CROSS-TALK BETWEEN INNATE AND ADAPTIVE IMMUNITY: TLR4/MYD88-DEPENDENT, LPS-INDUCED SYNTHESIS OF PGE2 BY MACROPHAGES OR DENDRITIC CELLS PREVENTS ANTI-CD3-MEDIATED APOPTOSIS OF T CELLS

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The immune system uses both innate and adaptative responses to interact and eliminate pathogenic microorganisms. Although these immune responses use distinct cellular and molecular mechanisms, they are interconnected in such way that they share several components. In addition, particularly through chemokines and inflammatory cytokines, one can regulate the activity of the other. This can be easily illustrated by the fact that INF-γ produced by T lymphocytes is a potent activator of the microbicidal activity of macrophages. Conversely, stimulation of dendritic cells (DC) via Toll-like receptors, which act as sensors for microbial products, leads to DC maturation and migration from peripheral tissues to draining lymph nodes, where they will come across and activate antigen-specific T lymphocytes.

One important feature of the adaptive immune response is that it restrains itself whenever antigen stimulation becomes unavailable. What this means is that every time after antigen-driven clonal expansion, the immune system must discard a bulk of immune cells to make room for the forthcoming expansion of another set of antigen-specific lymphocytes. Elimination of unwanted activated lymphocytes at the end of the immune response is achieved through the induction of suicide program know as apoptosis. In this case, more specifically this phenomenon is known as activation-induced cell death (AICD) and is dependent on Fas-FasL interaction.

We used the DO11.10 T cell hybridoma incubated with anti-CD3 antibody to mimic the AICD observed during the adaptive immune response. We then asked whether the innate immunity could modulate this form of cell death. Our results provided evidence that LPS-stimulated macrophages and/or DCs release PGE2 which, in turn, blocks AICD in DO11.10 cells by preventing the anti-CD3-driven upregulation of FasL in these cells. PGE2 production by macrophage and DCs is independent of TLR2, CD14 and IRF-3, but dependent of TLR4 and MYD88.

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