[Frontiers in Bioscience 13, 6872-6885, May 1, 2008]

Bridging innate and adaptive immunity through γδ T - dendritic cell crosstalk

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1. ABSTRACT

Like Natural Killer cells, γδ T cells and Natural Killer T cells display several *innate-like* features that confer them a broad reactivity against tumors and pathogens. By recognizing stress-induced conserved antigens upregulated a wide array of physiopathological contexts, these lymphoid subsets develop strong and early responses to a broad set of targets. One of the most exciting roles possibly played *in vivo* by non-conventional T lymphocytes, which exhibit a biased natural memory phenotype, is active regulation of adaptive immune responses through interactions with antigen presenting cells (APCs), such as dendritic cells. Here we will review recent studies reporting functional interactions between γδ T cells and APC and a possible involvement of these lymphocytes in bridging innate and adaptative immunity along infections and tumor development. Our discussion will focus on human γδ T cells and more specifically on Vγ9Vδ2 T cells, a major subset found in human peripheral blood.

2. INTRODUCTION: GENERAL FEATURES OF γδ T CELLS

2.1. Development, distribution and phenotype of γδ T cells

γδ T cells, defined by their expression of T cell receptors (TCR) encoded by γ and δ gene loci, are found in all vertebrate species studied so far, like MHC-restricted conventional αβ T cells and B cells (1-3). One of the striking hallmarks that distinguish γδ from αβ T cells is their potential for TCR diversity, which is considerable despite a highly restricted V gene repertoire. The limited combinatorial diversity of γδ TCR is counterbalanced by extensive junctional diversity, due to removal or addition of non-germline-encoded nucleotides at V-(D)-J junctions and alternate D segments reading frames, which allows generation of a γδ TCR diversity greater than that of conventional αβ T cells (theoretically ~10^{20} *versus* ~10^{15} TCR). However the extent of TCR junctional diversity

greatly varies from one γδ subset to another, with several ones expressing highly conserved so-called "invariant" TCRs in some tissue locations, as is the case for murine Vγ5Vδ1 or Vγ6Vδ1 T cell subsets (4).

One important feature of γδ T cells is the preferential expression of TCR V regions in distinct tissue locations (2, 3, 5). As an example, Vγ9Vδ2 T cells are preferentially found in the peripheral blood where they represent up to 95% of γδ T cells (from 1 to 10% of $CD3^+$) in healthy human adults. By contrast Vδ1 subsets are mainly detected in intestinal epithelia. In adult mice, γδ T cells bearing Vγ5Vδ1 TCR (also called DETC, for dendritic epidermal T cells) are localized in the skin whereas Vγ6 subsets are found in uterine epithelia and lungs. Such preferential localization of γδ T cell subsets is probably explained by their capacity to recognize and be expanded upon recognition of specific ligands whose expression is restricted to some tissues. In agreement with such a peripheral tissue expansion, absolute numbers of Vγ9Vδ2 T cells steadily increase in blood during the first years of life while they remain low in other sites. In parallel, Vγ9Vδ2 T cells rapidly acquire during perinatal life several markers shared with conventional memory T lymphocytes (6). This is consistent with their ongoing engagement and antigen-driven expansion, presumably induced upon interactions with related antigens expressed by environmental agents (bacteria, viruses, parasites) or upregulated upon infection.

2.2. Antigenic specificities of γδ T cells

Another striking feature of γδ T cells is their mode of antigenic activation when compared to that of conventional αβ T cells. While some γδ T cell subsets recognize MHC-like molecules such as CD1c (7) or T22 (8, 9), such molecules are at least in some instances recognized in a native form and not as antigen-presenting elements, unlike αβ T cells. Whether or not this particular mode of recognition applies to all γδ T cells remains unclear, since the cellular targets and fine antigenic specificity of most murine γδ T cells are still unknown. The presence of oligoclonal murine γδ subsets in particular areas such as epidermis and vagina suggests specificity towards highly conserved "innate" ligands, possibly upregulated upon cell stress (4). In humans, γδ T cells can recognize a broad range of "activated" target cells, either transformed or infected by microbial agents, see for a recent review (10). In particular Vγ9Vδ2 T cells recognize a wide array of solid (e.g. melanoma, renal / bladder / colon carcinomas) and hemopoeitic (e.g. lymphoma, myeloma…) tumor cells as well as cells infected by bacteria, parasites and viruses (11-22). Moreover subsets of human non-Vδ2 γδ T cells are activated by epithelial tumor cells or CMV-infected fibroblasts (23, 24). In fact although γδ T cells are frequently activated along infectious contexts involving exogenous Non-Self agents, they should be rather considered as autoreactive lymphocytes, since most ligands involved in their activation are of self origin. In this respect, the antigenic targets of γδ TCR so far identified, such as MICA/B (25), F_0-F_1 ATP synthase (26), CD1c (7) in humans, and T22 in mice (8), are all upregulated on transformed and/or infected cells, and therefore could represent immunogenic stress-induced cues associated with these pathological situations (10, 20, 27).

