Multipotent stromal cells skew monocytes towards an anti-inflammatory function: a role for HLA-G molecules

We have read with interest the paper by Melief *et al.*[1] reporting the ability of multipotent stromal cells (MSCs) to skew monocytes towards an anti-inflammatory IL-10 producing phenotype by production of IL-6 and preventing the differentiation of monocytes towards antigen-presenting immunogenic cells. The authors concluded their paper proposing "the hypothesis that MSC, by inducing IL-10 production in monocyte-derived cells, play a powerful regulatory role in multiple anti-inflammatory mechanisms, which could explain their clinical benefits in immunotherapy". The authors suggest "that IL-6 is important but not the only factor". In fact, previous studies demonstrated that prostaglandin E and not IL-6 seems to represent the key inhibitory mediator.[2] Moreover, several studies have reported the ability of MSCs, when co-cultured with activated peripheral blood mononuclear cells (PBMC) or directly activated by exogenous IL-10, to modulate membrane bound and soluble HLA-G antigens.[3-6] HLA-G antigens are non-classical HLA-class I molecules characterized by tolerogenic and anti-inflammatory functions. In particular, both membrane and soluble HLA-G molecules have been shown to inhibit natural killer cell (NK) and $CD8^+$ T-cell mediated cytolysis, $CD4^+$ T-lymphocyte proliferation and dendritic cell maturation. Moreover, the expression of HLA-G antigens has been associated to the induction of regulatory T cells.[6]

The production of sHLA-G molecules by MSCs[3-6] has also been suggested, in addition to other mechanisms, as a rationale for the immunomodulatory properties of MSCs in preventing graft-*versus*-host disease (GVHD). In particular, through *in situ* immune-histochemical studies and by a multiparametric cytofluorimetric approach, useful to distinguish MSC and monocytes in co-culture conditions, we have observed a significant correlation between the presence of increased levels of HLA-G and IL-10 in the MSC co-cultures with PBNCs and a significant correlation with lymphoproliferative inhibition.[4]

Several studies have demonstrated that HLA-G modulation is of benefit in organ transplantations, autoimmune diseases and pregnancy where the downregulation of the immune response is essential for a positive outcome. On the other hand, the presence of HLA-G antigens has been associated to clinical negative consequences in tumor and in viral infections where the tolerogenic function of these molecules permits immune-escape.[7] The documented production of IL-10 by monocytes in the presence of MSC could trigger the production of HLA-G molecules by both monocytes and MSC.[3,4] Our data and the results of Melief *et al.*[1] support these factors as key mechanisms for MSC-induced immune-regulation.

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