


Perspective

Natural Self-Ligand Gamma Delta T Cell Receptors ($\gamma\delta$ TCRs) Insight: The Potential of Induced IgG

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Abstract: A $\gamma\delta$ T cell acquires functional properties in response to the gamma delta T cell receptor $\gamma\delta$ TCR signal strength during its development in the thymus. The elucidation of the potential ligands of $\gamma\delta$ T cell receptors are of extreme importance; however, they are still not understood. Here we revise the actual state of the art of candidates to exert the function of $\gamma\delta$ TCR ligands, and propose a theoretical contribution about new potential ligands of $\gamma\delta$ TCRs, based on biological and hypothetical pieces of evidence in the literature. In conclusion, we hypothetically suggest a possible role of induced antibodies according to the individual's immune status, mainly of the IgG subclass, acting as $\gamma\delta$ TCR ligands. Considering that IgG production is involved in some essential immunotherapy protocols, and almost all vaccination protocols, our discussion opens a new and broad field to further exploration.

Keywords: gamma delta T; gamma delta TCR; gamma delta TCR ligands; IgG

1. $\gamma\delta$ T Cells

Matured in the mouse and human thymus, $\gamma\delta$ T cells are characterized by expressing T cell receptors TCRs composed of γ and δ chains, and represent the major resident T cell population [1]. In response to activation, these cells can produce several cytokines and chemokines with several modulatory and regulatory functions on innate and adaptive immunity [2–4].

This ability to transition between innate and adaptive immunity is a typical feature of this cell population, given by non-major histocompatibility complex non-MCH restricted antigenic specificity [5], as is the capability of initiating rapid immune responses to a large number of potential tissue stressors, exerting functions related to homeostasis and the host defense of epithelial barrier tissues, and the lymphoid stress-surveillance response [1,2].

Being one of the first generated T cells in the embryony period, $\gamma\delta$ T cells quickly spread to the peripheral tissues but are not found with a high frequency in the lymphoid tissues and blood of adult individuals. On the other hand, $\gamma\delta$ T cells are detected at a higher rate in mucosal and epithelial tissues [6,7]. In the mucosal environment, these cells are activated in response to stress, including environmental challenges, infections, and malignant transformation from the surrounding tissues, and they perform many functions depending upon the location and type of stress that has occurred, in other words, $\gamma\delta$ T cells act as sentinels [8].

In humans, about 5–40% of intraepithelial lymphocytes (IELs) in the paracellular space are $\gamma\delta$ T cells [9]. The $\gamma\delta$ TCR repertoire in the human intestine undergoes many changes during the development from fetus to adult. Thus, $\gamma\delta$ T cells may mediate different functions at each stage of maturation. Since the $\gamma\delta$ TCR repertoire is oligoclonal and stable over time, $\gamma\delta$ T cells may recognize a limited array of antigens that are highly conserved among different bacterial strains, mostly intracellular microbial pathogens (e.g., *Listeria*, *Mycobacterium*, *Plasmodia*, *Toxoplasma*). Additionally, $\gamma\delta$ IEL have

been shown to produce cytokines and growth factors, and to influence epithelial cell proliferation and differentiation, as well as the mucosal development of immunoglobulin A (IgA) secreting B cells [10].

About 15–25% of T cells in the liver express the $\gamma\delta$ TCR and thus exert essential functions in the homeostasis and diseases of this organ. It is also well known as a site of the extrathymic development of $\gamma\delta$ T cells during the human fetal period [11]. These cells have reportedly been shown to have their subsets altered during the progression of liver diseases, as they are probably of great importance in determining the fate of the inflammatory process in this organ [12]. A great example is $\gamma\delta$ T cells contributing to hepatocyte apoptosis via Fas ligands, resulting in the engagement and recruitment of cytotoxic T cells in cases of hepatofibrogenesis, thereby limiting liver fibrosis [13].

