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## Dendritic cells and $\gamma\delta$ T cells interaction during infections

T-cell derived signals combined to innate stimuli promote the activation of dendritic cells (DC) and regulate the adaptive immune response.<sup>1</sup> Understanding these signals is crucial to manipulate the immune system for new vaccination strategies and especially for infectious diseases. Both CD4<sup>+</sup> and CD8<sup>+</sup> T-cells have been involved in the activation of DCs<sup>2</sup> but the pool of antigen-specific  $\alpha\beta$  T-cells available to provide such signals at the site of infections would likely be small. Thus, Natural Killer (NK) cells and/or  $\gamma\delta$  T-cells seem to play a major role on DCs maturation in peripheral tissues.<sup>3</sup> The cooperation between different immune compartments could represent a crucial factor in the regulation of consequent immune responses triggered by DCs. In this context, human  $\gamma\delta$  T-cells play an important role as a first line of defence against pathogens and particularly a subset carrying V $\gamma$ 9V $\delta$ 2 TCR. These have a unique reactivity to small nonpeptidic phosphorylated antigens derived from mycobacteria,<sup>4</sup> certain bisphosphonates,<sup>5</sup> alkylamines<sup>6</sup> or abnormal metabolic routes<sup>7</sup> in a MHC-unrestricted manner. Several studies showed that  $\gamma\delta$  T cells may induce the maturation of DCs but whether and how the indirect signals derived from  $\gamma\delta$  T cells are integrated with the direct recognition of bacterial products by DCs is still unclear. Co-culture of immature DCs with activated V $\gamma$ 9V $\delta$ 2 T cells, in the presence of bacterial products such lipopolysaccharide (LPS), led to a significant increase of the expression co-stimulatory (CD40, CD80, CD83, CD86) and MHC molecules (Figure 1). Furthermore, activated  $\gamma\delta$  T cells up-regulate the expression of chemokine receptors (such as CCR7) on DCs more than DCs activated by LPS alone. Thus,  $\gamma\delta$  T cells may complement the migratory activity of DCs to lymphoid organs and the consequent T-cell antigen presentation. The functional interaction between DCs and  $\gamma\delta$  T cells increases the functional maturation of DCs and their capacity to polarize naïve T cells aug-

menting Th1 immune response in cord blood CD4<sup>+</sup>CD45RA<sup>+</sup> T cells (Figure 1). Moreover, this interaction results in a reciprocal activation that increases  $\gamma\delta$  T cell activation and pro-inflammatory cytokine production independently on the DCs maturation state (Figure 2). Moreover, DCs induce the proliferation of  $\gamma\delta$  T cells in the absence of IL-2 through the CD86 contact (Figure 2). The complex interplay between DC and  $\gamma\delta$  T-cells at the site of bacterial infection represents a network of paracrine and cell-contact interactions which boost the local proinflammatory response and more rapidly trigger the adaptive immunity.<sup>9,10</sup> In particular,  $\gamma\delta$  T cells may play an important role in anti-mycobacterial immunity.<sup>11</sup> Studies in human and animal models have demonstrated complex pattern of  $\gamma\delta$  T cell immune responses during early phases of mycobacterial infections and chronic tuberculosis. Multiple host and microbial factors can regulate diverse immune responses of phosphoantigen-specific  $\gamma\delta$  T cells during mycobacterial infection and their influence on dendritic cells system. Recently, Dieli F. *et al.* demonstrated in mice models the existence of the reciprocal activating interaction between  $\gamma\delta$  T cells and dendritic cells mediated only by pro-inflammatory and Th1 cytokines produced by both cell types.<sup>12</sup> In humans, this interplay needs further investigations.

