Editorial

Introductory Overview: γδ T-Cells at the Cross-Road of Innate and Adaptive Immunity

Abstract: γδ T-lymphocytes are a numerically small subset of T-lymphocytes which differ from conventional αβ T-lymphocytes primarily in respect to the ligands recognized by the T-cell antigen receptor. In this regard, human γδ T-cells differ significantly from their murine counterpart, because only human but not mouse γδ T-cells recognize small phosphorylated metabolites that are produced by many bacteria and parasites, but also by transformed eukaryotic cells. γδ T-cells contribute to local immune surveillance and are involved in immune defense against infection and tumor formation. Based on their potent anti-tumor activity, immunotherapeutic protocols aimed at the activation of tumor-reactive γδ T-cells have entered clinical studies.

Characteristic features of the adaptive immune system as represented by B- and T-lymphocytes are specificity and immunological memory. In view of the undisputed ability of the B- and T-cell receptor repertoire to recognize myriads of potential antigens with unprecedented specificity, it came as a surprise when a second T-cell receptor consisting of a γδ- rather than αβ T-cell receptor heterodimer was discovered [1,2]. In contrast to the conventional αβ T-cell receptor, there are only a few genes in the germline genome that can be used for functional V-(D)-J rearrangements. Nevertheless, the γδ T-cell receptor repertoire is tremendous, due to the extensive usage of non-genome-encoded mechanisms of diversification, such as insertion of N-nucleotides. The interest of the scientific community in γδ T-cells has seen ups and downs ever since their discovery more than 20 years ago. Many studies over the years have indicated that γδ T-cells play important roles in the immune defense against infection and cancer, but also in the control of tissue homeostasis [3]. Most functions are non-redundant to αβ T-cells and cannot be fulfilled by other cells of the immune system. A striking example is the selective and exclusive recognition of bacterial metabolic intermediates (pyrophosphates) of isoprenoid biosynthesis by human Vγ9Vδ2 T-cells [4,5]; these so-called phosphoantigens are not recognized by any other immune cell. However, despite intensive research, many details of the role of γδ T-cell in normal and pathophysiological conditions are still unsolved. The present Special Supplement of The Open Immunology Journal highlights some of the current issues in γδ T-cell research.

An important area of research concerns the nature of antigens and ligands that are recognized by the γδ T-cells but not by conventional αβ T-cells. In this regard, it is interesting to note that γδ T-cells preferentially recognize ligands that are induced by cellular stress as it occurs e.g. during infection or cellular transformation [6,7]. Very interesting examples are pyrophosphates that are produced by many bacteria and parasites *via* the so-called non-mevalonate pathway or by eukaryotic cells *via* the mevalonate pathway. Intermediates of the microbial pathway are active at pico-to nanomolar concentrations, whereas intermediates of the eukaryotic pathway such as isopentenyl pyrophosphate (IPP) require micromolar concentrations to be recognized by the human Vγ9Vδ2 TCR. In his article, Gennaro de Libero discusses the nature and occurrence of such phosphoantigens but also of other ligands that have been shown to stimulate human γδ T-cells. Phosphoantigens are small, non-peptidic molecules that are not presented by MHC class I or class II molecules, yet require some sort of presentation to γδ T-cells. Phosphoantigen-reactive Vγ9Vδ2 T-cells are potent effector cells that display cytotoxic effector function but also produce a range of cytokines, notably pro-inflammatory cytokines including tumor necrosis factor-α and interferon-γ. Zheng W. Chen has extensively studied the *in vivo* distribution and migration of phosphoantigen-responsive γδ T-cells in *Mycobacterium tuberculosis* infection and upon *in vivo* application of phosphoantigen into macaques. In his contribution, Zheng W. Chen reviews these studies and highlights important modulatory effects of human γδ T-cells on regulatory T-cells (Treg). Interestingly, the production of endogenous pyrophosphates by eukaryotic cells can be manipulated by licensed drugs. Aminobisphosphonates (n-BP) are in clinical use for the treatment of patients with osteoporosis and bone metastasis in certain types of cancer. In addition to direct effects on osteoclasts and tumor cells, n-BP induce an intracellular accumulation of the phosphoantigen IPP by inhibiting an IPP-degrading enzyme [8]. Therefore, the treatment of tumor cells with n-BP increases the sensitivity of tumor cells to γδ T-cell mediated lysis [7]. Human γδ T-cells also express certain Toll-like receptors (TLR)