Although $\gamma\delta$ T cell subsets can be defined by the expression of the γ and δ chains, two significant $\gamma\delta$ T cell subsets are defined by their capacity to produce IL-17 or IFN- γ in mice. These subsets are not established in humans [14]. In this regard, a study has revealed that, in mice, $\gamma\delta$ T cells encountering the antigen in the thymus were neither required nor inhibitory for their development, but when triggered through the T cell receptor, naive $\gamma\delta$ T cells produced IL-17, whereas ligand-experienced cells produced IFN- γ [15].

Previous studies demonstrated that IL-17-producing $\gamma\delta$ T cells collaborate with an effective immune response against infections [16–19] and with the pathogenesis of autoimmunity [20,21]. These cells exert nonredundant immunological functions [22]. Otherwise, IFN- γ -producing $\gamma\delta$ T cells are related to the development of murine fulminant viral hepatitis infection [23] and exert protective/regulatory functions in tumor immunity [24,25].

Unlike murine models, $\gamma\delta$ T cell subsets in humans are generally defined based on the V δ TCR chain, narrowing down into two major populations: V δ 2+ and V δ 2– $\gamma\delta$ T cells. V δ 2+ T cells are developed mainly in the fetal liver and thymus [26,27], and are the predominant $\gamma\delta$ T cell population in the peripheral blood of adult humans [28]. They can also be recruited to inflamed tissues to help with pathogen clearance or to promote inflammation. On the other hand, the V δ 2– $\gamma\delta$ T cell subset can be found in epithelial tissues, such as the skin [29] and intestines [9], and appears to form resident populations in the liver [30]. They mainly consist of V δ 1+ T cells, with fewer V δ 3+ and V δ 5+ T cells.

It is also important to highlight that in humans, IFN- γ -producing $\gamma\delta$ T cells can mediate the innate resistance to *Escherichia coli*, limiting systemic immunopathology [31]. Besides that, TCR- $\gamma\delta$ T cells have emerged as essential players in allogeneic hematopoietic cell transplantation (alloHCT) and immune cell therapy [32].

Since the early 1990s, the relationship between specificity and V γ and V δ gene usage was described [28] and, currently, human $\gamma\delta$ T cells can be classified according to the expression of δ genes (δ 1–3) and γ genes (γ 2–5, γ 8, γ 9, and γ 11) [33]. Murine $\gamma\delta$ TCR chain expression can be related to a tissue site (e.g., γ 1, γ 4, and γ 6 in the lung), and this differential expression influences the antigen-specific recognition properties of tissue-infiltrated $\gamma\delta$ T cells between each tissue and, consequently, influences their collaboration with the development of an adaptive immune response [3].

Besides, in the context of adaptive immune responses, it was demonstrated that $\gamma\delta$ T cells can favor murine antibody production by B cells by secreting IL-4 and IL-10 [34].

The $\gamma\delta$ TCR signaling during the early stages of maturation in the thymus can influence the mature $\gamma\delta$ T cells' cytokine secretion profile [35]. With the use of a molecule that can act as a ligand of $\gamma\delta$ TCRs, such as the major histocompatibility complex (MHC) class Ib ligands (H2-T10/22), it was demonstrated that $\gamma\delta$ TCR interaction can play an essential role in shaping the TCR repertoire of $\gamma\delta$ T cells [36].

These observations indicate that the elucidation of the potential ligands of $\gamma\delta$ TCRs and their relations with the induction of functional properties in $\gamma\delta$ T cells is of extreme importance. However, this has been discussed by renowned scientists in the literature since the late 1980s [37,38], and even after some evolutionary analysis, the mechanisms involved in $\gamma\delta$ TCR-dependent $\gamma\delta$ T cell activation are still not understood [33]. The search for the identification of $\gamma\delta$ TCR ligands was named “the quest to solve a 500-million-year-old mystery” [39].