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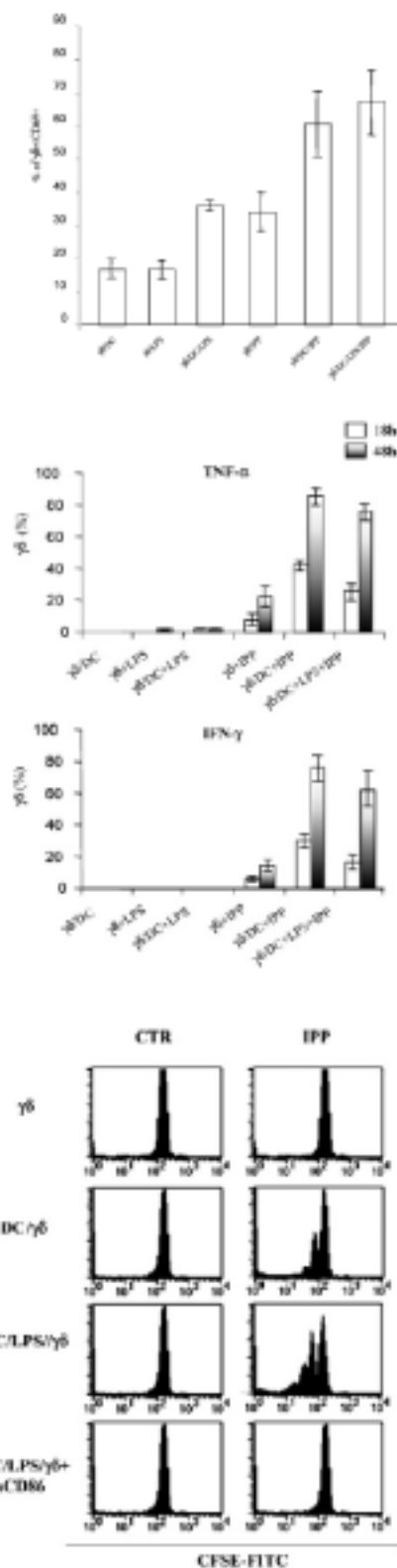
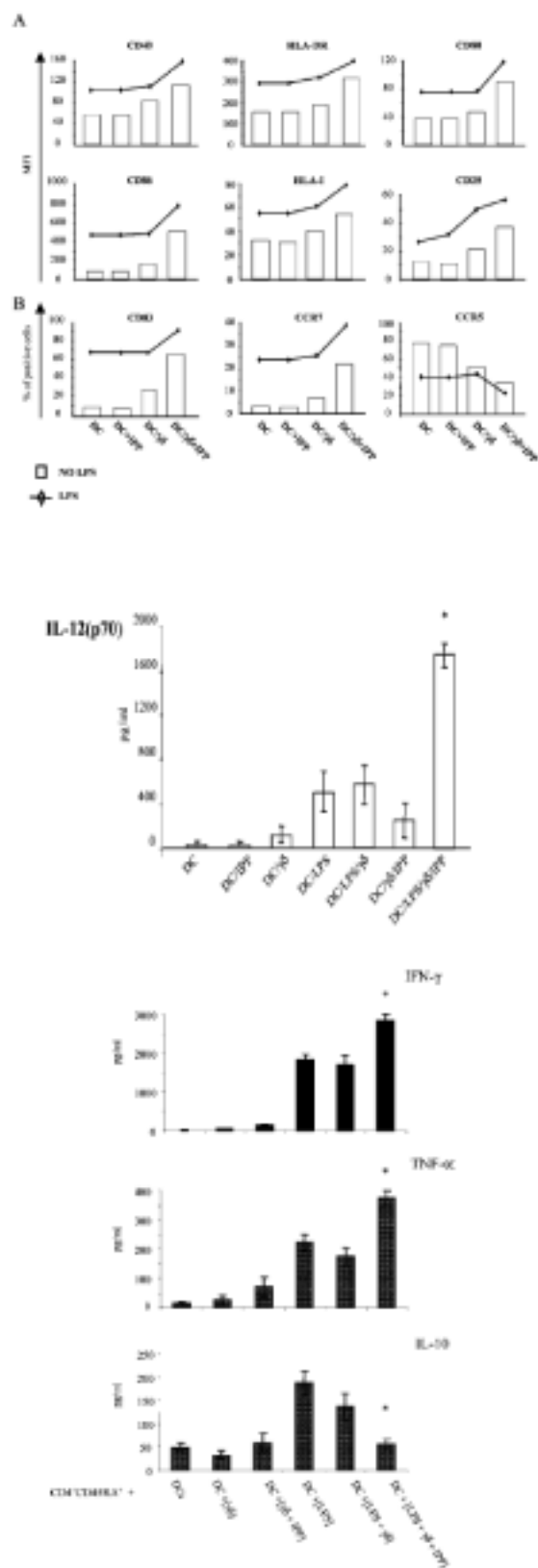


Figure 1. Influence of activated human  $\gamma\delta$  T cells on DC maturation, IL-12 production and Th1 polarizing capacity in co-cultured naïve CD4 T cells.

Figure 2. Influence of imDCs and mDCs on  $\gamma\delta$  T cell activation, cytokine production and proliferation.

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