Human Vγ9Vδ2 T cell pool, a major PBL subset found in most primates but absent in rodents, is probably the γδ subset whose specificity has been best studied. These lymphocytes are strongly activated by small non peptidic compounds, also called phosphoantigens (P-Ags), which are metabolites of the mevalonate isoprenoid pathway in mammalian cells, such as isopentenyl-pyrophosphate (IPP). Hydroxy-dimethyl-allyl-pyrophosphate (HDMAPP), an analogue of IPP but showing much stronger stimulating activity for Vγ9Vδ2 T cells, is produced through a metabolic pathway shared by many microorganisms, like mycobacteria, but absent in mammals (28-30). Strongly active P-Ags have been synthesized under GMP-grade in large batches for clinical use in cancer immunotherapy (31, 32). Aside from P-Ags, several pharmacological inhibitors of the mevalonate pathway can specifically trigger activation of Vγ9Vδ2 T cells. In particular aminobisphosphonates (ABPs) and alkylamines promote IPP accumulation in treated cells by inhibition of the farnesyl pyrophosphate synthase enzyme, thus mimicking dysregulation of the isoprenoid synthesis pathway that takes place in tumor cells (33, 34). Vγ9Vδ2 T cell activation by P-Ags is TCR and cell-to-cell contact dependent and MHC independent (35, 36). However there are no clear experimental evidence for cognate P-Ag / TCR interactions and the modalities of P-Ag recognition (direct or indirect, e.g. through modification of surface molecules on target cells) is still debated.

Engagement of surface receptors other than TCR clearly contributes to Vγ9Vδ2 T cell response. Some studies have highlighted the key role played by adhesion molecules such as ICAM-1/LFA-1 or CD166/CD6 in Vγ9Vδ2 T cell activation following tumor cell recognition (18, 37, 38). NK receptors frequently expressed by Vγ9Vδ2 T cells can also costimulate (i.e. NKG2D) or inhibit (i.e. ILT2 or NKG2A/CD94) their antigenic activation (39). In this case, reactivity of Vγ9Vδ2 T cells seems to be tightly regulated by a close interplay between activating and inhibitory NK receptor signaling (40).

2.3. *in vitro* functions of γδ T cells

In humans, subsets of γδ T cells can be distinguished by their differential expression of surface markers (CD45RA/RO, CD27, CD28, CD62L, CD16,..), chemokine receptors (CCR7, CCR5, CXCR5,..) (6, 41-44) and more importantly by their functional response following antigenic activation (proliferation, cytokine production, cytolytic activity). Frequency of each subset (naïve, central memory, memory effectors and terminally differentiated effectors) within peripheral γδ T cells in healthy individuals can greatly vary according to sex, age or the individual immune history. However central memory and effector memory subsets generally predominate (42, 44). The former subset represents the main pool of memory γδ T cells available, and is typically characterized by its strong proliferative responses, whereas the latter one yields

swift and strong cytokine and cytolytic responses but poorly proliferate after antigenic activation.

Following *in vitro* P-Ag stimulation, γδ T cells, and especially human Vγ9Vδ2 T cells, can divide in the presence of pro-proliferating cytokines (e.g. IL-2) and secrete high amounts of pro-inflammatory cytokines such as TNF-α and IFN-γ (10, 35, 45). A subset of $CD45RA^-$ $CD27^+$ identified for CXCR5 expression and also called follicular helper γδ T cells, was recently shown to produce after activation substantial amounts of IL-4 and IL-10 and subsequently provide B cell help for immunoglobulin production (41, 43). Following contact with tumor cells or infected antigen presenting cells (APCs), Vγ9Vδ2 T cells not only produce cytokines but also release cytolytic granules (granzymes A and B, perforin and granulysin) that mediate cytolysis and elimination of intracellular pathogens like mycobacteria (13). Additional mechanisms of cell death induction involving Fas/Fas-L and TRAIL may also participate in γδ T cell-mediated killing of cellular/microbial targets, as suggested by some studies (46, 47).

3. INTERACTION BETWEEN γδ T LYMPHOCYTES AND DENDRITIC CELLS

3.1. Optimal activation of γδ T cells in the presence of monocytic cells

γδ T cells are specifically activated in a TCR- and cell-to-cell contact-dependent manner. Requirements for antigen presentation remain unclear since target cells cannot be sensitized to γδ T cell recognition after pre-incubation with soluble P-Ags and extensive washes (M.C.Devilder and S.Allain, unpublished data). Owing to the "natural memory" phenotype of most γδ subsets and their capacity to efficiently recognize a wide range of target cells, one would expect that optimal γδ T cell activation does not require the presence of professional APCs. However, more and more studies suggest instead a significant contribution of APCs to this process. For instance activation of primary Vγ9Vδ2 T cells by ABPs strictly requires monocytic adherent cells, and species-specific interactions are needed for optimal engagement of γδ T cells in such a setting (37, 48). The classical explanation for this APC requirement is that ABPs act preferentially on cells showing high pinocytic activity such as monocytes, dendritic cells (DCs) and macrophages. However, this interpretation does not rule out the need for additional soluble and/or membrane-associated factors that could be delivered by professional APCs.

In light of the above and other studies describing interactions between DCs and several non conventional lymphoid subsets like iNKT and Natural Killer (NK) cells, we and others performed an in depth analysis of γδ T cell / APC interactions to better define : (i) the kind of γδ T cell responses that are enhanced by professional APCs and their underlying molecular partners, (ii) the consequence of DC - γδ T cell interactions on subsequent DC activation and priming of adaptive immune responses, and (iii) the way to manipulate these cell partners for immunotherapeutic purposes.