Taking into consideration the modulatory effects mediated by $\gamma\delta$ T cells in the mechanism of immune inflammation, here we briefly revise the state of the art and propose a theoretical contribution to generate some discussions about new potential ligands of $\gamma\delta$ TCRs. With this purpose, we collected biological and hypothetical pieces of evidence from the literature.

2. Antigen Recognition Mechanism

As is known, $\alpha\beta$ T cells recognize antigens as antigen fragments after being processed by antigen-presenting cells (APC), followed by the binding of these fragments to various sites on the major histocompatibility complex (MHC) molecule of the APC, and posterior presentation at the cell surface to the TCR, and then activation and proliferation of the T cells [40–44]. However, there are far fewer pieces of evidence showing the mechanisms involved in antigen recognition by $\gamma\delta$ T cells. However, it is essential to remember that these two lineages of cells differ not just at a molecular level, they also have a different antigenic repertoire, even though specific antigens are capable of stimulating both populations.

In this context, two significant points allow us to tell the difference between these two populations within the process of antigen recognition. The first is that some $\gamma\delta$ T cells do not seem to require the classical MHC for antigen recognition, since the majority of $\gamma\delta$ T cell hybridomas do not require the MHC for activation [45]. Furthermore, studies from another group have gathered data on a murine TCR gamma delta clone (TgI4.4) capable of recognizing a herpes simplex virus type 1 (HSV-1) transmembrane glycoprotein in an MHC class I- and II-independent manner [46]. On the other hand, there are shreds of evidence that $\gamma\delta$ T cells may recognize some antigens, like tetanus toxoid, in an MHC-restricted fashion [47].

Although some $\gamma\delta$ T cells were able to recognize proteins without processing, such as mouse class II MHC molecule IE^k, T10, T22, and herpes simplex virus glycoprotein I, others were unable to recognize peptides bound to these proteins [48–51]. In addition, these studies have demonstrated that some $\gamma\delta$ T cell clones seem to recognize antigens without the need for intracellular antigen processing, which means this recognition process is made directly on the surface.

Taken together, these pieces of evidence allow us to suggest that $\gamma\delta$ T cells can recognize unprocessed antigens at the cell surface, exempting APCs as a requirement for antigen recognition by those cells. However, APCs may exert other functions when they can be stimulated by the products of gamma delta T cell activation into producing cytokines and growth factors, collaborating with the enhancement of the ongoing immunological response.

3. Evidenced and Proposed $\gamma\delta$ TCR Ligands

As discussed above, $\gamma\delta$ TCR signaling can determine the activity of $\gamma\delta$ T cells [14,52,53], therefore a precise functional understanding of $\gamma\delta$ T cells depends on the elucidation of the molecules capable of triggering their activation via $\gamma\delta$ TCRs.

Reasoning from this fact, here we will not discuss all pieces of the evidence of the direct interaction of several ligands with $\gamma\delta$ TCRs [54–58], but mainly those that are likely to generate future mechanistic or biological approaches in vivo.

First and foremost, a very recent study was able to demonstrate that $\gamma\delta$ TCR ligands can be expressed by several cells, including both human tumor cell lines and individual human primary cells. This study could also illustrate the spectrum of ligand(s) expression for human synovial V δ 1 $\gamma\delta$ T cells, as well as the physiology that regulates their expression, but it did not accurately identify the molecules that can act as $\gamma\delta$ TCR ligands in those cells [59].

In this context, it was shown that spatially distinct regions of $\gamma\delta$ TCRs, as demonstrated by the hypervariable region 4 (HV4) of V γ 4 chains, can determine the antigen responsiveness of $\gamma\delta$ T cells, increasing the complexity of the understanding of $\gamma\delta$ TCR ligand recognition [60].

