Seminars in Immunology 22 (2010) 199–206

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Human Vγ9Vδ2 T cells: From signals to functions

Steven Nedellec, Marc Bonneville*, Emmanuel Scotet*

INSERM, U892, Centre de Recherche en Cancérologie Nantes-Angers, Nantes, France

ARTICLE INFO

Keywords:
Human gamma delta T cells
T cell receptor
Co-stimulation
Signal transduction
Functions

ABSTRACT

Human Vγ9Vδ2 T cells, a major innate-*like* peripheral T cell subset, are thought to play *in vivo* a key role in innate and adaptive immune responses to infection agents and tumors. Vγ9Vδ2 T cell activation is tightly regulated by a variety of activating or inhibitory receptors which are specific for constitutively expressed or stress-modulated ligands. However, the mechanisms and signal transduction pathways regulating their broad effector functions, such as cytotoxicity and cytokine responses, remain poorly understood. Here we provide an updated overview of the activation modalities of Vγ9Vδ2 T cells by highlighting the respective role played by T cell receptor (TCR) *versus* non-TCR stimuli, and focus on recent studies showing how Vγ9Vδ2 T cells integrate the numerous activating and inhibitory signals and translate them into a particular effector and biological function. A better understanding of these critical issues should help optimize immunotherapeutic approaches targeting Vγ9Vδ2 T cells.

1. Introduction

Since the fortuitous discovery of γδ T cells about 25 years ago, many studies have brought insights into the recognition repertoire, development, distribution and function of this T cell subset, particularly in murine models, see [1] and [2] for recent reviews. These studies have highlighted four salient features of murine γδ T cells: (i) recognition of conserved stress-induced Ag conferring broad anti-tumor and anti-infectious reactivity, (ii) early acquisition of a memory/preactivated status in "naïve" individuals (i.e. not exposed to the *bona fide* eliciting agent), (iii) peripheral tissue location generally outside classical secondary lymphoid organs (with marked tropism for epithelia) and finally (iv) expression of a highly restricted γδ TCR repertoire in particular tissue location, presumably as the consequence of the coordinated acquisition of a restricted set of TCR, homing receptors and functional properties during their development. Many of these features are also shared by human γδ T cells, and in particular by Vγ9Vδ2 T cells, the best characterized γδ subset that predominates in adult peripheral blood. As recently reviewed, Vγ9Vδ2 T cells undergo a post-natal peripheral blood expansion associated with early acquisition of a memory phenotype and acquisition of strong cytolytic and primarily Th1-like effector functions. Moreover they are activated and expanded along various infectious and tumor contexts, thanks to recognition of isoprenoid pathway metabolites produced by both prokaryotes and eukaryotes. Here we would like to give an updated overview on the activation modalities of Vγ9Vδ2 T cells, and focus on recent studies showing how Vγ9Vδ2 T cells integrate the numerous activating and inhibitory signals and translate them into a particular effector and biological function.

Vγ9Vδ2 T cell activation results from engagement of numerous surface receptors with either inhibitory or activating properties, which primarily involve stress-sensing T cell receptors and natural killer (NK) receptors (Fig. 1).

2. TCR-dependent activation of Vγ9Vδ2 T cells

2.1. Phosphoantigens

Human Vγ9Vδ2 T cells can be efficiently activated by small phosphorylated compounds called phosphoantigens (P-Ags). This reactivity seems restricted to the Vγ9Vδ2 T cell subset [3–5]. P-Ags were first described as metabolites of the mevalonate isoprenoid pathway in mammalian cells, such as isopentenylpyrophosphate (IPP) [4]. This class of compounds contains in fact several members, naturally produced or synthetic, able to slightly or heavily activate Vγ9Vδ2 T cells [6]. Actually, the most potent natural P-Ag described so far is a phosphorylated intermediate produced by *Eubacteria* and *Protozoa* but not by eukaryotes, called hydroxy-methyl-butenyl pyrophosphate (HMBPP, also known as HDMAPP for hydroxy-dimethyl-allyl-pyrophosphate). This compound has a 1000 fold stronger stimulating activity of Vγ9Vδ2 T cells than IPP, probably due, in part, to its non-human origin [7]. To a lesser extent the synthetic bromohydrin pyrophosphate (BrHPP) is also considered as a strong activator of Vγ9Vδ2 T cells and is frequently used in experimental procedures [8].

