

## Dendritic cells and gammadelta ( $\gamma\delta$ ) T cells with

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through TCR engagement, other classes of stimulatory molecules such as bisphosphonates and alkylamines may activate  $V\gamma9V\delta2$  T cells indirectly, leading to IPP accumulation by blocking the MVA pathway (5,8).

### What is known today about circulating $\gamma\delta$ T cells?

**Angelo Martino and Fabrizio Poccia:** Murine  $\gamma\delta$  T cells are the first lineage of T lymphocytes that appear in the mouse thymus, and later, predominate in epithelia. Intestinal, lymphoid and dendritic epidermal  $\gamma\delta$  T cells develop normally in both athymic and MHC class I/II deficient mice. The expression of distinct V-gene segments not only marks different subsets, but is often associated with a more-or-less specific preponderance in blood circulation or recruitment in different tissue (1). Similarly

to the mouse, the expression of human  $\gamma\delta$  TCR variable segments is associated with tissue prevalence for instance, the  $V\delta1$  T-cell subset appears to have largely resident characteristics. Human  $V\delta1$  T cells form a large subpopulation of gut, skin and lung lymphocytes, whereas  $V\gamma9V\delta2$  T lymphocytes mainly frequent the adult peripheral blood (2).  $\gamma\delta$  T cells participate directly with NK cells and NK-T cells in the innate immune response against tumor cells or pathogen-infected cells (3,4).

### Are $V\gamma9V\delta2$ T cells a special subgroup of $\gamma\delta$ T cells?

**Angelo Martino and Fabrizio Poccia:** Human  $V\gamma9V\delta2$  T cells are the main blood/lymphoid organ  $\gamma\delta$  T-cell subpopulation and typically recognize phosphomonoester molecules synthesized in the mevalonate (MVA) and 1-deoxy-d-xylulose-5-phosphate (DOXP) metabolic pathways (3). These low molecular weight phosphate-containing, non-processed antigens are called "phosphoantigens" and are produced by different gram-positive and gram-negative bacteria as well as by eukaryote parasites or derived from abnormal metabolic routes of eukaryotic cells. These unique features characterize  $V\gamma9V\delta2$  T cells as a "special" peripheral lymphoid subset with a "sentinel" function (3-5), showing broad anti-tumor and antimicrobial reactivity in vitro and in vivo. Accordingly, these cells display

several features shared by innate effectors such as: (i) their ability to be early activated during the immune response, owing to recognition of conserved non-peptidic antigens rapidly up-regulated upon stress/infection or transformation, (ii) their high frequency in most individuals and (iii) their natural pre-activated/memory status presumably resulting from exposure to conserved stimuli early during life. The non-peptidic antigens able to activate  $V\gamma9V\delta2$  T cells are prenyl pyrophosphates (6), bisphosphonates (7) and alkylamines (8). The first antigen to be fully described was isopentenyl pyrophosphate (IPP), a pyrophosphomonoester intermediate of the MVA biosynthetic pathway (3,5). While pyrophosphomonoester antigens may directly activate  $V\gamma9V\delta2$  T cells