It has been shown that murine $\gamma\delta$ T cells depend on the type of adjuvant used in immunization to shift the production of IL-17 [61]. On the other hand, it was described that human $\gamma\delta$ T cell subsets can

recognize both natural and synthetic phosphoantigens (pAgs) [62]. However, the mammalian molecule isopentenyl pyrophosphate (IPP) stimulates $\gamma\delta$ T cells at a 10,000-fold higher concentration compared to phosphoantigens derived from bacteria. This last observation suggests that IPP cannot exert a physiological role as a $\gamma\delta$ TCR ligand [63]. Additionally, a report has indicated that pAgs do not interact directly with $\gamma\delta$ TCRs, in fact, the $V\gamma9V\delta2$ T cell activation is due to the recognition of an allosteric change in the extracellular domain of a cell surface molecule, butyrophilin 3A1 [64]. The F1-ATPase molecule was proposed as a $\gamma\delta$ TCR ligand in a tumor recognition study [65], but the evidence for this is still incomplete. A detailed discussion about $\gamma\delta$ TCR ligands, summarized in Figure 1, and the knowledge generated in both species, will follow.

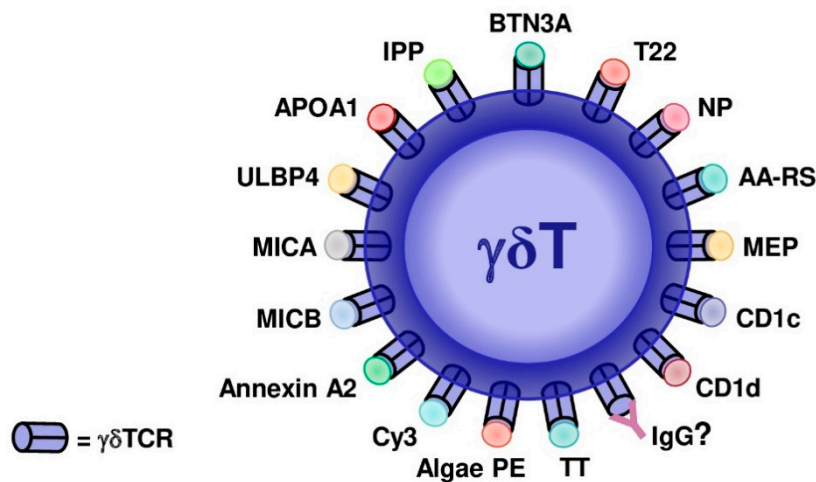


Figure 1. Evidenced and proposed $\gamma\delta$ TCR ligands in mice and humans. Butyrophilin-3 (BTN3A), nonclassical MHC molecule T22, 4-hydroxy-3-nitrophenylacetyl (NP), aminoacyl-tRNA synthetases (AA-RS), monoethyl phosphate (MEP), CD1c, CD1d, toxoid of *Clostridium tetani* (TT), algal phycoerythrin (PE), cyanine 3 (Cy3), annexin A2, MICB (MHC class I chain-related protein B), MICA (MHC class I chain-related protein A), ULBP4, APOA-1 (apolipoprotein A-1), isopentenyl pyrophosphate (IPP), and IgG are illustrated. ? = proposed non-evidenced ligand.

3.1. Algal Phycoerythrin (PE)

A noted B cell antigen, the algal protein phycoerythrin (PE), can act as a murine and human $\gamma\delta$ TCR antigen [66]. In this study, it was demonstrated that the recognition of algal PE by activated naive $\gamma\delta$ T cells induces the production of IL-17 and yields the functionality to respond to cytokine signals, collaborating with the perpetuation of the immune response [66].

3.2. Annexin A2

More recently, using in vitro experiments in which tumor cells were exposed to various stress situations, it was observed that $\gamma\delta$ T cells could recognize tumor cells. This direct recognition is mediated by a cell stress-related molecule, annexin A2. However, it seems that it occurs only with a specific subset of $\gamma\delta$ T cells, the $V\gamma8V\delta3$ TCR-expressing $\gamma\delta$ T cells [67].

