# Antigen Specificity of Human TCR γδ Cells

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**Abstract:** T cells expressing the TCR γδ constitute a small fraction of T cells in circulating blood whereas they are abundant in some peripheral lymphoid organs and mucosal sites. The TCR Vγ9/Vδ2 heterodimer is expressed on a large fraction of human TCR γδ cells. This receptor is activated by endogenous and bacterial phosphorylated metabolites, which accumulate in tumour transformed cells and in bacteria-infected cells. While the nature of the stimulatory ligands is known, it remains to be discovered how these novel antigens are handled within tumour and infected cells, how they are displayed on the surface of antigen presenting cells and whether a dedicated antigen-presenting molecule is involved. This review discusses the published data on the nature and structure of the human TCR γδ, the evidence of recognition of self and bacterial antigens, the events leading to accumulation of these metabolites and regulating their antigenicity. A hypothesis is presented on the possible mechanisms of antigen presentation to the TCR Vγ9/Vδ2 and the physiological role of TCR γδ cells in the immune response.

## INTRODUCTION

The TCR γδ is the second type of TCR, and was identified on a population of T cells after the discovery of TCR αβ-expressing cells. The gene encoding the γ chain was identified just after the TCR β gene and accidentally thought to encode the TCR α chain. Careful analysis of the predicted protein sequence revealed that it did not fit with the TCR α protein isolated from TCR αβ cells and led to the hypothesis that a second TCR might exist. TCR γδ cells were thereafter isolated from the pool of circulating CD4 and CD8 double negative T cells and it was immediately clear that this was a novel population of T cells expressing a new type of TCR [1]. This exciting period was followed by the identification of the TCR δ genes [2] and the final demonstration that T lymphocytes may express two different types of TCR in a non-overlapping fashion [3-5]. When human TCR γδ cells were compared to those present in mouse, it was clear that the type of TCR genes, the tissue distribution, and the mechanism of thymic development were very different. This led to a progressive distinction of the studies conducted in rodents and humans, which only show similar findings in some cases.

Despite the discovery of TCR γδ cells was made more that 20 years ago, several important aspects of the physiological role of this T cell population remain obscure. This is true for both human and rodent TCR γδ cells. The main stimulatory antigens, the requirements of antigen presentation, the type of selection events occurring in the thymus, their role in the immune homeostasis and in the pathogenesis of diseases still await definition.

This review focuses on human TCR γδ cells and discusses the immunological role of these cells. Since the function of this T cell population is the direct consequence of antigen recognition, special emphasis is given to the structure of the TCR γδ, to known stimulatory antigens, and to the possible mechanisms of antigen presentation.

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## TCR GENE ORGANIZATION, Vγ/Vδ PAIRING AND TCR STRUCTURE

The TCR γ and δ loci map to chromosomes 7 and 14, respectively. The TCR γ locus includes two constant gene segments, Cγ1 and Cγ2, and five joining elements, J1, JP, and JP1 (upstream of Cγ1), JP2 and J2 (upstream of Cγ2).

Among the fourteen identified variable γ (Vγ) genes only six encode functional proteins [6] and are classified into two subgroups designated VγI (comprising Vγ2,3,4,5,8) and VγII (comprising only the Vγ9 gene). Importantly, Cγ1 and Cγ2 genes differ in their capacity to form disulphide bonds with the Vδ chain: Cγ1 exon 2 encodes the cysteine residue forming a disulfide bridge with the Vδ chain, whereas Cγ2 has a polymorphism of exon 2 and lacks this cysteine residue [7, 8]. The outcome is that only TCR γδ receptors using Cγ1 are disulfide linked. Whether a covalently linked heterodimer is absolutely required for the function of the TCR γδ has not been exhaustively investigated yet.

The TCR δ locus is located within the TCR α locus, and comprises one Cδ gene segment located 3' of four Jδ segments and downstream the Jα segment cluster. Four diversity (D) elements are located at the 5' of the Jδ cluster.

Despite the large number of Vα genes that could rearrange to Dδ and Jδ gene segments, only six different Vδ chains are the most frequently expressed on the surface of TCR γδ cells [9]. Vδ2 is the most 3' Vδ gene, followed in a 3'-5' direction by Vδ 8, 7, 5, 1, 6 and 4, while Vδ3 is located at 3' of Cδ.

