



Enhancement of Immune Responses During Early Stage of Inflammation by MSCs

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DESCRIPTION

The proinflammatory activities of MSCs may be helpful in the initial phase of inflammation and help in rising a suitable immune response. During the acute phase of inflammation, neutrophils migrate toward the site of inflammation where they accumulate within minutes and act mostly through phagocytosis. In mice, the recognition of microbial molecules by tissue-resident MSCs results in augmented production of growth factors, such as IL-6, IL-8, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), and macrophage Migration Inhibitory Factor (MIF), that recruit neutrophils and enhance their proinflammatory motion. Moreover, TLR3 triggered human BM-MSCs (MSC2) promote the *in vitro* existence of resting and activated neutrophils in an IL-6, IFN- β , and GM-CSF-dependent way.

In adding to neutrophils, immune reactions may be improved by MSCs through the production of chemokines that recruit lymphocytes to sites of inflammation. Human MSCs produce the chemokines CXCL-9, CXCL-10, and CXCL-11 upon stimulation with proinflammatory cytokines. *In vitro* studies with murine and human MSCs propose that these stimulatory effects only occur when MSCs are exposed to insufficient levels of proinflammatory cytokines, such as TNF- α and IFN- γ . Under these immune-enhancing conditions, murine MSCs provoke insufficient levels of NO to inhibit T cell proliferation. Indeed, inhibition of iNOS or its genetic ablation resulted in strong enhancement of T cell proliferation by murine MSCs. Under similar situations, human MSCs produce inadequate IDO (rather than iNOS) to suppress T cell proliferation. These data recommends that iNOS for murine cells or IDO for human cells may serve as a molecular switch between immune-suppressive to immune-enhancing effects of MSCs.

Suppression of immune responses and inflammation by MSCs

When exposed to enough levels of proinflammatory cytokines, MSCs may react by accepting an immune-suppressive MSC phenotype to reduce inflammation and promote tissue homeostasis through polarization toward anti-inflammatory cells and M2 macrophages *in vitro*. Co-culture of monocytes with human or mouse BM-MSCs promotes the formation of M2

macrophages and this is dependent on both cellular contact and soluble factors, including Prostaglandin E2 (PGE2) and catabolites of IDO activity such as kynurenine. Moreover, activation of MSCs with IFN- γ , TNF- α , and LPS upsurges the expression of Cyclooxygenase 2 (COX2) and IDO in BM-MSCs, thus further promoting a homeostatic response toward M2 macrophage polarization. Through the release of chemokine (C-C motif) ligands CCL2, CCL3, and CCL12, human and mouse BM-MSCs can recruit monocytes and macrophages into inflamed tissues and promote wound repair.

This polarizing effect of MSCs on M2 macrophages is closely linked with the capability of MSCs to favor the development of regulatory T cells (Tregs), which are involved in immunosuppression. TGF- β is a factor that is constitutively produced by MSCs and that directly induces Tregs in a monocyte-dependent manner. M2 polarized macrophages also produce IL-10, which is straight immune suppressive. In addition, M2 macrophages produce CCL18, a factor that in conjunction with TGF- β promotes the group of Tregs. The MSC-derived factors that induce the differentiation of monocytes toward M2 macrophages have not been recognized.

These data underline the importance of the interactions between MSCs and the innate immune system in balancing proinflammatory and anti-inflammatory responses in order to reserve tissue integrity. The principal role of macrophages in the initiation of the anti-inflammatory effect of MSCs is depicted in.

Role of MSCs in orchestrating adaptive immune responses

The adaptive immune system is antigen-specific and allows the development of immunological memory. It comprises CD4+ T-helper and CD8+ cytotoxic T lymphocytes that deliver a tailored antigen-specific immune response following antigen processing and presentation by Antigen Presenting Cells (APCs). T helper cells comprise a subpopulation of cells, Tregs, which are specialized in suppression of T cell-mediated immune responses. The innate immune system plays a crucial part in the initiation and subsequent direction of adaptive immune responses, as well as in the removal of pathogens that have been targeted by an adaptive immune response.

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