3.3. BTN3A (Butyrophilin-3)

A study using cell stress-related molecule phosphoantigen (PAg) up-regulation in tumor and mycobacteria-infected cells, demonstrated that a human $\gamma\delta$ T cell could also recognize butyrophilin-3 (BTN3A) molecules. However, similar to annexin A2, it seems to occur only with a specific subset of $\gamma\delta$ T cells, in this case, the $V\gamma9V\delta2$ TCR-expressing $\gamma\delta$ T cells [68]. Luckily, $V\gamma9V\delta2$ T cells represent the major $\gamma\delta$ T cell subset in human peripheral blood, with values ranging from 50% to 95% of $\gamma\delta$ T cells, besides the fact that they stand out as being able to sense several infected and malignant cells [69].

3.4. T22

It was demonstrated that the non-classical MHC molecule, T22, could act as a ligand for $\gamma\delta$ TCRs in mice [70] and the MHC-like molecule, CD1, in mice and humans [71]. Performing a study that aimed to identify CD1d-sulfatide-specific T cells in healthy individuals, Bai L and collaborators surprisingly observed that the majority of fresh sulfatide-specific T cells belonged to the $\gamma\delta$ lineage, and they mainly expressed V δ 1 chains in their TCRs [72]. This study provided the first demonstration of MHC-like-restricted, antigen-specific recognition by $\gamma\delta$ TCRs [72].

3.5. CD1c

The CD1c, a molecule expressed by human dendritic cells (DCs) and B cells when presenting antigens to T cells, can be recognized by $\gamma\delta$ TCRs when loaded with *Mycobacterium tuberculosis* phosphomycoketide [73]. This same study evidenced that the V δ 1 domain participates in recognition by $\gamma\delta$ TCRs and demonstrates that CD1c can complex with lipids, including lysophosphatidylcholine, sulfatide, and mannosyl-phosphomycoketide [73].

Although these molecules cannot mediate in vivo interaction with $\gamma\delta$ TCRs, shaping their maturation process, they may be especially crucial in the recognition of pathogens by peripheral $\gamma\delta$ T cells. Otherwise, the definition of $\gamma\delta$ T cells' functions mainly occurs during their maturation in the thymus, suggesting that other ligands that can reach this organ are involved in the development of $\gamma\delta$ T cell functions.

3.6. Haptens

Studies about $\gamma\delta$ T cell hapten recognition emerged from the idea that these cells possibly recognize antigens similarly to B cells [48]. A study using immunized mice with Cy3-chicken gamma globulin (Cy3-CGG) in aluminum hydroxide demonstrated that haptens, such as cyanine 3 (Cy3) and 4-hydroxy-3-nitrophenylacetyl (NP), can be recognized directly by specific $\gamma\delta$ TCRs, and are able to induce a T cell response [74]. Thus, these molecules are capable of up-regulating CD44^{hi} and CD62L^{lo}, which is equal to an activated phenotype in $\gamma\delta$ T cells.

3.7. Non-Peptides

The initial observation about non-peptide recognition was obtained with a non-peptide antigen derived from *M. tuberculosis* that could be recognized by murine and human $\gamma\delta$ T cells [75]. From there, a subsequent study demonstrated that a variety of non-peptide molecules could stimulate human $\gamma\delta$ T cells [76]. In the same study, it was shown that monoethyl phosphate (MEP), a synthetic alkyl phosphate, was able to activate these cells and stimulate their proliferation in vitro [76]. In both cases, all $\gamma\delta$ T cells stimulated by these molecules expressed V γ 2/V δ 2 TCRs.

In a comparative approach, it was demonstrated that mycobacterial antigens recognized by $\gamma\delta$ T cells were chemically and chromatographically similar to MEP, and both were able to expand primary V γ 2/V δ 2 T cells [76].