3.2. γδ T cell responses in the presence of dendritic cells

3.2.1. Dendritic cells

DCs represent the prototypic professional antigen presenting cell, specialized for optimal Ag uptake and presentation to T cells. DCs are primarily located in areas in direct contact with the environment, i.e. where the likelihood to encounter invading pathogens is the highest. DCs are considered as sentinels who patrol through peripheral blood, peripheral tissues, lymph and secondary lymphoid organs. They continuously recirculate and enter secondary lymphoid organs, where they actively participate to either T cell tolerance or priming, depending on their functional status. In peripheral tissues, resting DCs, which are classically termed immature DCs (iDCs), have high capacities for antigen uptake and endocytosis. Following the activation switch induced by integration of several maturation stimuli, DCs undergo morphologic, phenotypic and metabolic changes that ultimately lead to their activation into mature DCs (mDCs). Thanks to their strong expression of classical MHC molecules and polarizing cytokines (e.g. IL-12), mDCs have the unique ability to prime conventional naïve αβ T cells. iDCs differ from mDCs not only by their phenotypic features (e.g. differential expression of MHC and costimulatory molecules (e.g. CD80, CD83, CD86,..)) but more importantly by their functional capacities. iDCs are considered as tolerance inducers whereas T cell priming of naïve T cells rather involves mDCs. This balance between tolerance and immunity probably depends on the DC maturation and T cell memory status, which could therefore, dictates their signaling requirements, based on the generally accepted model of primary *versus* secondary *versus* tertiary signals delivered by DCs and their microenvironment.

3.2.2. Vγ9Vδ2 T cell responses in the presence of dendritic cells

We recently performed an analysis of the interplay between Vγ9Vδ2 T cells and human DCs during specific antigenic activation. By comparing functional activation levels obtained after *in vitro*/*ex vivo* activation by soluble P-Ags and ABPs in the presence of different co-culture partners, we first extended the observations from Minato and colleagues (§3.1) by showing the importance of human monocyte-derived DCs during specific Vγ9Vδ2 T cell activation. These observations, that showed enhanced γδ T cell responses in the presence of DCs, when compared to T or B cells coculture conditions, were recently confirmed (49). DCs potentiated all cytokine responses but neither cytolytic nor proliferative responses of Vγ9Vδ2 T cells, and quite unexpectedly iDC turned out to be much better inducers than mDCs.

Owing to the memory phenotype of Vγ9Vδ2 T cells and their close functional relationships with other innate-like subsets, we then tested whether the potentiating effect of iDCs on T cell cytokine responses was restricted to Vγ9Vδ2 T cells or applied more generally to other natural or conventional memory subsets. Similar potentiation of cytokine production (but not of cytolytic activity) was observed in conventional MHC class I-restricted virus or tumor-specific human effector/memory

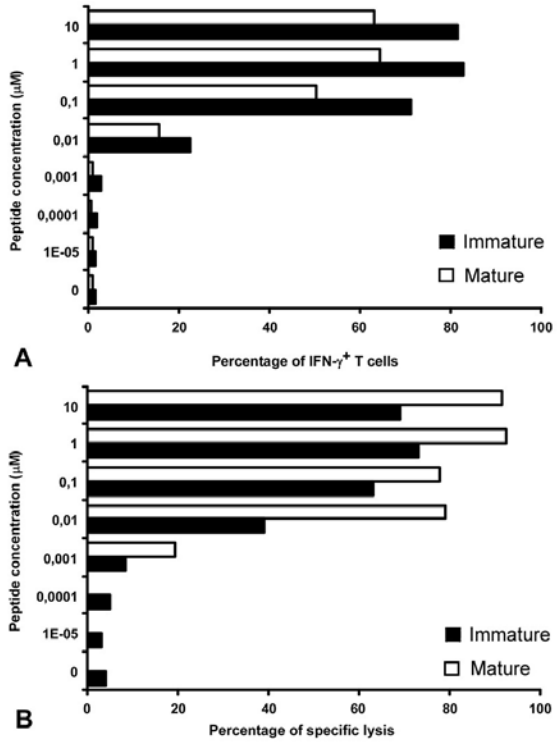

Figure 1. Immature dendritic cells potentiate the peptide-specific cytokine response of conventional memory human αβ T cells. Human dendritic cells were differentiated from fresh PBMCs-derived monocytes purified from of a human HLA-A2$^+$ healthy donor by incubation for 5 days with IL-4 and GM-CSF. Memory human CD8$^+$ αβ T cells (clone #A2.10) reacting against a viral HLA-A2-restricted peptide (EBV BMLF1-GLCTLVAML) were cocultured with either immature or mature dendritic cells in the presence of grading doses of synthetic peptide. A: Intracellular IFN-γ was detected in αβ T cells by flow cytometry after 5 hours of coculture (ratio 1:1). B: Cytolytic activity of the T cell clone was measured by a standard 4 hours ^{51}Cr release assay at a 10:1 effector/target ratio.

CD8$^+$ αβ T cells upon coculture with either iDCs or mDCs (Figure 1). These observations, in line with our results obtained with *ex vivo* sorted PBMC-derived CD4 or CD8 T cells, strongly suggest that T helper (Th) 1 and Th2 cytokine responses, but not other functions, can be potentiated by iDCs during specific activation of memory T cell subsets. However this phenomenon might involve restricted memory T cell subsets only, whose functional avidity is high enough to allow their efficient activation under limiting conditions (e.g. at low levels of Ag, cytokines or costimulators expression). Therefore although this iDC potentiation effect applies to both conventional and non-conventional memory T cells, the latter might be preferentially involved under physiopathological situations owing to their "innate" reactivity towards broadly expressed stress ligands. In this regard, NK cells can readily recognize iDCs, which may lead in some instances to elimination of the latter cells (50). Similarly efficient activation of non conventional CD1-restricted T cells, such as Vδ1 and iNKT cells, by iDCs has been reported (51, 52).

