Multipotent stromal cells skew monocytes towards an anti-inflammatory function: the link with key immunoregulatory molecules

We thank Campioni *et al.* for their response to our recent publication[1] in which they focus on the relevance of other molecules besides IL-6 and IL-10 for the immunomodulatory functions of multipotent stromal cells (MSC).

In our publication, we had focused on the mechanistic roles for IL-6 and IL-10 in the immunosuppressive effects of MSC. However, we agree that other factors may be important as well. We discuss here how the various, sometimes paradoxical, observations can be combined into an integrated view on the mechanism of immunodulation by MSC.

Although IL-6 had previously been proposed to be involved in the inhibitory effect of MSC on the differentiation of monocytes to dendritic cells (DC),[2,3] the cell source had not been assigned. IL-10 was also previously indicated to be a key factor in monocyte-to-DC differentiation[4] and to be related to MSC-modulated immune suppression.[5] In our study, we showed that IL-6 is produced by unstimulated MSC and that it initiates an effect on monocytes resulting in their differentiation towards a monocyte-derived cell population (MDC), similar to type-II activated macrophages with concomitant enhanced production of IL-10. Also, IL-6 expression by MDC was significantly enhanced upon co-culture with MSC.

In their letter, Campioni et al. correctly point out that other factors, especially prostaglandin E2 (PGE2) and HLA-G, have previously been implicated in the immunomodulatory functions of MSCs. In fact, using a similar test system, it has been reported that PGE2 and not IL-6 represents the key inhibitory mediator.[6] We agree that the data from that study strongly suggest a major role for PGE2 in the MSC-mediated inhibition of monocyte-to-DC differentiation. It is assumed, however, that PGE2 is MSC-derived. Since the presented data are based on the measurement of PGE2 concentrations in monocyte/MSC co-culture systems, it cannot be excluded that the PGE2 is produced by monocytes or MDC. While Spaggiari *et al.* have shown that IL-6 is not induced by PGE2, the possibility that monocyte-derived IL-6 is involved in PGE2 production by MSC cannot be excluded. This would agree with their observation that PGE2 production by MSC is up-regulated in monocyte/MSC co-cultures.

HLA-G is also a major player in immune regulation by MSC.[7-9] It has been shown that HLA-G is directly regulated by IL-10.[9,10] Since MSC skew monocytes to MDC[11,12] which display prominent IL-10 expression, this seems a logical link to the HLA-G related immunosuppressive action of MSC. This is in perfect agreement with the observation that monocytes/MDC are indispensable for MSC to exert many of their immunosuppressive functions.[13-15]

We have combined the various observations into our current working model for immune regulation by MSC, as shown in Figure 1.

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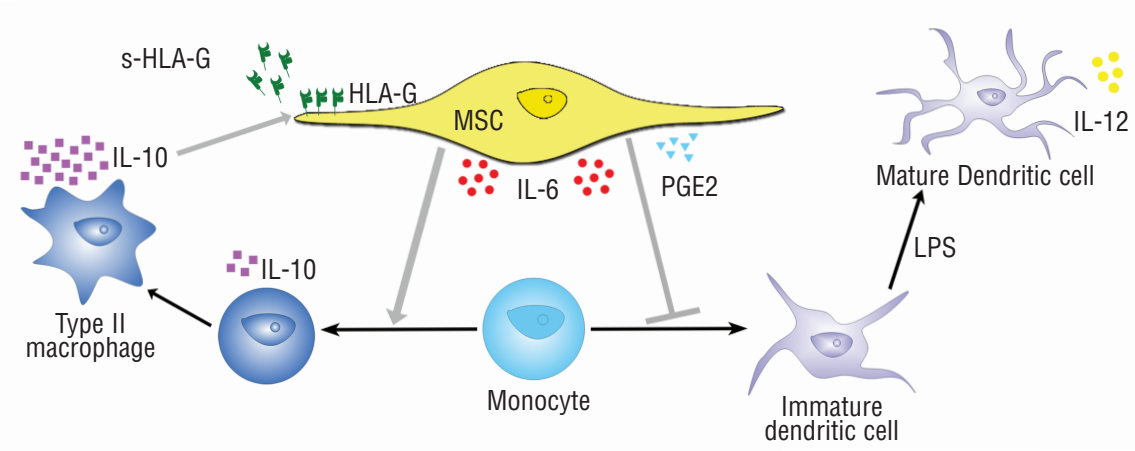

Figure 1. Immunomodulation by MSC. MSC express IL-6 and PGE2 that skew monocyte differentiation toward the formation of IL-10-expressing MDC. This IL-10 activates MSC to up-regulate (soluble and membrane-bound) HLA-G expression, which is linked to immunomodulatory effects on NK and adaptive immune cells. Through cell-cell contact, IL-10, IL-6 or another factor secreted after monocyte-MSC interaction, MSC are activated to up-regulate their PGE2 expression, further enforcing the monocyte-to-MDC skewing.

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