



[haematologica reports]
2006;2(3):21-23

MARTINO A
POCCIA F

Laboratory of Cellular
Immunology, National Institute
for Infectious Diseases
"L. Spallanzani", Rome, Italy

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.¹ Understanding these signals is crucial to manipulate the immune system for new vaccination strategies and especially for infectious diseases. Both CD4⁺ and CD8⁺ T-cells have been involved in the activation of DCs² 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.³ 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 γ 9V δ 2 TCR. These have a unique reactivity to small nonpeptidic phosphorylated antigens derived from mycobacteria,⁴ certain bisphosphonates,⁵ alkylamines⁶ or abnormal metabolic routes⁷ 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 γ 9V δ 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⁺CD45RA⁺ 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.^{9,10} In particular, $\gamma\delta$ T cells may play an important role in anti-mycobacterial immunity.¹¹ 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.¹² In humans, this interplay needs further investigations.

References

1. Sporri R, Reis e Sousa C. Newly activated T-cells promote maturation of bystander dendritic cells but not IL-12 production. *J Immunol* 2003;171:6406-3.
2. Degli-Esposti MA, Smyth MJ. Close encounters of different kinds: Dendritic cells and NK cells take centre stage. *Nat Rev Immunol* 2005;5:112-124.
3. Mailliard RB, Egawa S, Cai Q, Kalinska A, Bykowskaya SN, Lotze MT, et al. Complementary dendritic cell-activating function of CD8⁺ and CD4⁺ T-cells: helper role of CD8⁺ T-cells in the development of T helper type 1 responses. *J Exp Med* 2002;195:473-83.
4. Constant P, Davodeau F, Peyrat MA, Poquet Y, Puzo G, Bonneville M, et al. Stimulation of human gamma delta T-cells by nonpeptidic mycobacterial ligands. *Science* 1994;264:267-70.

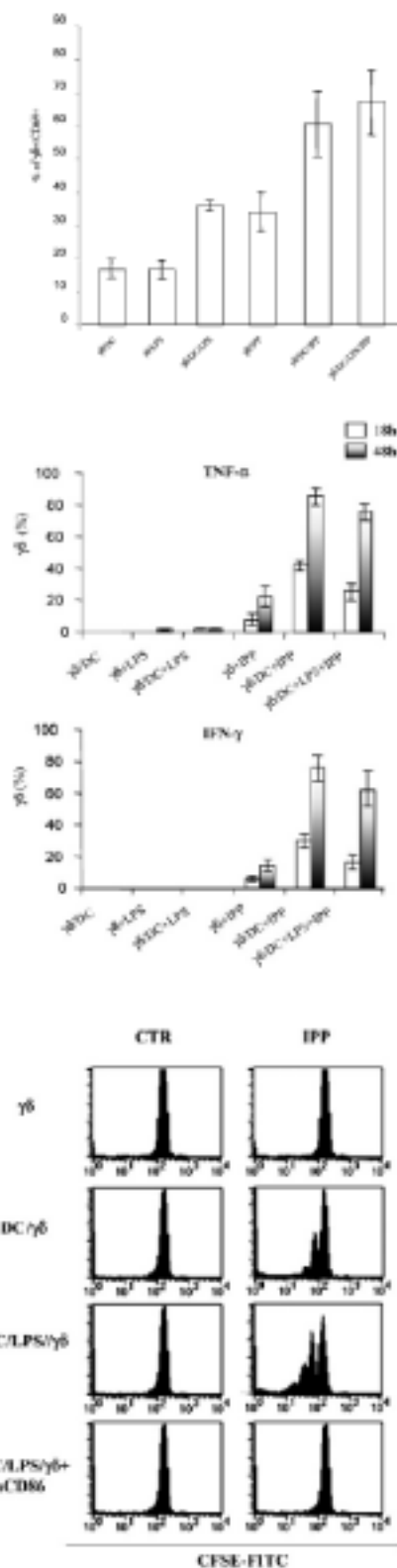
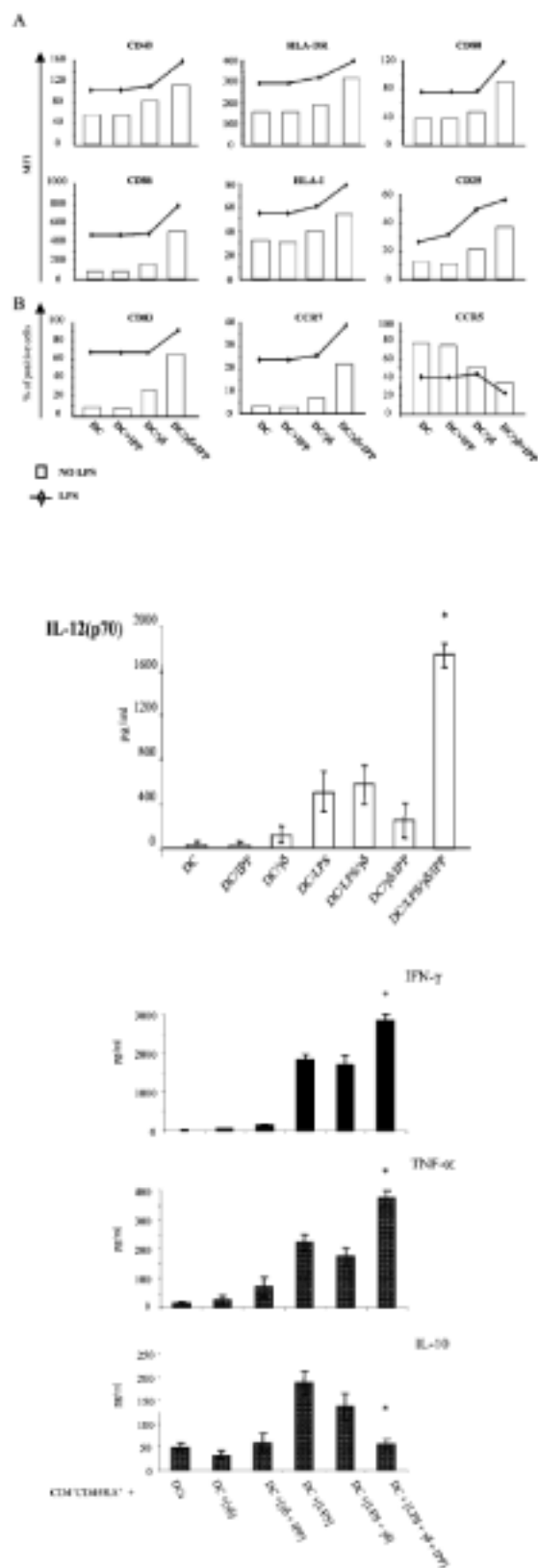