One of the most striking findings of human TCR γδ cells is that, despite the potentially large number of different heterodimer combinations, the large majority of circulating cells express a receptor made of covalently linked Vγ9 and Vδ2 chains. This association is frequent in the periphery of

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the adult population, whereas mixed combination of Vγ and Vδ chains are present in the human thymus [10].

The joining region of the TCR γδ is characterized by a high variability, since in addition to the J region in some cases up to three D segments are present [11]. Another source of variability is represented by P nucleotides that were identified for the first time in mouse thymic γδ T cells [12]. Human TCR γδ cells also show high level of junctional diversity in T cells isolated from thymus and peripheral blood. Peripheral TCR γδ cells have a very different V chain repertoire from thymic cells [10], frequently use a Vγ9JPCγ1 chain with limited number of N nucleotides, that is paired to a Vδ2 chain with a unique junctional motif. These findings suggest that a selection force drives expansion in the periphery of T cells expressing these unique rearrangements. Another study demonstrated the presence of Vδ1 and Vδ2 oligoclonal populations in the circulating blood of adults and newborns [13]. When these cells were stimulated with bacteria, the expanding TCR γδ cells did not show further TCR repertoire selection, thus suggesting that the events selecting the peripheral repertoire are already operating in newborns.

The structure of the TCR Vγ9/Vδ2 heterodimer has been solved and has shown an unusual conformation [14]. The elbow angle formed by the interdomain between the Vγ/Vδ and Cγ/Cδ regions is only 110º and is much smaller that those of TCR αβ and Fabs. This unique shape suggests that the interaction with the antigen and a putative antigen-presenting molecule is different from that of TCR αβ interacting with peptide-MHC or lipid-CD1 complexes. This is also supported by the finding that the CDR-containing surface is made of many protrusions and clefts whereas that of the TCR αβ is more flat. These differences point out that a putative TCR γδ-dedicated antigen-presenting molecule may be very different from the flat platform of the MHC and CD1 molecules.

## NATURE OF ANTIGENS STIMULATING HUMAN TCR γδ CELLS

This review focuses on the antigens that have been consistently found stimulating human TCR γδ cells and whose structures have been identified. The molecules that stimulate rare cell populations or individual T cell clones and therefore may represent rare antigens are briefly mentioned.

The major population of human TCR γδ cells, that uses the Vγ9/Vδ2 heterodimer, recognizes self and microbial phosphorylated metabolites generated in the eukaryotic mevalonate pathway and in the microbial 2-C-methyl-d-erythritol 4-phosphate (MEP) pathway. Initial studies showed that non-peptidic ligands isolated from mycobacterial cell lysates were stimulatory for Vγ9/Vδ2 T cell clones [15]. These ligands contain phosphate moieties essential for stimulation [16]. A major breakthrough was the isolation of three stimulatory compounds, all non-peptidic and containing phosphate residues [17]. Although this study did not provide the nature and structure of the relevant antigens, it showed for the first time that multiple compounds are stimulatory. One active molecule was later identified as isopentenyl diphosphate (IPP), which is made of a short prenyl group and two phosphates and has a small molecular weight (245 Daltons) [18, 19]. Importantly, synthetic molecules confirmed its antigenicity [18]. When a series of natural molecules structurally similar to IPP were tested, they also were active although with a lower potency than IPP [19]. IPP is an intermediate metabolite of the mevalonate pathway, which is present in all eukaryotic cells and is essential for cell survival. The mevalonate pathway is required for the generation of prenyl groups, involved in protein prenylation and in anchoring proteins to membranes. IPP is also required for the synthesis of terpenoids, and for protein N-glycosylation, as well as for the synthesis of cholesterol and steroids, including pregnenolone, corticosteroids and sex hormones. Some bacteria also have the mevalonate pathway and generate the same type of intermediate metabolites as eukaryotic cells.

Subsequent studies, conducted with *M. tuberculosis*, showed that another molecule different from IPP and with a molecular weight of 262 Daltons is a strong agonist [20]. The MEP pathway of isoprenoid biosynthesis, which substitutes the mevalonate pathway in some bacteria, is involved in the generation of this activatory microbial ligand [21]. This molecule was identified as (E)-4-hydroxy-3-methyl-but-2-enyl diphosphate (HMBPP) [22], which has the mass of 262 Daltons, and is an intermediate metabolite of the MEP pathway. HMBPP levels change when the genes encoding enzymes of the MEP pathway are manipulated: it accumulates in *E. coli* mutant cells deficient in lytB-encoding gene [23] and is missing in bacterial cells lacking dxr and gcpE-encoding genes [24]. In the first case bacterial lysates are more stimulatory for TCR γδ cells, whereas in the second case the stimulatory activity is abrogated.

