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$\gamma\delta$ T-cells: cross-talk between innate and adaptive immunity

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For convenience, immune responses are frequently categorized as "innate" versus "adaptive" on the basis of the time course kinetics and contributing cells and mediators. Cells of the innate immune system, including monocytes, granulocytes, or natural killer (NK) cells, lack clonally variable antigen-specific receptors but express pattern recognition receptors such as Toll-like receptors (TLR), which rapidly initiate cytokine production upon recognition of conserved microbial or endogenous danger signals. In contrast to the innate immune system, a hallmark of the adaptive immunity is immunological memory, the basis of any successful vaccination. T-lymphocytes and B-lymphocytes, effector cells of the adaptive or specific immune system, are characterized by the expression of clonally variable antigen receptors that are built up from rearranged gene segments coding for variable (V), diversity (D), joining (J) and constant (C) genes. The majority of mature T cells expresses a T cell receptor (TCR) composed of an α/β protein heterodimer which is non-covalently linked to the signal-transducing CD3 complex. Signaling through the TCR is initiated by the activation of src protein tyrosine kinases leading to the phosphorylation of CD3 immunoreceptor tyrosine-based activation motifs (ITAMs) followed by recruitment of ZAP-70 and activation of associated adapter proteins [1]. $\alpha\beta$ T cells are further divided into subsets based on expressed co-receptors or distinct patterns of cytokine production. $CD4^+$ T cells recognize via their TCR peptides derived from exogenous antigens and presented in the context of MHC class II molecules, whereas $CD8^+$ T cells recognize their cognate antigenic peptides generated endogenously, e.g., during viral infection via presentation by MHC class I molecules [2]. In recent years, it became obvious that $CD4^+$ T cells are functionally heterogeneous and comprise distinct (yet occasionally overlapping) subpopulations. Today, there is general agreement that there are (at least) 4 well-characterized $CD4^+$ T cell populations that can be distinguished on the basis of cytokines and the expression of specific transcription factors: T helper 1 cells produce interferon-γ as a key cytokine and express the transcription factor Tbet; T helper 2 cells produce interleukin-4/interleukin-10 as key cytokines and express the transcription factor GATA-3; T helper 17 cells produce the pro-inflammatory interleukin-17 and express the transcription factor RORγt; and regulatory T cells (Treg) which inhibit immune responses and express the transcription factor FoxP3. There is, however, substantial plasticity in the lineage commitment of $CD4^+$ T cells, pointing to the importance of the local microenvironment for the functional $CD4^+$ T cell development [3].

It came as a surprise when it was discovered in the mid-1980s that there is a second group of rearranging genes giving rise to an "alternative" TCR instead of the "conventional" $\alpha\beta$ TCR. The rearranging genes were termed $\gamma\delta$, and cell surface expression of this $\gamma\delta$ TCR in association with CD3 could be demonstrated [4]. During the 25 years since their discovery, the interest of immunologists in $\gamma\delta$ T cells has witnessed many ups and downs. The initial excitement was followed by periods of moderate interest when the role of $\gamma\delta$ T cells appeared more or less redundant to other ($\alpha\beta$ T cell) immune cells. A large body of evidence indicated that $\gamma\delta$ T cells contribute to anti-infective and tumor immune responses and regulate local immune surveillance [5]. In fact, certain microbes including *Mycobacterium tuberculosis* turned out to be extremely potent antigens for $\gamma\delta$ T cells [6]. An important step toward

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an understanding of why the immune system has afforded to maintain two separate T cell receptors throughout evolution was the identification of antigens that can be recognized by γδ T cells but not by any other immune cells including αβ T cells. In this respect, the identification of non-peptide phosphate-containing low molecular weight mycobacterial compounds that were selectively recognized by human γδ T cells expressing a Vγ9Vδ2 TCR was a major breakthrough [7]. Subsequently, pyrophosphate antigens for Vγ9Vδ2 T cells produced by eukaryotic (isopentenyl pyrophosphate, IPP) or prokaryotic cells [(E)-1-hydroxy-2-methyl-but-2-enyl 4-diphosphate, HMB-PP] in the course of isoprenoid synthesis, have been molecularly identified as the Vγ9Vδ2-selective ligands. Such molecules are not recognized by αβ T cells. Vγ9Vδ2 cells account for 50–95% of the peripheral blood γδ T cell population. Since γδ T cells usually comprise 2–6% of blood $CD3^+$ T cells, this means that up to 2–4% of all T cells can be rapidly activated (e.g., to secrete cytokines) by such γδ-specific ligands, i.e., much larger cell numbers in comparison to the frequency of antigen-specific αβ T cells.