Figure 1. Influence of activated human $\gamma\delta$ T cells on DC maturation, IL-12 production and Th1 polarizing capacity in co-cultured naïve CD4 T cells.

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

5. Kunzmann V, Bauer E, Wilhelm M. $\gamma\delta$ T cell simulation by pamidronate. *N Engl J Med* 1999;340:737-8.
6. Bukowski JF, Morita CT, Brenner MB. Human $\gamma\delta$ T cells recognize alkylamines derived from microbes, edible plants, and tea: implications for innate immunity. *Immunity* 1999;11:57-65.
7. Gober HJ, Kistowska M, Angman L, Jenö P, Mori L, De Libero G. Human T cell receptor $\gamma\delta$ cells recognize endogenous mevalonate metabolites in tumor cells. *J Exp Med* 2003;197:163-8.
8. Ismaili J, Olislagers V, Poupot R, Fournie JJ, Goldman M: Human $\gamma\delta$ T-cells induce dendritic cell maturation. *Clin Immunol* 2002;103:296-302.
9. Martino A, Casetti R, D'Alessandri A, Sacchi A, Poccia F. Complementary function of $\gamma\delta$ T cells and dendritic cells in the response to isopentenylpyrophosphate and lipopolysaccharide antigens. *J Clin Immunol* 2005;25:228-35.
10. Martino A, Poccia F. Close encounters of different kinds: dendritic cells and $\gamma\delta$ T cells heighten therapeutic applications. *Immunol Lett* 2005;101:115.
11. Chen ZW, Immune regulation of $\gamma\delta$ T cell responses in mycobacterial infections. *Clin Immunol* 2005;116:202-7.
12. Dieli F, Caccamo N, Meraviglia S, Ivanyi J, Sireci G, Bonanno CT, et al. Reciprocal stimulation of $\gamma\delta$ T cells and dendritic cells during the anti-mycobacterial immune response. *Eur J Immunol* 2004;34:1-9.