* Corresponding authors at: INSERM UMR892, Centre de Recherche en Cancérologie Nantes-Angers, IRT UN, 8 quai Moncousu, 44007 Nantes cedex, France. Tel.: +33 228080223.
E-mail addresses: bonnevil@inserm.fr (M. Bonneville), Emmanuel.Scotet@inserm.fr (E. Scotet).

1044-5323/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.smim.2010.04.004

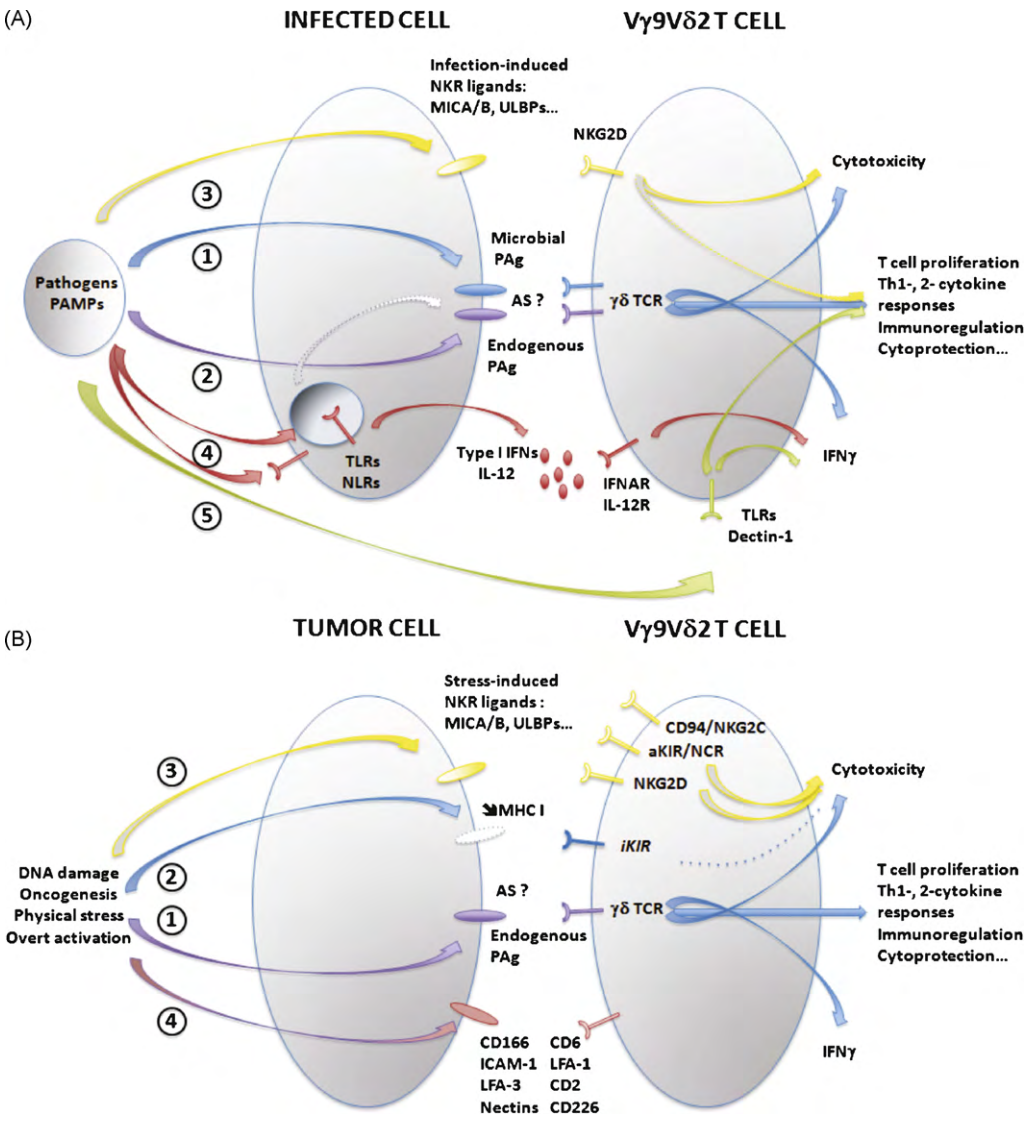

Fig. 1. Different pathways leading to human Vγ9Vδ2 T cell activation during infection and cellular stress. Vγ9Vδ2 T cell functions (e.g. cytotoxicity, cytokines, proliferation) can be induced by within activated Vγ9Vδ2 T cells in distinct physipathological conditions. (A) Following stimulation with microbial products like pathogen associated molecular patterns (PAMPs) or following infection, human Vγ9Vδ2 T cells are activated by a combination of pathways involving membrane and/or soluble molecular partners. Microbial phosphoantigens (PAg) (1) and/or upregulated self-isoprenoid metabolites (2) activate γδ T cells through a TCR-dependent process which is likely mediated by stress-associated surface molecules (e.g. ATPsynthase: AS). Surface or soluble stimuli lower γδ TCR activation threshold or reduce the need for γδ TCR stimulation. Natural killer receptor (NKR) ligands like MICA/B and ULBPs are upregulated at the surface of infected/stressed target cells (3) and engage activating NKR (aNKR), like NKG2D. PAMPs bind sensor receptors (e.g. exogenous/endogenous Toll-like receptors (TLRs), Nod-like receptors (NLRs), scavenger receptors) and participate to γδ T cell activation through a indirect cytokine-driven (4) process (e.g. type I IFNs/IFNAR, IL-12/IL12R) and and/or a direct (5) co-stimulation. (B) Stressed/transformed tumor cells upregulate endogenous PAg metabolites and activate γδ T cells through a TCR-dependent process (1). Vγ9Vδ2 T cell activation threshold is lowered following