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EDITORIAL

Mesenchymal stromal cells: more than inhibitory cells

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Mesenchymal stem cells,[1] cautiously re-named recently multipotent mesenchymal stromal cells (MSCs)[2] because of their heterogeneous multipotency at single cell level and their similarities with fibroblasts,[3] have been strongly suggested in the last decade as powerful inhibitory cells for the vast majority of immune effector cells. The redundancy of the molecular pathways involved in the immune modulation suggests that this property, shared by MSCs of different tissue origin,[4] including lymphoid organs,[5,6] and by fibroblasts[3,7] has a pivotal role in tissue homeostasis in normal and pathological inflammatory reactions. One of the main concerns about the *in vivo* use of MSCs is that they might interfere with the normal protective immune responses against pathogens. Different data derived from the clinical use of MSCs in graft-versus-host disease and allogeneic hematopoietic stem cell transplantation[8,9] and from *in vitro* experiments[10–12] showed that anti-viral immune reactions may normally occur either following systemic administration or in presence of MSCs. In addition, the triggering of some Toll-like receptors expressed by MSCs such as TLR3 and TLR4 by viral (poly I:C) or bacterial (lipopolysaccharide) components, respectively, may hamper MSCs inhibitory functions.[13] However, when the bacterial infection is generalized and triggers a systemic inflammation, such as in sepsis, MSCs are licensed by inflammatory cytokines to acquire the inhibitory phenotype, leading to the control of sepsis-associated complications.[14]

In 2004, a paper by Meisel *et al.*[15] showed that one of the mechanisms involved in immune modulatory effect of MSCs is based on the activity of indoleamine 2,3-dioxygenase, whose role in the regulation of dendritic cell functions was already clear.[16,17] Other groups confirmed these data using different immune effector cells.[18,19]

In this *Leukemia* issue, Meisel *et al.* go further showing that human MSCs, once primed with inflammatory cytokines, have anti-microbial effector functions against different pathogens, including bacteria, protozoal parasites and viruses, and that indoleamine 2,3-dioxygenase has a role in the underlying molecular mechanisms. Indoleamine 2,3-dioxygenase activity appears to be modulated and may drive MSCs towards anti-microbial rather than inhibitory functions, according to the entity and nature of the stimulus that determines the degree of tryptophan depletion. This bimodal phenomenon reminds what occurs in interferon-γ-dependent licensing of MSCs, where MSCs functional polarization towards antigen-presentation rather than inhibitory activity depends on a narrow window of interferon-γ concentration.[18,20] Altogether, these data show how difficult it is to foresee the final effects of MSCs once they are injected *in vivo* and reach inflamed tissues, where microenviromental cellular and soluble factors have a pivotal polarizing role.

Another point of interest focused by Meisel *et al.* in their paper in this Leukemia issue is related to the evidence of significant differences between human and murine MSCs in their anti-microbial activity. Infact, mouse MSCs fail to express indoleamine 2,3-dioxygenase upon the same kind of cytokine stimulation, instead preferentially expressing inducible nitric oxide synthase, and do not inhibit bacterial growth. These results raise the question about the reliability of mouse models in supporting experimentally the protocols for the clinical application of MSCs in humans, particularly those aimed to obtain immune regulatory effects *in vivo*. Pre-clinical mouse models are universally accepted and required by regulatory agencies to perform clinical trials for immune regulatory therapies based on MSCs. Maybe time has come to state, as Meisel *et al.* suggest, that 'any effects observed in murine models cannot be readily translated into the clinical setting and that some biological features of human MSC might only be delineated in a human *in vitro* system'. This awareness could allow the investigators and the regulatory agencies to save time and money that could be employed for a better quality assessment of the cellular product either in different animal models (non-human primates) or directly in patients.

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