The human stress antigens MICA and MICB are MHC class I-related molecules originally described as ligands of NKG2D receptors expressed in NK cells. They have also been described as ligands of $\gamma\delta$ T cells that express the variable region V δ 1, therefore acting as stress-induced self-antigens [77]. However, this correlation is limited to the intestinal epithelium because it corresponds to the environment where this subset of $\gamma\delta$ T cells is prevalent, and where MICA and MICB are mainly expressed. The same study also showed that there is a correlation between these T cells and epithelial tumors, which, regardless of their type, express MICA/MICB. The reason behind this correlation is that the more MICA/MICB is expressed, the higher the number of $\gamma\delta$ T cells found in the tissue [78]. In this regard, another study using soluble MICA tetramers as a binding reagent to demonstrate specific interactions with various V δ 1 $\gamma\delta$ TCRs expressed on T cell lines lacking NKG2D, showed that MICA delivers both the TCR-dependent signal and the NKG2D-dependent costimulatory signal. This dual function may be

useful to prevent inaccurate $\gamma\delta$ T cell activation in cases of cross-reactivity with other cell surface compounds [79].

Another interesting molecule worth mentioning is ULBP4, which is also a ligand for NKG2D, along with MICA/MICB. In a study conducted by Kong's group, ULBP4 not only can play a role as a ligand for TCR $\gamma\delta$, binding directly to it, but can also trigger the expansion of gamma delta T cells from tumor-infiltrating lymphocytes in humans [80].

Since molecules expressed on the surface of tumoral cells seem to be seen as an attractive criterion to draw the attention of $\gamma\delta$ T cells, apolipoprotein A-1 (APOA-1) should not be left out of this discussion. A tumor recognition study led by Scotet's group has shown that when in the presence of APOA-1, tumors expressing F1-ATPase can trigger the activation of V γ 9V δ 2 T cells by selectively binding to the V γ 9V δ 2 TCR [65].

3.8. Peptides

Despite the notoriety of non-peptidic antigens, there is a variety of protein-derived molecules that can trigger $\gamma\delta$ T cell activation. In humans, the earliest evidence points to the tetanus toxoid of *Clostridium tetani*, capable of stimulating specific $\gamma\delta$ T cell responses [47]. Another study has shown that processed Ig λ light chains in humans [81], and even processed insulin in mice [82], are also recognized by $\gamma\delta$ T cells. Additionally, cell surface-expressed proteinaceous ligands have been identified, including the classical MHC I and II molecules, as well as the non-classical MHC I-related molecule, T22, in mice [70], CD1c in humans [73], and CD1d in both mice and humans [72], as discussed above.

3.9. Aminoacyl-tRNA Synthetases (AA-RSs)

Another study that aimed to investigate the antigen specificity of $\gamma\delta$ -TCRs, in humans that develop myositis, could demonstrate that V γ 1.3V δ 2-TCR (M88) recognizes aminoacyl-tRNA synthetases (AA-RSs), an antigen that can also be targeted by an autoantibody called anti-Jo-1. The observation that AA-RSs are targeted by a $\gamma\delta$ T cell and by an autoantibody reveals an unprecedented link between T cell and antibody responses in autoimmune myositis [83].

3.10. Dectin-1 (CLEC7A)

C-type lectin domain family 7 member A, also called dectin-1, is a human protein encoded by the CLEC7A gene that was initially identified by subtractive cDNA cloning, using mRNA extracted from murine DCs [84]. In addition to inducing Th17 cells, it was demonstrated that dectin-1 could also directly trigger the production of IL-17 by a subset of $\gamma\delta$ T cells [85].

In 2014, it was demonstrated in a murine model of hepatic regeneration with the disruption of TCR δ and *Clec7a*, that $\gamma\delta$ T cells can regulate this process through the production of IL-22 and IL-17. This mechanism occurs by direct effects on hepatocytes and by the promotion of a regenerative phenotype in hepatic leukocytes. These observations suggest that dectin-1 is required for $\gamma\delta$ T cell-promoted hepatic regeneration [86].

Table 1 summarizes the experimental pieces of evidence about $\gamma\delta$ TCR ligands, considering the differences between mouse and human $\gamma\delta$ T cells.