1874-2262/09 2009 Bentham Open

including the polyI:C-responsive TLR3 [9]. Stefanie Ohnesorge *et al.* present interesting studies on the differential polyI:C responsiveness of IPP- *versus* n-BP-activated human γδ T-cells, supporting the view that different mechanisms contribute to the activation of γδ T-cells by phosphoantigen and n-BP (i.e., direct recognition of phosphoantigen by γδ T-cells *versus* indirect activation through generation of phosphoantigen by n-BP; ref. [10]). The potent cytotoxic effector function of γδ T-cells together with the ability to selectively activate γδ T-cells with synthetic phosphoantigens or n-BP has stimulated great interest to explore their potential efficacy in tumor immunotherapy [11]. Richard D. Lopez discusses the currently followed strategies to bring γδ T-cell based immunotherapy into clinical application. These include *in vivo* activation of γδ T-cells by phosphoantigens or n-BP, and the adoptive transfer of *in vitro* expanded γδ T-cells.

Although the universal recognition of related pyrophosphates by T-cells expressing just one given TCR (Vγ9Vδ2) is perhaps the most important role of human γδ T-cells, it is obvious that there additional γδ T-cell subsets with important, partially still unknown, functions. Charlotte Behr and co-workers discuss the current knowledge of the appearance of Vδ2-negative γδ T-cells, their effector functions, and their suspected role in viral immunity and anti-tumor defense.

This Special Supplement of course also addresses special functions of murine γδ T-cells. It is needless to say that a large body of what we know about γδ T-cells has been generated in experimental mouse studies [12]. Yet, mice and humans are strikingly different when it comes to γδ T-cells. For instance, the mouse harbors a dense network of γδ T-cells in the skin, termed dendritic epidermal T-cells (DETC) which all express a canonical γδ TCR [13]; γδ T-cells are not present in such high frequency in the human skin [14]. Perhaps even more striking is the absence of phosphoantigen-reactive γδ T-cells in the murine γδ TCR repertoire. This means that the mouse cannot react to the microbial (and tumor cell generated) metabolites which are thought to convey an important role to human γδ T-cells in infection and tumor immunity. Willi K. Born and co-workers present a balanced overview on the significance of murine γδ T-cells in local immunity, with a focus on lung inflammation. As summarized in this article, pulmonary γδ T-cells play a role in allergic airway inflammation, but also contribute to resolve infection-induced pulmonary inflammation. Finally, the contribution of Kensuke Shibata and Yasunobu Yoshikai summarizes recent studies on the identification of IL-17 producing mouse γδ T-cells. IL-17 producing T-cells (Th_{17}) have been identified as a functionally separate T-cell lineage, in addition to Th_1 and Th_2 cells. As discussed in this report, IL-17 producing γδ T-cells differ from conventional Th17 cells with respect to appearance during thymic ontogeny and tissue localization, supporting the notion that they fulfill non-redundant functions in the immune system.

It becomes evident from the collection of papers in this Special Supplement that γδ T-cells are versatile cells at the crossroad of innate and adaptive immunity. They share with conventional αβ T-cells most effector functions (i.e., cytokine production and cytolytic activity) but differ from αβ T-cells most strikingly with regard to the antigen/ligand recognition. Importantly, γδ T-cells use their TCR as a "pattern recognition receptor" (PRR), almost similar to classical PRRs such as TLRs, because the canonical Vγ9Vδ2 TCR recognizes pyrophosphates as a microbial pattern [15]. In this sense Vγ9Vδ2 T-cells share features of innate immune cells because they rapidly (within hours) produce cytokines. Moreover, recent studies have uncovered yet another surprising activity of the very same Vγ9Vδ2 T-cell subset: Activated γδ T-cells can act as antigen-presenting cells [16] and are capable of cross-presenting processed peptide antigens to naïve CD8+ αβ T-cells [17]. Together with accumulating evidence that the very same γδ T-cell population can also regulate αβ T-cell responses (Traxlmeir *et al*, J Immunotherapy, in press), it is presently difficult to reconcile how so many different functions can be exerted by just one T-cell subset in a controlled fashion. The recent burst of new results, summarized to a large extent in this Special Supplement, ensures that γδ T-cell research will continue to be at the forefront of immunology – particularly in view of perspectives for clinical application.

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