3.2.2.1 Candidate molecular partners involved in iDCs-mediated enhancement of Vγ9Vδ2 T cell cytokine responses

In the above situations, effector cell activation assessed by cytokine release is mediated by either primary recognition receptors, like TCR or NCR (natural cytotoxicity receptor), or soluble/membrane-bound costimulators or a combination of both. Induction of effector functions and especially pro-inflammatory cytokine (e.g. IFN-γ) production by T cells can be achieved in a TCR-independent manner through local release of soluble factors or interactions with membrane associated molecules.

Although a direct role of IL-15 in the induction of IFN-γ production by T cells remains controversial, the synergistic effect of IL-12 and IL-18, which are both produced by DCs, on memory αβ T cell IFN-γ responses is supported by strong experimental evidence in both mice and humans (53, 54). We recently confirmed that such a cytokine combination could efficiently induce IFN-γ release by Vγ9Vδ2 T cells, even in the absence of APCs (M.C. Devilder, data not shown). However, iDC-mediated potentiation of Vγ9Vδ2 T cell cytokine responses cannot be merely or solely explained by the local action of paracrine factors released by iDC, as suggested by the following results. In particular enhancement of IFN-γ, TNF-α and IL-4 responses in iDC-Vγ9Vδ2 cocultures was cell-to-cell contact dependent. Moreover the presence of P-Ags, either exogenously added (e.g. BrHPP) or endogenously overproduced (e.g. ABP treatment), was required since γδ T cells were not activated by iDCs alone. Altogether our observations indicate that iDC-mediated potentiation of cytokine release involves both TCR signals and iDC-derived membrane-bound costimulators. Several candidate partners preferentially expressed either on iDCs or γδ T cells, such as adhesion molecules, TNF/TNFR costimulators and/or NKRs (NK receptors), could contribute to such a process:

Adhesion partners like ICAMs/LFA-1, CD58/CD2 and CD166/CD6 are required for efficient triggering of Vγ9Vδ2 T cell effector responses following recognition of tumor cells (37, 38, 55) and activation of Vδ1 T cells during microbial infections (56). While ICAMs/LFA-1 and CD58/CD2 interactions might primarily raise the overall avidity of Vγ9Vδ2 T cells for their targets, CD166/CD6 ligation might provide additional costimulatory signals underlying potentiation of cytokine responses. Accordingly CD6 is expressed by mature T cells including human Vγ9Vδ2 T cells, but the expression of CD166, so far detected on fresh human monocytes (57), remains to confirmed on DCs, and more particularly on iDCs.

The TNF gene superfamily so far includes 19 members which are, except lymphotoxin and APRIL, type II membrane-associated proteins that bind TNF receptor family members. Almost all TNF family products are

expressed by cells of the immune system, including DCs, and most of them act as membrane-associated factors through cell-to-cell contacts, see (58) for a recent review. Among possible candidates belonging to this family, LIGHT and HVEM, which are expressed on iDCs and T cells respectively (59, 60), have been tested for their ability to costimulate Vγ9Vδ2 T cell cytokine responses following activation by soluble P-Ags. However blocking experiments failed to support any implication of LIGHT/HVEM interactions in iDC-induced potentiation of cytokine responses. Future studies will focus on other members of the TNF/TNFR family known to transduce reverse signals implicated in costimulation (61).

T cell responses are modulated by the integration of activating and inhibitory signals delivered by NKRs, which were first characterized on NK cells and later found on T cells, such as $CD8^+$ αβ and γδ T cells. Among these, NKG2D, a homodimeric C-type lectin-like receptor expressed by almost all NK, iNKT and Vγ9Vδ2 T cells, can function as a costimulatory receptor. NKG2D interacts with different stress-inducible molecules like MHC class I chain–related molecules A and B (MICA and B) and UL-16–binding proteins (ULBP), which are frequently expressed on tumor and infected cells. Moreover NKG2D engagement enhances effector T cell responses induced after TCR crosslinking (39, 40, 62-68). NKG2D ligands are upregulated in cells infected by bacteria or viruses (39, 64, 69) or along DC activation and monocytic differentiation (70, 71). However since NKG2D ligands are better expressed on maturing DCs than iDC (72), contribution of NKG2D to the potentiation of Vγ9Vδ2 T cell cytokine responses seems unlikely.

3.2.2.2. γδ T cell responses induced by activated dendritic cells

DCs can sense pathogens and cell stress through recognition by pattern recognition receptors (PRRs) of conserved molecular determinants, called pathogen-associated molecular patterns (PAMPs). The Toll-like receptor (TLR) group, made of at least 10 members which are type I transmembrane proteins, is the best characterized class of PRR in mammalians. TLRs can be classified into two groups, according to their subcellular location and function, see (73) for a review. Cell surface associated TLRs (TLR1, 2, 4, 5, 6) are specialized in the recognition of microbial products, as well as self molecules upregulated upon stress or apoptosis. For instance TLR4 recognizes both Gram(-) bacteria-derived lipopolysaccharide (LPS) and high-mobility-group box 1 (HMGB1) alarmin (74). Intracellular TLRs (TLR3, 7, 8 and 9) are localized in late endosomes-lysosomes compartments and recognize nucleic acids, like double-stranded RNA for TLR3, thus allowing detection of viruses and Non-Self-derived nucleic acids.