3.11. IgG Antibodies as $\gamma\delta$ TCR Ligands

In almost all of the studies cited above, the search for a $\gamma\delta$ TCR ligand was focused on the identification of membrane-like or membrane-expressed molecules with no discussion about ligands that can have soluble forms, such as antibodies.

IgG antibodies are versatile molecules expressed by B cells and can also be detected in other cell membranes after interaction with Fc γ receptors. This molecule is also secreted by B cells, and its soluble form can reach almost all of the tissues of an organism.

Table 1. $\gamma\delta$ TCR ligands with biological effects described in the literature. Classes of ligands and their effects on humans and mice.

Proposed Ligand	Class	Effect in Human $\gamma\delta$ T Cells	Effect in Mouse $\gamma\delta$ T Cells	References
Aminoacyl-tRNA synthetases (AA-RSs)	Enzyme	Destruction of skeletal muscle fibers in myositis.	Not reported in the literature due to the incapability of generating transgenic mice.	[83]
Algal phycoerythrin (PE)	Protein	Production of IL-17.	Production of IL-17.	[66]
Annexin A2	Protein	Proliferation of a V δ 2 ^{neg} $\gamma\delta$ T-cell subset.	Not reported in the literature.	[67]
Butyrophilin-3 (BTN3A)	Peptide	Intracellular PAg accumulation leading to activation of V γ 9V δ 2 T cells.	Not reported in the literature.	[68,69]
CD1c	MHC molecule	Lysis of CD1c-expressing tumor cells.	Not reported in the literature.	[71,72]
Cyanine 3 (Cy3)	Hapten	Not reported in the literature.	Up-regulation of CD44 in Cy3-specific $\gamma\delta$ T cells, IL-17 production, and expression of receptors for IL-1 and IL-23.	[74]
4-hydroxy-3-nitrophenylacetyl (NP)	Hapten	No reported in the literature.	Up-regulation of CD44 ^{hi} and CD62L ^{lo} (activated phenotype).	[74]
Mycobacterial antigen from <i>M. tuberculosis</i>	Non-peptide	Activates the V γ 2/V δ 2+.	In vivo activation of $\gamma\delta$ T and participation in the primary immune response to <i>M. tuberculosis</i> .	[75]
Monoethyl phosphate (MEP)	Non-peptide	Activates the V γ 2/V δ 2+.	Not reported in the literature since V γ 2V δ 2 T cells are restricted to primates.	[76]
TC22	MHC molecule	Not reported in the literature.	G8 bound T22 almost exclusively through its CDR3 δ loop with only minor contacts from other CDR loops.	[70]
MICA/MICB	MHC class I-related molecules	Increase in the number of $\gamma\delta$ T cells found in the tumoral tissue.	Not reported in the literature.	[77–79]
ULBP4	MHC class-related molecules	Expansion of $\gamma\delta$ T cells from tumor-infiltrating lymphocytes.	Not reported in the literature.	[80]
Apolipoprotein A-I (APOA-I)	Protein	Activation of V γ 9V δ 2 T cells by tumors expressing F1-ATPase in the presence of APOA-1.	Not reported in the literature.	[65]
Dectin-1 (CLEC7A)	Protein		Triggers the production of IL-17 by a subset of $\gamma\delta$ T cells.	[86]

Although, theoretically, these molecules may also interact specifically with $\gamma\delta$ TCRs, studies evaluating this hypothesis are very scarce in the literature. Among the few pieces of evidence in this

issue, it was demonstrated that a monoclonal antibody that can recognize murine $\gamma\delta$ TCRs (clone UC7-13D5), induces the *in vivo* generation of $\gamma\delta$ T cells [87]. Another study demonstrated that an anti- $\gamma\delta$ TCR antibody can be used to expand $\gamma\delta$ T cells *in vitro* and may be used as cellular therapy in the treatment of lung cancer [88] or lymphoid malignancies [89]. These observations generate a very interesting fraction of new possibilities on each antibody that can act as a ligand of $\gamma\delta$ TCRs, and need to be discussed across a broader spectrum as will follow.