The measured potencies of IPP and HMBPP show an enormous difference. The ED50 of IPP is ~20 μM, whereas that of HMBPP is ~70 pM, *i.e.* more than $10^5$ times lower.

Several considerations have to be made before drawing any conclusion about the activity of these compounds. First, comparison of IPP and HMBPP activity has always been performed using T cell activation experiments in which both compounds were added exogenously to the culture. This does not reflect physiological conditions, because IPP is generated within the APC, whereas HMBPP is released in the extracellular milieu by dead bacteria. In the presence of serum, exogenous HMBPP is very stable [25], whereas IPP is unstable [26] and its instability might contribute to the low ED50. Tumour cells accumulate IPP at concentrations at least 500 times lower than the ED50 measured using exogenous IPP (our own observations and [27]), nevertheless they stimulate TCR Vγ9/Vδ2 cells in a IPP-dependent manner [28], providing evidences that endogenous IPP is active at much lower concentrations than the ED50 measured with the exogenous one.

Another important issue is that an antigen generated within the APC is presented more efficiently than the same antigen provided exogenously. This is the case for viral peptide antigens presented by MHC class I molecules and the same may apply to endogenous IPP.

Taken together, these observations show that IPP is a physiological endogenous ligand of TCR Vγ9/Vδ2 cells *in vivo* and do not exclude that under other circumstances such as infections in which large amounts of bacterial cells

accumulate within tissues, HMBPP stimulates this T cell population.

HMBPP might be for example responsible for the expansion of TCR Vγ9/Vδ2 cells observed in some infectious diseases [29]. A careful examination of the presence of the MEP pathway in disease-causing microorganisms showed that only those that produce HMBPP induce the expansion of TCR γδ cells [30]. Whether this expansion improves protection to infections is a matter of debate. It might represent a strategy used by microbes to alter immune regulation and induce a generalized inflammatory reaction without protective efficacy. This strategy is exploited by pathogens with different mechanisms and stimulating other T cell populations [31].

Other microbial compounds have been reported to stimulate TCR Vγ9/Vδ2 cells. 3-formyl-1-butyl pyrophosphate has been described as an additional antigen produced by mycobacteria [32]. Synthetic analogs of this compound showed low potency [33] and further investigations did not find evidence for the production of this molecule [34].

A mycobacterial antigen named TUBag3, whose structure remains unknown, was found to contain a 5'UTP moiety and to be active at nanomolar concentrations [35]. An antigen was also isolated from the facultative intracellular bacterium *Francisella tularensis*. This antigen contains phosphate moieties important for T cell activation, is active at nanomolar concentrations but it has not been identified [36]. Whether it is related to HMBPP found in other bacteria remains to be determined.

Interestingly, killed Streptococci, which are bacteria lacking the MEP pathway [37], induce activation and proliferation of TCR Vγ9/Vδ2 cells [38]. This finding suggests that mechanisms different from bacterial release of HMBPP are involved in TCR γδ stimulation.

One such a mechanism has been recently demonstrated [39]. Immediately after infection, whether or not bacteria are producing HMBPP, a modification of the mevalonate pathway occurs in infected cells, involving the transient dysregulation of hydroxy-methylglutaryl-CoA reductase (HMGR) enzymatic activity. HMGR function is tightly regulated at multiple levels and its phosphorylation reduces its activity. Within 60 minutes after infection, HMGR becomes dephosphorylated in infected cells and induces an increased synthesis of endogenous mevalonate metabolites, including IPP. As a result, infected cells very efficiently stimulate TCR Vγ9/Vδ2 cells and induce the release of large amounts of cytokines from these cells as soon as 5 hours post-infection. In the presence of antibiotics, which kill bacteria, the mevalonate pathway is counter regulated and after 24 hours, normal levels of metabolites are established again. These events occur in the presence of very small numbers of bacteria (1-10 bacterial cells infecting one antigen-presenting cell) and also when bacteria are killed with antibiotics shortly after infection. These conditions do not allow the accumulation of large numbers of bacterial cells and thus it is probable that HMBPP does not accumulate in sufficient amounts to be stimulatory. Remarkably, the same mechanism is observed with bacteria lacking the MEP pathway [39], thus suggesting that HMBPP is not involved in TCR γδ stimulation. This is a new mechanism whereby TCR Vγ9/Vδ2 cells are stimulated during the very early phases of bacterial infection, before any other specific immunity could be induced.