### What is the role of IL-2 and IFN- $\gamma$ during stimulation of $\gamma\delta$ T cells?

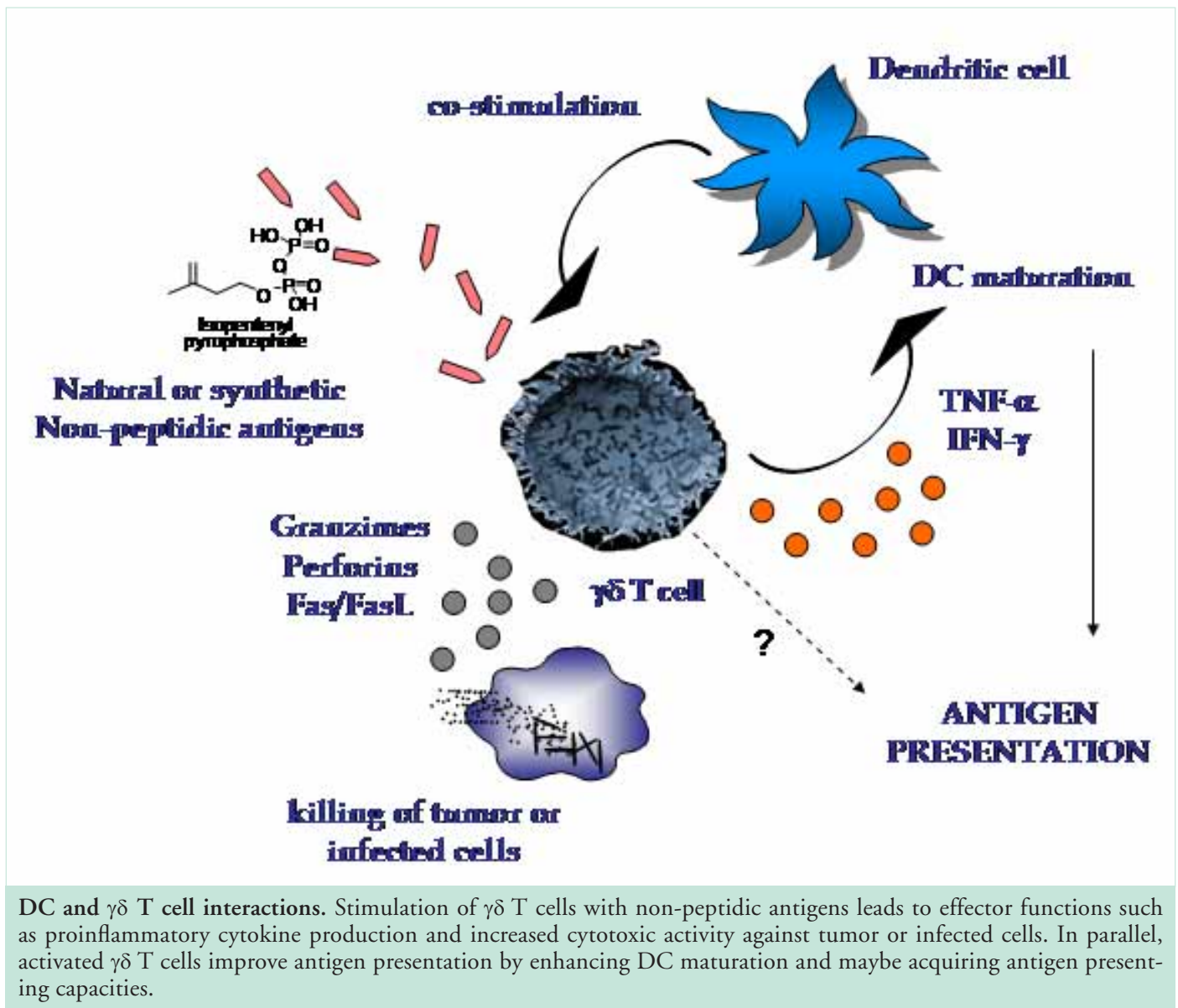
**Angelo Martino and Fabrizio Poccia:** IL-2 is a crucial growth factor for T lymphocytes that is poorly produced by activated  $\gamma\delta$  T cells.  $V\gamma9V\delta2$  T cells proliferation in vitro induced by phosphoantigens requires exogenous IL-2, indicating that the presence of IL-2 signal is an essential co-factor for  $\gamma\delta$  T cell proliferation. Recently, we have demonstrated that IL-2 administration is a strict requirement for in vivo  $V\gamma9V\delta2$  T cell expansion upon by non-peptidic antigens in the peripheral blood (9). Differently, we demonstrated that purified  $\gamma\delta$  T cells, co-cultured with dendritic cells and phosphoantigens, proliferate in the

absence of IL-2 but require the CD86 cell-mediated contact (10). Thus, the  $\gamma\delta$  T cell need of co-stimulation may change in lymphoid organs and inflamed tissues where DC are present.  $\gamma\delta$  T cells may release large amounts of IFN- $\gamma$  and other other pro-inflammatory cytokines and chemokines (11). The IFN- $\gamma$  production by  $\gamma\delta$  T cells is one of the main soluble factor involved in their antiviral activity against viruses as different as HCV, SARS-CoV and orthopoxviruses (12-14). Both IFN- $\gamma$  as well TNF- $\alpha$  or IL-12 are not implicated in the co-stimulation of  $\gamma\delta$  T cells, whereas type I IFN may directly contribute to  $\gamma\delta$  T cell activation (15).

### Are Dendritic cells involved?

**Angelo Martino and Fabrizio Poccia:**  $\gamma\delta$  T cell activity affect also the specific immune response by enhancing dendritic cell (DC) maturation and directly promoting the specific immune response. A reciprocal activating interaction between dendritic cells and  $V\gamma9V\delta2$  T cells has been demonstrated recently by our group in the presence of non-peptidic antigens (10). Dendritic cells participate to the activation of  $\gamma\delta$  T cells enhancing their antigen activation in terms of cytokine production, expression of activation marker and proliferation. On the other hand activated  $\gamma\delta$  T cells are able

to induce DC maturation, production of TNF- $\alpha$  and Th1 polarizing capacity (10). Thus, the complex interplay between DCs and  $\gamma\delta$  T cells represent a network of paracrine and cell-contact interactions which may boost the local proinflammatory response and more rapidly trigger the adaptive Th1 immunity to lymphoid organs (16). Recently, a direct role of human  $V\gamma9V\delta2$  T cells as professional APC has been suggested by Brandes M. et al. (17), indicating a new perspective for  $\gamma\delta$  T cell-mediated immunity if these data will be confirmed.



### Can $\gamma\delta$ T cells be stimulated for therapeutic use?

**Angelo Martino and Fabrizio Poccia:** Since the activity of  $V\gamma 9V\delta 2$  T cells *in vitro* and *in vivo* can be stimulated by many non-peptidic molecules the possibility to stimulate  $\gamma\delta$  T cells for therapeutic use is a goal of recent studies both for cancer and infectious disease. Bisphosphonates are frequently used in the treatment of bone demineralization disorders and has been demonstrated to enhance the activation and catalytic activity of  $\gamma\delta$  T cells in cancer patients

(18). Also, pyrophosphomonoester drugs of synthetic origin such as BrHpp (phosphostim) are currently being tested in Phase I cancer trials. The reciprocal interactions of DC and  $V\gamma 9V\delta 2$  T cells heighten the impact of this cellular cross-talk in the design of new immune-based therapies. The relatively low *in vivo* toxicity of  $V\gamma 9V\delta 2$  T cell stimulating drugs makes possible novel therapeutic strategies for infectious and neoplastic diseases.

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