interactions between surface molecules like downregulated MHC class I molecules/inhibitory killer cell immunoglobulin-like receptors (iNKR) (2), upregulated NKR ligands/aNKR/activating KIR (aKIR)/natural cytotoxicity receptors (NCR) (3), and adhesion partners (e.g. ICAM-1/LFA-1, CD166/CD6) (4).

P-Ag recognition is MHC-independent and does not require professional Ag presenting cells. However, a cellular contact is needed for a full Vγ9Vδ2 T cell activation. Most of human cell types are able to present P-Ags to Vγ9Vδ2 T cells, suggesting the involvement of a presenting molecule widely distributed and non-polymorphic, but distinct from classical MHC class I, MHC class II, or CD1 [9]. However, there is still no evidence for the existence of a cognate P-Ag/TCR direct interaction, since attempts to co-crystallize P-Ags with the Vγ9Vδ2 TCR have not succeeded [10].

2.2. Aminobisphosphonates and alkylamines

Besides P-Ags, other pharmacological compounds such as aminobisphosphonates (N-BP) and alkylamines were shown to stimulate Vγ9Vδ2 T cells activity [11,12]. A wide variety of tumor cell lines pre-treated with N-BP (especially pamidronate or zoledronate) could efficiently activate Vγ9Vδ2 T cells to proliferate and produce cytokines in a TCR-dependent manner [13]. Because N-BP are inhibitors of the farnesyl pyrophosphate synthase (FPPS), an enzyme acting downstream of IPP synthesis along the isoprenoid pathway, γδ T cells activation by N-BP-treated target cells might be a consequence of the accumulation of endogenous P-Ags [5]. Moreover, Vγ9Vδ2 T cells cannot be activated by non-human N-BP treated target cells [14], suggesting implication of species-restricted molecules during this activation process. Similarly to N-BP, alkylamines were shown to inhibit FPPS activity. Thus, Vγ9Vδ2 T cells should be activated through accumulation and presentation of P-Ags in such treated cells.