The recognition of microbial and eukaryotic pyrophosphates by γδ T cells provides an interesting link to the suspected role of γδ T cells in infection and tumor defense. Microbial pyrophosphates such as HMB-PP are active at the pico- to nanomolar range, whereas micromolar concentrations of eukaryotic pyrophosphates such as IPP are required to stimulate γδ T cells. While the IPP concentration in normal cells is too low to activate γδ T cells, tumor cells frequently produce much higher concentrations which then can be sensed by γδ T cells [8]. It would thus appear that human Vγ9Vδ2 T cells use their TCR as a pattern recognition receptor for sensing dysbalanced pyrophosphate levels that could result from either infection (exogenous HMB-PP) or malignant transformation (overproduced endogenous IPP). Importantly—and highly relevant for clinical perspectives—it turned out that IPP levels in eukaryotic cells can be manipulated by clinically used drugs. Aminobisphosphonates (e.g., zoledronic acid, Zometa®) are used in the clinic for treatment of patients with osteoporosis or cancer patients with bone metastasis. Interestingly, these drugs inhibit an IPP-degrading enzyme, thereby leading to intracellular accumulation of IPP which can then be recognized by the γδ T cells. In fact, pre-treatment of tumor cells with aminobisphosphonates greatly increases their susceptibility toward γδ T cell-mediated lysis. [9]. These exciting recent developments have promoted a strong interest in potential clinical perspectives of γδ-targeting immunotherapies [10, 11].

To provide a forum for discussion and scientific exchange of immunologists with a keen interest in these unique immune cells, bi-annual international conferences were initiated by W. Born and R. O'Brien. The first γδ T cell Conference was held in Denver, USA, in 2004, followed by further conferences in La Jolla, USA (2006), Marseilles, France (2008) and Kiel, Germany (2010). The present special issue of *Cellular and Molecular Life Sciences* contains 10 reviews by international experts in the field of γδ T cell research, all of whom participated in the Kiel conference in 2010. The topics addressed in these contributions include basic principles of γδ T cell activation (i.e., characterization of recognized antigens, identification of co-stimulatory requirements, modulation by Toll-like receptor ligands, specific cytokine production), the function of skin-resident γδ T cells, the dynamics of γδ T cell interactions with other cells, and the role of human γδ T cells in infection and tumor immunity. In addition to the current status of exploring γδ T cells for immunotherapy of solid tumors and leukemias and lymphomas, and which strategies tumors might use to escape from γδ T cell attack are also discussed. Finally, the provocative findings that human γδ T cells can actually serve as potent antigen-presenting cells are summarized. This feature nicely illustrates the unique role of γδ T cells at the crossroads of innate and adaptive immunity: Vγ9Vδ2 T cells are rapidly activated by microbial phosphoantigens and produce cytokines including TNFα and interferon-γ. Soon after activation, γδ T cells acquire the capacity to take up and process antigen and to present it to $CD4^+$ and $CD8^+$ T cells, and thereby help to initiate peptide-specific αβ T cell responses [12]. Taken together, it appears that human Vγ9Vδ2 T cells display a surprisingly broad range of functional activities, i.e., pro-inflammatory cytokine production, potent killer cell activity, regulatory (suppressive) functions [13], and antigen-processing and -presenting capacity. It remains to be investigated in more detail whether certain functions can be attributed to distinct subpopulations of Vγ9Vδ2 γδ T cells.

Together, γδ T cells thus display features of both the innate and adaptive immune system. Although they express T cell antigen receptors, the germline-encoded TCR repertoire is very small, and many γδ T cells use their TCR for the recognition of conserved molecules, similarly to pattern recognition receptors. Additionally, γδ T cells express functional "classical" pattern recognition receptors including Toll-like receptors [14, 15] and Nod-like receptors [16, 17]. Many recent findings have shed new light on the significance of γδ T cells. The present collection of articles highlights our current knowledge and discusses future developments in the field.

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