During infections by pathogens, DC activation is tightly regulated by PAMP recognition by PRRs, including C-type lectins, mannose receptors and TLRs. Human myeloid DC can express multiple TLRs, depending on the subset analyzed, and *in vitro*-differentiated DC have been shown to express all TLRs excepting TLR7 and TLR9, see (73) for a review. Once iDCs are activated through TLR engagement, they rapidly mature as measured by upregulation of costimulatory molecules and production of pro-inflammatory cytokines whose nature (IL-12, TNF, IL-6 and type I IFNs), will depend on the kind of PAMPs and TLR implicated. Interestingly, both the expression patterns of TLRs and interaction with their specific ligands regulate cytokine production by DCs, through the induction of different signalling pathways (75, 76). All TLRs are associated with the myeloid differentiation factor 88 (MyD88) adaptor molecule, leading to nuclear translocation of NF-κB, with the exception of TLR3, which solely signals through Toll-interleukin-1 receptor (TIR)-domain containing adapter inducing IFN-β (TRIF). TLR4 has also been shown to induce the latter pathway, also termed MyD88-independent pathway, which recruits TRIF and triggers IFN-β production. In myeloid DCs, engagement of TLR3 and TLR4 therefore leads to the rapid release of type I IFN (mainly IFN-β), involved in various antiviral and antibacterial defense mechanisms.

PAMPs can control T cell responses either indirectly, by activating APCs (e.g. DC maturation) and/or, directly, through binding to TLRs expressed by defined T cell subsets. Although expression of TLRs by T lymphocytes remains debated, recent studies showed that engagement of TLR3, TLR5 or TLR7/8, which can be expressed by NK cells or memory T cell subsets, including Vγ9Vδ2 T cells, synergizes with suboptimal NKG2D or TCR stimuli and enhances some effector functions, like IFN-γ release (77-80). Some subsets of murine γδ T cells, like DETCs or Vγ6Vδ1 subsets, can also express TLR4 or TLR2 respectively, and be activated by PAMPs (81-83). However, such a direct effect of TLR engagement on T cells, which has been often identified as discrete costimuli and described only for few TLRs, might not be the main way through which PAMPs could control T cell responses. Instead, it seems more likely that PAMPs primarily regulate T cell responses through APC (e.g. iDC) activation. Interestingly, recent studies highlighted the role played by TLR-activated DCs in T cell activation, through bystander activation mediated by DC-released soluble factors. As an example, Kamath et al. have shown, in mice, that DCs and NK cells can stimulate bystander T cell activation in response to TLR agonists (TRL3, 4, 7 and 9) through secretion of IFN-□ and IFN-□, the latter cytokine being released by NK cells (84). However, bystander activation of T cells through binding of soluble factors to rather ubiquitously expressed receptors (such as IFNARs) can not explain how restricted T cell subsets, and especially innate-like T cell subsets, are specifically stimulated in some conditions. In this regard, upon engagement of either TLR4 or TLR9, DCs induce activation of iNKT cells, a process that depends on both the upregulation of endogenous iNKT ligands, like glycosphingolipids (GSLs), and soluble factors, like IL-12 or type I IFNs (85-87). IFN-γ release by iNKT cells is a cell-to-cell contact and a TCR-dependent process in which baseline lymphocyte autoreactivity, generally too weak to trigger cytokine release by itself, needs to be further enhanced by upregulation of GSLs/CD1d complexes and pro-inflammatory soluble factors

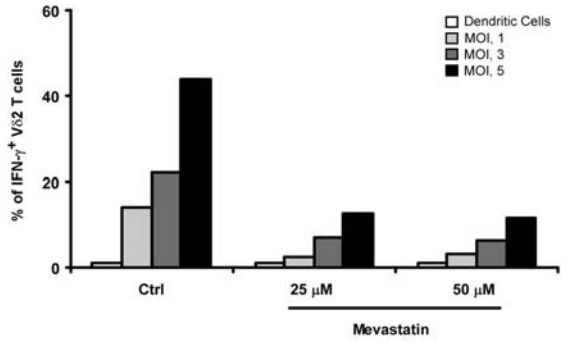

Figure 2. Mevastatin, a pharmacological inhibitor of the endogenous cellular HMG-CoA reductase, inhibits the IFN-γ response of human Vγ9Vδ2 T cells in the presence of *M. BCG*-infected dendritic cells. Human immature dendritic cells, obtained as previously described, were treated with mevastatin (25 and 50 μM) and subsequently infected for 2 hours with enhanced GFP-*M. BCG* at MOI of 1, 3 and 5. DCs were washed and cocultured with a human Vγ9Vδ2 T cell clone. Intracellular IFN-γ was detected in γδ T cells by flow cytometry after 5 hours of coculture (ratio 1:1). Mevastatin did not alter *M. BCG* infection of iDCs and was checked for its capacity to inhibit pamidronate (but not soluble P-Ags)-induced Vγ9Vδ2 T cell responses (not shown).