Aminobisphosphonates (nBP) are a family of drugs that behave as potent activators of TCR Vγ9/Vδ2 cells [40, 41]. These drugs are used to prevent bone resorption and in the treatment of Paget's disease, osteoporosis and bone tumors. nBP block the enzyme farnesyl pyrophosphate synthase (FPPS) [42], and thus the synthesis of cholesterol and the prenylation of proteins including Ras and Rac. The direct consequence of this functional block is apoptosis of cells that have internalized sufficient drug amounts. Internalization of nBP is a necessary prerequisite for TCR Vγ9/Vδ2 cell activation. Since FPPS is an enzyme that utilizes intermediate mevalonate metabolites generated after IPP synthesis, nBP-loaded cells accumulate abnormal levels of IPP [28] and this is why TCR Vγ9/Vδ2 cells get activated. Several evidences demonstrate that this is the mechanism of nBP action and that nBP do not act through direct engagement of TCR. IPP accumulation is efficiently prevented by addition of statins, drugs blocking the HMGR enzyme, which synthesizes IPP precursors. The effects of statins are detected only when they are added before or at the same time as nBP, thus strongly supporting the possibility that their inhibitory effects occur because they prevent accumulation of IPP. Furthermore, the inhibition exerted by statins is specific for TCR γδ cells stimulated by nBP and not by exogenous IPP and is not observed on TCR αβ cells [28]. Subsequent studies have confirmed that statins block the stimulatory activity of nBP [43]. Therefore, nBP are not TCR γδ cognate antigens, but induce the accumulation of stimulatory metabolites of the mevalonate pathway. As nBP are compounds used in the clinic, this novel mechanism of action has prompted their use in novel anti-tumour therapies [44-46] and has inspired development of novel nBP analogs with high capacity to induce IPP accumulation [26, 47].

A third group of stimulatory molecules are primary alkylamines [48]. These substances stimulate TCR Vγ9/Vδ2 cells in a TCR-dependent manner and are naturally found in bacterial cell cultures and in some edible plants. Their activity is exerted at extremely high concentrations (mM range!) and this casts some doubts whether they may behave as physiological ligands *in vivo*. An intriguing issue is that alkylamines are positively charged molecules, whereas the strongly activatory mevalonate and MEP metabolites are negatively charged molecules. The fact that the diphosphate moiety of IPP and HMBPP are absolutely required for the TCR γδ stimulation, has raised the question of which mechanism is responsible for alkylamine activity. One study showed that alkylamines behave as very weak inhibitors of FPPS [49] and it was proposed, but not demonstrated, that this mechanism leads to accumulation of IPP, thus resembling the mechanism of action of nBP. However, alkylamines inefficiently block FPPS, thus raising the possibility that other mechanisms may apply. Additional studies are necessary to understand the mechanisms inducing activation of TCR γδ cells by alkylamines.

Another stimulatory molecule is *Staphylococcus aureus* enterotoxin A (SEA) that directly interacts with the TCR Vγ9 chain independently of the paired Vδ chain [50]. The

mechanism of recognition of this superantigen is different from that of phosphorylated metabolites and requires the interaction with MHC class II molecules [51]. TCR γδ cells kill target cells and release cytokines upon interaction with SEA but do not proliferate. This is different from SEA stimulation of TCR αβ cells, and has been ascribed to the very low potency of this toxin when it binds to the Vγ9 chain.

Other two molecules stimulating the TCR Vγ9/Vδ2 cell population are the heat shock protein (HSP) 70 and the ATP F1 synthase. In an original paper, antibodies against the human HSP70 were found to inhibit recognition of tumour cells by TCR γδ clones [52]. Similar findings were also obtained using a monoclonal antibody against the same HSP molecule [53] and later studies have supported these findings [54-56]. However, despite two decades having passed since the first published study, to date there is no biochemical evidence of surface expression of this protein and no progress has been made to demonstrate a cognate interaction of HSP70 with the TCR γδ.

