ImmunoTools *special* Award 2014

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Modulation of suppressor populations as a strategy to revert immunosuppression associated to late phases of sepsis

Our interest is focus on the study of sepsis-derived immunosuppression. Secondary infections due to post-sepsis immunosuppression are a major cause of death in septic patients. This is one of the main problems in Intensive Care Units. Exposure to lipopolysaccharide (LPS), the main component of the membrane of Gram-negative bacteria, has been considered the initial phase and one of the causes of the immunosuppression frequently observed in late sepsis. A population of myeloid precursors, characterized as Gr-1^{+} CD11b^{+}, has been described to suppress the immune response in different experimental and clinical pathologies. We have been studying the role of myeloid-derived suppressor cells (MDSC) and also T regulatory cells in the development of immunosuppression caused by chronic injection of LPS in a mouse model. We have reported an increase of MDSC in our model using flow cytometry to detect this population in different lymphoid and non-lymphoid organs such as the lung, and we use different drugs to modulate their activity/number. In this sense, the administration of *all*-trans Retinoic Acid (ATRA), a derivative of Vitamin A with immunomodulatory properties, to LPS-treated mice was able to restored T cell proliferation of T cells obtained from lymph nodes, and this was associated to a decreased number of live MDSC. ATRA also improved the primary humoral immune response and increased the number of all lymphocyte populations in lymphoid tissues (Martire-Greco, D. *et al*. **Clinical Science**, 2014). Our results demonstrate that ATRA restores immunocompetence, modulating the number of leukocytes and the survival of MDSC, representing a supplementary potential strategy in the treatment of the immunosuppressive state of sepsis.

We are now studying the mechanisms by which ATRA modulates the activity of MDSC using *in vitro* experiments with purified mouse MDSC. Additionally, we are also exploring other possible mechanisms that may contribute to sepsis-derived immunossuppression, such as dendritic cell apoptosis and lymphocyte exhaustion. In this sense, we are interested in investigating mouse/human dendritic cell differentiation/activation/death in the presence/absence of LPS, and the influence of ATRA in these processes. For this purpose we will use different antibodies and cytokines to generate dendritic cells from mouse bone marrow or human monocytes and study their state in response to LPS/ATRA.

Additionally, we are also studying the migration and interaction of suppressor populations with LPS-treated endothelial and/or lung epithelial cells *in vivo* and using an *in vitro* model with cell lines of human origin. For this purpose, we are asking for some mouse chemokines, mouse and human endothelial factors and myeloid markers.