A similar activation process has been documented for γδ T cells, and more particularly for human Vδ1$^+$ and Vγ9Vδ2 T cells. Following contact with different Gram(-) bacterial products, which contain substantial amounts of TLR ligands like LPS, activated human DCs can induce activation of Vδ1$^+$ T cells, as evidenced by triggering of proliferation and IFN-γ release (56). This activation process requires cell-to-cell contacts involving adhesion and costimulatory molecules (CD2/LFA-3, ICAM-1/LFA-1 and NKG2D/MICA) and IL-12, released by activated DCs. Kunzmann *et al.* have shown that CD11c$^+$ DCs, by secreting type I IFNs in response to poly I:C stimulation, exert a costimulatory effect during antigenic activation of Vγ9Vδ2 T cells (88). Our own analyses of Vγ9Vδ2 T cell responses to *M. BCG*-infected human iDCs suggest that an infectious stress can modulate production of endogenous metabolites stimulating Vγ9Vδ2 T cells (Figure 2). Therefore Vγ9Vδ2 T cell activation by infected DCs may involve both stress-induced endogenous TCR ligands such as P-Ags and soluble factors, like pro-inflammatory cytokines. However, this assumption will need to be formally proven by more direct demonstration of enhanced IPP levels and/or ligands for Vγ9Vδ2 costimulators on iDCs following stress induction.

What could be the physiological relevance of innate-like T cell activation by TLR-activated DCs? Firstly, through triggering of pro-inflammatory cytokine production by DCs and upregulation of adhesion and membrane associated molecules, PAMPs could act as costimulators synergizing with TCR signalling. This could be a key issue in pathological situations where antigen levels (yet to be defined for γδ T cells) are too low to yield optimal TCR triggering. Many of the DC-derived cytokines mediating the costimulation effect observed after PAMP binding are pro-inflammatory factors involved in Th1 cytokine response polarization, such as IFN-γ. Importantly nucleic acid patterns recognized by TLR show strong indirect costimulatory effects on innate-like T cell subsets. Since viruses presumably do not express known TCR ligands for iNKT and γδ T cells, it is therefore tempting to speculate that TLR engagement, well mimicked by poly I:C or CpGs, represents a stress cue necessary and sufficient to stimulate innate-like T cell subsets, through its dual ability to upregulate both ligands for primary recognition receptors and costimulators.

Finally, iNKT and γδ T cell responses could directly impact on DC outcome by either eliminating infected DCs and pathogens (direct effectors) or participate in the efficient priming adaptive of immune responses (adjuvant T cells) (see below).

3.3. Dendritic cell responses following contact with γδ T cells

3.3.1. Impact of γδ T cells on immune responses

Modulation of innate (NK cells and macrophages) and adaptive (αβ T cells) responses by γδ T cells through production of pro-inflammatory cytokines and chemokines was first evidenced in several murine models of bacterial and parasitic infections (89, 90) and see (3) for a review. These observations were more recently extended to non-human primates models, which carry like their human counterparts high frequency of P-Ags-reactive Vγ9Vδ2 PBL. In line with *in vitro* and *ex vivo* studies performed in humans (91, 92), contribution of both mycobacteria-reactive Vγ9Vδ2 and αβ T cells to *in vivo* protective immunity against mycobacterial infections was demonstrated in macaques primed with *M. BCG* and challenged with *M. Tuberculosis* (93).

γδ T cells may also downmodulate immune responses, as demonstrated in a murine model of Coxsackievirus B3-induced myocarditis where Vγ1 and Vγ4 T cell subsets respectively prevent or promote disease (94). Similarly human Vδ1$^+$ cells infiltrating human breast tumors can suppress both tumor-specific T cells and DCs, through release of yet undefined soluble factors (95).

3.3.2. Dendritic cells instruction induced by activated γδ T cells

Several studies including our recent work indicate that after antigenic activation, innate lymphocytes (NK, iNKT and γδ T cells) trigger in turn DC maturation (21, 51, 96-100), and see (101) for a review, through a cross-talk involving both membrane associated partners and soluble factors. This maturation is evidenced by phenotypic modifications such as the upregulation of costimulatory molecules (e.g. CD80, CD83 and CD86) as well as bioactive IL-12 release by DCs and acquisition of T cell priming capacities. In these settings, induction of DC maturation critically depends on both CD40/CD40L interactions and pro-inflammatory cytokines released by activated lymphocytes, such as TNF-α and IFN-γ. In Lyme arthritis, human Vδ1$^+$ T cells which accumulate in inflamed

synovial fluids instruct DCs by triggering their maturation through CD95/CD95L interactions (100).

One may wonder how Vγ9Vδ2 T cells, despite their strong cytolytic activity, can promote DC maturation. Actually, at suboptimal Ag doses allowing Vγ9Vδ2 T cell activation, DCs are resistant to cell lysis and can rapidly mature. Under these conditions only those DCs interacting in a specific manner with Vγ9Vδ2 T cells undergo rapid maturation, unlike "bystander" DCs. Although resistance of DC to cytolysis and apoptosis following contact with conventional T cells remains debated (102, 103), it could reflect an increased resistance of DCs to pro-apoptotic cFLIP stimuli, as already reported in $V\delta1^+$/DCs interactions (100), and/or engagement of inhibiting KIRs whose ligands (MHC class I) are upregulated on maturing DCs (104).

