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LETTER TO THE EDITOR

Cotransplantation of mesenchymal cells and a higher relapse rate: a role for HLA-G molecules?

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We have read with interest the paper by Ning *et al*.[1] reporting a correlation between the cotransplantation of mesenchymal stem cells (MSCs) in allogeneic haemapoietic stem cell transplantation and a higher recurrence rate of malignant haematologic diseases. The authors concluded their paper by suggesting that 'the use of MSCs must be handled with extreme caution before a large-scale trial is performed'. Recently, several studies have reported the ability of MSCs, when co-cultured with activated peripheral blood mononuclear cells or directly activated by exogenous Interleukin 10, to modulate membrane bound and soluble human leukocyte antigen-G (HLA-G) antigens.[2–4] HLA-G antigens are nonclassical HLA-class I molecules characterized by tolerogenic and anti-inflammatory functions. In particular, both membrane and soluble HLA-G molecules have been demonstrated to inhibit Natural killer and CD8+ T cell mediated cytolysis, CD4+ T lymphocyte proliferation and dendritic cell maturation. Furthermore, the expression of HLA-G antigens has been associated with the induction of regulatory T cells.[4] Overall, it is currently accepted that HLA-G molecules, by direct and indirect mechanisms, can inhibit innate and adaptive immune responses. The production of sHLA-G molecules by MSCs[2–4] has suggested, in addition to other mechanisms, a rationale for the immunomodulatory properties of MSCs in preventing graft versus host disease (GVHD).

Several researches have demonstrated that HLA-G modulation represents a beneficial event in organ transplantations, autoimmune diseases and pregnancy where the downregulation of the immune response is essential for a positive outcome. In contrast, the presence of HLA-G antigens has been associated with clinical negative consequences in cancer and viral infections where the tolerogenic function of these molecules permits the mutated/infected cells to avoid the innate and adaptive immune responses. In particular, the HLA-G expression by cancer tissues and the relationship between plasma sHLA-G levels and cancer development[5–8] confirm the role of HLA-G molecules in sustaining the immune escape of cancer cells.

The association between the cotransplantation of MSCs and the development of malignant haematologic diseases reported by Ning *et al*.,[1] could be related to the functional ability of HLA-G molecules, on the one hand, to counteract GVHD but on the other to permit the relapse of the disease. This hypothesis underlines the necessity of further studies to analyze plasma sHLA-G concentrations in MSCs of cotransplanted patients in a longitudinal follow-up. The detection of a significant correlation between sHLA-G concentrations, GVHD prevention and relapse rate could identify a possible cutoff in sHLA-G plasma levels responsible for the occurrence of these two phenomena.

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