More recently, ATP F1 synthase has been indicated as stimulatory of the TCR Vγ9/Vδ2 [57]. ATP F1 synthase is an intracellular protein complex involved in ATP generation. In some tumour cells it is expressed at low amounts on the plasma membrane and co-precipitates with MHC class I molecules [58]. A monoclonal antibody interacting with apolipoprotein A1 was shown to inhibit TCR γδ activation and this inhibitory effect was ascribed to ApoA1 association with ATP F1 synthase. When purified bovine ATP F1 synthase complex is attached to beads, it induces a very weak activation of some TCR γδ clones. However, many APC stimulate very efficiently TCR Vγ9/Vδ2 cells despite they lack ATP F1 synthase complex on the plasma membrane, thus indicating that this protein complex is not involved in antigen presentation of phosphorylated metabolites. Further studies are required to understand whether ATP F1 synthase complex has a physiological relevance in stimulating TCR γδ responses *in vivo*.

The second major population of circulating human TCR γδ cells utilizes the Vδ1 chain that is paired with a variety of Vγ chains.

The antigen specificities of these cells remain poorly defined. TCR Vδ1 cells are involved in recognition of HIV- [59-62] and Cytomegalovirus-infected cells [63, 64], although the stimulatory antigens remain unknown.

TCR γδ cells with predominant use of Vδ1 are also expanded in the gut mucosa of celiac disease patients [65-67]. Interestingly, this TCR γδ cell population is abundant also in the gut mucosa of patients without villous atrophy [68], thus questioning their role in local lesions pathogenesis.

Some TCR Vδ1 cells can also be activated by CD1c- [69-72] and CD1d-expressing APC [72, 73]. The frequency of CD1-restricted TCR γδ cells remains to be investigated and thus it is still unclear whether they are rare or frequent cells. One population recognizes phosphatidylethanolamine (PE) from pollens [72, 73]. These T cells discriminate fine structural characteristics of plant PE acyl chains, which are rarely present in PE from eukaryotic cells and support IgE production *in vitro*. Since the frequency of pollen-specific cells in the circulating blood of patients with pollen allergy changes during pollen season, the CD1-restricted T cells have been indicated as important cells participating in the development of the allergic syndrome.

Finally, some TCR γδ cells with the Vδ1 chain may recognize allogeneic MHC molecules [74, 75]. Whether these reactivities are important in transplant rejection remains unclear.

## EVIDENCE FOR A UNIQUE TYPE OF RECOGNITION AND REQUIREMENT FOR ANTIGEN PRESENTATION

Several evidences suggest that recognition of phosphorylated metabolites is different form that of protein antigens presented by MHC molecules and of lipid antigens presented by CD1 molecules. Here, evidences of the importance of antigen structure, TCR sequence and antigen presentation are discussed.

One study showed that a variety of T cell clones expressing Vγ9/Vδ2 TCR with different VDJ junctional regions cross-react with a variety of ligands [19]. This study also showed a constant hierarchy of the potency of tested ligands, *i.e.* the same agonists were always the most stimulatory, independently of TCR junction. According to these findings it is possible that the TCR Vγ9/Vδ2 recognizes a unique conserved antigenic structure and that different phosphorylated ligands may concur to the generation of the same stimulatory motif. This recognition is very specific as both the ligand and the TCR structures are important.

The relevance of the ligand structure has been emphasized by a large number of studies. The use of a series of HMBPP and IPP synthetic analogs led to the conclusion that a core region containing the intact diphosphate group and the C-C double bond is essential for the biological activity [25, 29, 76-79]. Furthermore, introduction of highly reactive groups in IPP backbone, generates analogs with high potency [80]. QSAR analysis pointed out the importance of the H-bond donor (the OH group), of the hydrophobic feature (the methyl group), and of negative ionisable groups (the phosphate groups) [81]. Despite the large amount of data, it remains unclear whether these unique structural features are important in establishing a high affinity interaction with the TCR γδ, with a putative antigen-presenting molecule or both.

The importance of the TCR structure has been demonstrated as well. Initially, the reactivity was mapped to cells expressing the Vγ9-Cγ1 rearranged chains covalently paired with the Vδ2 chain [82]. These findings were confirmed by reconstitution studies showing that both the Vγ9 and Vδ2 chains are required and that the modifications in the CDR3 sequence of the γ chain abrogate reactivity [83, 84]. Later it was demonstrated that the lysine present in the Jγ1.2 gene segment is absolutely required for stimulation by IPP, HMBPP and alkylamines [85]. It was also demonstrated that the Vδ2 chain expressed by most TCR Vγ9-Vδ2 show diverse amino acid composition and length, with a highly distinctive junctional motif [86] and a conserved hydrophobic amino acid residue at position 97 [87]. The role of this Vδ2 CDR3 residue in IPP recognition has not been clarified.