Such γδ T cell-driven mechanisms leading to DC instruction could be a key issue in physiopathological situations where pathogens induce suboptimal or altered DC maturation. In this respect at human Vγ9Vδ2 T cells efficiently trigger and accelerate BCG-infected DC maturation at "physiologically relevant" low multiplicity of infection (MOI) (21). This could allow rapid establishment of adaptative immune responses for mycobacteria control and clearance (105). Since Vγ9Vδ2 T cells can kill intracellular mycobacteria in infected macrophages through granulysin release (13), it will be interesting to determine whether pathogens are efficiently cleared after interaction with infected DCs and whether this process correlates with the number of mycobacteria engulfed by DCs (MOI level). Brucellosis, which share several features with tuberculosis, is another pathological situation where the adjuvant functions of Vγ9Vδ2 T cells on DC maturation and T cell priming could be logically tested. Indeed, this pathology is due to intracellular infection by *Brucella suis*, a bacteria able to activate human Vγ9Vδ2 T cells (106, 107), to prevent DC maturation following infection, and to impair their capacity to secrete IL-12 and prime naïve T cells (108).

3.4. Physiological relevance of dendritic / γδ T cell interactions

Most studies of human γδ T / DC interactions have been performed *in vitro/ex vivo*, using GM-CSF/IL-4 differentiated DCs. Such modeled cellular interactions between DCs (in an immature or maturing state) and memory T cells should be transposed to more physiological contexts where both cell types might have opportunities to meet and interact.

In vivo interactions between DCs and memory T cells can lead to activation of conventional $CD8^+$ T cells and protective immunity in several infectious models, see (109) for a review. These studies suggest that DCs are the primary APCs for initiation of memory $CD8^+$ T cells proliferation (through transpresentation of IL-15, an important cytokine involved in T cell homeostasy), but did not allow to conclude whether or not induction of effector functions was strictly DC-dependent. Regarding the γδ system, our preliminary results suggest that *M. BCG*-infected DCs promote efficient expansion of *ex vivo* PBMCs-Vγ9Vδ2 T cells, which can be considered for most of them as primed lymphocytes (MC Devilder and S. Allain, unpublished data), and induce differentiation of central memory into effectors T cells expressing high amounts of perforin (110). Altogether these observations suggest that DCs are the preferred partners for γδ T cell recall, expansion and acquisition of effector responses. However, our unpublished observations suggest that γδ T cell responses, although strong, rapidly wane few hours following *M. BCG* infections despite the persistence of live mycobacteria inside DCs. This also suggests that γδ T cells should rapidly meet infected DCs to have a chance to sense infection and instruct infected iDCs.

Whether or not γδ T cells and DCs have the opportunity to rapidly meet and interact in defined territories along infectious process or development of tumors remains to be shown. Memory γδ T cell subsets express chemokine receptors allowing them to either migrate to inflamed tissues (effector subsets) or lymph nodes (naïve and central memory subsets) (42). Accordingly γδ T cells are distributed in nonlymphoid organs and tissues (e.g. lung, kidney,..) during progression of mycobacterial infections, suggesting specific migration to infected site (111). This has been confirmed and extended in a recent study performed in primates, which reported *trans*-endothelial migration and interstitial localization of Vγ9Vδ2 T cells associated with granuloma infiltration along *M. tuberculosis* infection (112).

Therefore memory γδ T cells might rapidly migrate to inflamed tissue following infections, where they could boost recall and effector responses through DCs interactions, as suggested by a recent study describing conventional memory T cells / DCs interactions in nonlymphoid organs (113). Upon activation, γδ T cells have also been shown to express lymph node homing receptors (e.g. CCR7), like their naïve and central memory γδ T counterparts (41, 42). Hence they could also migrate to secondary lymphoid organs and provide help to T/B-cells or interact with DCs. In this regard, iDCs, and especially those derived from blood-borne progenitors, are not only present in peripheral tissues but also in secondary lymphoid organs (114, 115). Antigens can be transported to secondary lymphoid organs through APCs like neutrophils which have been shown, like DCs or inflammatory monocytes, to migrate via afferent lymphatics to lymphoid tissue and to shuttle live microorganisms like *M. BCG* (116) which could infect lymphoid organs resident DCs.

4. CONCLUSION AND PERSPECTIVES

A lot of work has been performed during the last decade in the non conventional lymphocyte research field, as illustrated by the growing number of publications describing a cross-talk between DCs and innate-like lymphocytes. Despite these efforts, the molecular mechanisms underlying this process and the impact of these interactions on immune responses, especially during infectious diseases and tumor development, is not completely understood. Antigenic targets recognized by

most murine and human γδ T cell subsets remain unknown. Owing to their high frequency in the peripheral blood of most primates and their ability to recognize a wide range of activated target cells, Vγ9Vδ2 T cells represent the best characterized γδ T cells subset to date. However, the modalities of non-peptidic antigen production as well as their processing, presentation and binding mode to γδ TCR are yet unclear. In particular it will be important to confirm and determine how DCs/pathogens or interactions involving stress-induced molecules (e.g. PAMPs-mediated) can trigger expression of endogenous γδ TCR ligands (such as mevalonate pathway metabolites). If confirmed these observations would indicate that "autoreactive" γδ T cell subsets (20) not only sense stress signals through tumor cells but also through DCs (combined or not with exogenous ligands produced by many microorganisms).

