cell-cell contact between hMSCs and T lymphocyte induces the secretion of HLA-G molecules and IL-10, a cytokine that is able to up-modulate HLA-G production [17]. The use of neutralizing antibodies against HLA-G and IL-10 have demonstrated the importance of soluble HLA-G, induced by IL-10, for the suppressive effect of hMSCs towards cell proliferation [18,19], cytotoxic activity and IFN-γ secretion by NK cells, and the ability to induce regulatory T cells (CD4+CD25hiFoxP3+ cells formation) [20]. These data suggest a fundamental role for HLA-G antigens in the tolerogenic function of hMSCs.

The selective use of HLA-G positive hMSCs could be a valuable tool in improving current protocols of hMSCs use as immunosuppressant cell therapy [21]. In fact, stable HLA-G expression by lentiviral system in hMSCs appeared to enhance the immunosuppressive effect of MSCs [22].

In conclusion, hMSCs are newly detected targets for immunomodulatory activity and HLA-G molecules could be an important factor of this mechanism.

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