Importantly, the thymic and placental repertoires of Vγ-Vδ pairs are different from those of circulating TCR γδ cells in adult blood, suggesting peripheral expansion of selected TCR pairs with defined antigen-specificity [10, 88-91]. In one study, when the unproductive TCR δ locus was investigated, six V genes and six non-V elements were found rearranged and the same set of genes was found rearranged both in the productive and in the unproductive chromosome, indicating that molecular mechanisms play a major role in the restriction of the TCRDV gene repertoire [9]. However, the fact that the peripheral but not thymic Vγ and Vδ repertoires are skewed towards the TCR Vγ9Vδ2 pair, supports the hypothesis that while molecular mechanisms influence the rearrangement of TCR loci, an antigen selection mechanism shapes the TCR γδ repertoire in the periphery.

The importance of APC has been recognized for a long time, although their exact role remains poorly defined. Initially, it was found that activation of TCR Vγ9/Vδ2 cells by mycobacterial metabolites is very efficient only in the presence of APC and was not restricted by classical MHC molecules [82]. These findings have been confirmed in many subsequent studies [92-96]. APC must be of human origin [29] and can be derived from different donors and from different tissues [28]. Recently, using a photoactivable HMBPP analog, specific binding on MHC- and CD1-negative cells has been reported [97]. This analog most probably binds to a putative antigen-presenting molecule that is protease sensitive [98]. Taken together, these studies suggest that active metabolites bind to dedicated antigen-presenting molecules that appear to be non polymorphic, ubiquitous and active only if of human origin.

## FUNCTIONAL SIGNIFICANCE OF MEVALONATE METABOLITES RECOGNITION

Several considerations are important to outline a possible mechanism of recognition of endogenous IPP and bacterial HMBPP by the TCR Vγ9/Vδ2.

First, IPP is an endogenous molecule that is generated within the cytoplasm of APC. In order to interact with the TCR, IPP must pass the cell membrane. This cannot occur in a passive manner because the negative charge of IPP prevents membrane diffusion. Therefore, a mechanism of active transport is anticipated, which facilitates the export of IPP and its interaction with the TCR.

Secondly, the size of IPP is too small to trigger a large molecule such as the TCR γδ. IPP aggregates are unlikely to be formed and direct binding of HMBPP or IPP to recombinant TCR has not been detected [14].

Thirdly, the phosphorylated metabolites are predicted to form complexes of short duration with the putative antigen-presenting molecule, because when they are washed before addition of T cells in culture, their activity is lost [28, 94].

Fourth, the number of TCR Vγ9/Vδ2 cells is impressively large as compared to other T cell populations sharing antigen specificity. On average 1-5 out of 100 T cells in blood and in some secondary lymphoid organs express the TCR Vγ9/Vδ2. This is the highest frequency of a steady state T cell population ever found in normal individuals and a persistent stimulation might have dangerous pro-inflammatory effects. Therefore, a tightly controlled mechanism should prevent continuous display of stimulatory complexes.

Taken together, these findings suggest that the TCR Vγ9/Vδ2 population is selected for recognition of cells with altered mevalonate metabolism, such as infected and tumour cells. Whenever these cells appear, they can immediately signal to TCR γδ cells and induce fast (within 2 hours) release of cytokines, which influence the very early phases of immune response. This sentinel system can be rapidly shut down and regulated by the disappearance of antigen on the surface of APC. This is the case with transiently infected cells, whereas tumour cells with stable mevalonate alterations maintain continuous stimulatory capacity. This important difference of the mevalonate dysregulation in tumour cells suggests to exploit TCR Vγ9/Vδ2 cells in anti-tumour immunotherapy.

In conclusion, important antigens stimulating human TCR γδ cells have been identified and initial clarification of the mechanisms of antigen presentation is being carried out. Although many questions remain to be answered, recent studies have revealed surprising novel basic rules of T cell immunity and promise to offer new approaches to immunotherapy.

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## ABBREVIATIONS

IPP = Isopentenyl diphosphate

HMBPP = (E)-4-hydroxy-3-methyl-but-2-enyl diphosphate

HMGR = Hydroxy-methylglutaryl-CoA reductase

MEP = 2-C-methyl-d-erythritol 4-phosphate

nBP = Aminobisphosphonates

FPPS = Farnesyl pyrophosphate synthase

SEA = Staphylococcus aureus enterotoxin A

HSP = Heat shock protein

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