In order to further assess receptors and signalling pathways regulating γδ/DC crosstalk, we now put our efforts on the comparative analysis of dynamic signal transduction profiles (calcium signals, kinetics of phosphorylation of transduction signal intermediates) following Vγ9Vδ2 TCR engagement, in the presence or not of DCs with various stimuli (ABPs, mycobacteria,..). Our preliminary results indicate induction of uncommon calcium signal profiles (as compared to αβ T cells), characterized by a delayed calcium flux increase in Vγ9Vδ2 T cells activated by soluble P-Ags in the presence of iDCs (S. Nedellec and C. Sabourin, unpublished data). These results, which are in line with previous studies reporting delayed Erk phosphorylation levels following IPP stimulation (117), suggest that cell partners establish a cross-talk before induction of strong TCR signaling.

Following interactions with DCs, activated γδ T cells have been shown to divide, differentiate and exert effector functions like cytokine release. They might also acquire new functions, as suggested by an intriguing study documenting acquisition of APC functions by activated γδ T cells, through upregulation of costimulatory molecules and MHC complexes at their surface (118). A better understanding of the factors involved in the modulation of DC and γδ T cell functions following their reciprocal interactions, should provide important insights into the mechanisms underlying γδ T cell activation and functional polarization. On a more applied standpoint, a precise knowledge of γδ T / DC crosstalk and more generally of the cellular and soluble factors contributing to optimal survival, renewal and functional maturation of γδ T cells should allow rational design of immunotherapeutic protocols targeting this subset. In this regard, several phase I/II trials using GMP-grade phosphoantigens or aminobisphosphonates in association with IL-2, have been performed in patients with renal and colon carcinomas as well as myeloma, hepatocarcinoma and prostate cancer (22, 32, 119-121). The main goal was to design optimal conditions for passive or active amplification of T cells, in order to clear tumor cells, either indirectly through - mediated activation of immune effectors and/or directly through direct recognition and cytolysis of cancer cells by this γδ subset. However, while efficient *in vivo* Vγ9Vδ2 T cell expansions could be achieved after single treatment with P-Ags and IL-2, both pre-clinical studies in primates and clinical trials in humans revealed a progressive decrease of γδ proliferative responses upon repeated P-Ags injections (122). Such a phenomenon, referred to as "tachyphylaxy", could result from antigenic stimulation in an inadequate or suboptimal cellular context. Owing to their potentiating effect on T cell responses and their ability to greatly improve *in vivo* proliferative responses of iNKT cells to synthetic agonists, DCs might be used to optimize Vγ9Vδ2 stimulation protocols and prevent tachyphylaxy after repeated treatments.

5. ACKNOWLEDGEMENTS

The authors would like to apologize to colleagues whose contributions to this research field could not be cited due to space limitations. Our research is supported by grants from the Institut National de la Santé et de la Recherche Médicale (INSERM), Agence Nationale de la Recherche (ANR #A05118GS and #PRIB/017), Association pour la Recherche sur le Cancer (ARC#3662 and #4953), Institut National du Cancer (INCa) and from the Commission of the European Union Programme 6FP (LSH-CT-2003-503367) TB-VAC and (E06005NP/EEA06004GNP) Cancer Immunotherapy.

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Abbreviations: iNKT: invariant natural killer T, APC: antigen presenting cell, DC: dendritic cell, TCR: T cell receptor, DETC: dendritic epidermal T cell, MHC: major histocompatibility complex, HLA: human leucocyte antigen, CMV: cytomegalovirus, EBV: Epstein-Barr virus, PBL: peripheral blood lymphocyte, Ag: antigen, P-Ag: phosphoantigen, IPP: isopentenyl pyrophosphate, HDMAPP: hydroxy-dimethy-allyl-pyrophosphate, GMP: good manufacturing practice, ABP: aminobisphosphonate, MIC: MHC class I-related chain, NK: natural killer, KIR: killer cell immunoglobulin-like receptorTNF: tumor necrosis factor, TNFR: TNF receptor, IFN: interferon, IL: interleukin, TRAIL: TNF-related apoptosis-inducing ligand, iDC: immature DC, mDC: mature DC, PBMC: peripheral blood mononuclear cell, Th: T helper, NCR: natural cytotoxicity receptor, APRIL: a proliferation-inducing ligand, LIGHT: lymphotoxin-like inducible protein that competes with glycoprotein D for binding herpesvirus entry mediator on T cells, HVEM: Herpes virus entry mediator, ULBP: UL16 binding protein, PRR: pattern recognition receptor, PAMP: pathogen-associated molecular pattern, TLR: Toll-like receptor, LPS: lipopolysaccharide, NF-κB: nuclear factor-κB, TRIF: Toll-interleukin-1 receptor-domain containing adapter inducing IFN-β, IFNAR: IFN alpha receptor, GSL: glycosphingolipid, *M. BCG*: *Mycobacterium bovis bacille bilié de Calmette Guérin*, *M. Tuberculosis*: *Mycobacterium Tuberculosis*, cFLIP: cellular FLICE-like inhibitory protein, MOI: multiplicity of infection, GM-CSF: granulocyte macrophage-colony stimulating factor, CCR: chemokine CC motif receptor , CXCR :chemokine CXC motif receptor, HMG-CoA: hydroxy-methyl-glutaryl-coenzyme A

Key Words: T lymphocytes, gamma delta T cells, Dendritic Cells, Stress, Infection, Toll-like Receptors, Review

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