In 2017, it was hypothetically suggested that IgG could be a natural ligand of lymphocyte receptors, including $\gamma\delta$ TCRs, and mediate some functional modulations of $\gamma\delta$ T cells according to an individual's IgG repertoire. This hypothesis considered that this molecule could reach primary lymphoid organs, including the thymus, in soluble and membrane-expressed forms, and accurately interact with the clonal receptors expressed on those cells [90].

Very briefly, what underlies this hypothesis is the fact that mammalian organisms naturally have the potential to spontaneously produce IgG antibodies that express idiotypes capable of recognizing any natural protein [91]. This characteristic includes all self-proteins, hence all receptors are expressed in $\gamma\delta$ T cells since their initial stages of maturation.

More recently, this hypothesis became experimentally evidenced with the demonstration that both murine and human IgG can modulate the frequency of IL-17-producing $\gamma\delta$ T cells depending on the IgG donor's immune status [92]. In the same study, it was demonstrated for the first time that murine IgG could directly interact with the thymic $\gamma\delta$ T cell membrane (in the absence of Fc γ Rs), although the co-localization of IgG and $\gamma\delta$ TCR has not been evaluated. Another recent study has also demonstrated that IgG can modulate the production of IFN- γ and IL-10 by human thymic $\gamma\delta$ T according to the donor's immune status [93]. Corroborating this hypothesis, similar studies evaluating the potential of IgG molecules as mediators of modulatory effects on lymphocytes during their maturation have demonstrated several effects on human TCD4, TCD8, iNKT, and B cells [94–98].

A direct relation between $\gamma\delta$ T cell activation and the murine antibody-mediated immune response in an antigen-specific manner was also recently revealed [99]. In this study, the possible role of IgG as a $\gamma\delta$ TCR ligand was not evaluated, but the relationship between antigen-specific antibodies and $\gamma\delta$ T cell activation in two murine models was shown [99]. This last piece of evidence demonstrated the importance of $\gamma\delta$ T cells in protein-induced immune responses and autoimmunity.

So far, these observations cannot adequately explain the IgG role as a $\gamma\delta$ TCR ligand, but they could have been considered within the list of candidates for ligands of these receptors, as recently revised [39].

Considering that under *in vivo* conditions, IgG can reach thymic lymphocytes during its maturation process [100–103], these recent studies open a broad discussion, suggesting that IgG can exert a role modulating the maturation of $\gamma\delta$ T cells at primary sites. Furthermore, the functional modulation mediated by IgG may vary according to individual repertoire specificity; it is possible that the role of $\gamma\delta$ T cells in inducing tissue inflammation is influenced by the IgG response to antigen exposition and its natural IgG repertoire.

Very recently, a hypothesis called the “hooks without bait” theory was presented in the literature to discuss the role of natural and induced IgG repertoires as modulatory ligands, not only for $\gamma\delta$ T cells, but in a broader context that includes T and B cells [104].

These observations are important in humans because of their wide variation in ambient exposure conditions and natural antibody repertoires, compared to murine observations obtained under controlled ambient exposure conditions and, therefore, homogeneous antibody diversity.

If the repertoire of IgG (the individual's group of idiotypes) can influence $\gamma\delta$ T cell functions by interacting with $\gamma\delta$ TCRs, they will modulate $\gamma\delta$ T cells according to the expressed γ and δ chains. As discussed above, the expression of γ and δ chains is related to homing, functionality, and the antigen-specific recognition properties of $\gamma\delta$ T cells. Therefore, if the IgG repertoire could indeed specifically interact with $\gamma\delta$ TCRs, this could result in the functional modulation of $\gamma\delta$ T cells according to their antigen recognition pattern.

If confirmed, this hypothesis will corroborate the elucidation of several aspects of $\gamma\delta$ T cell biology.

These biological aspects include the functional roles of $\gamma\delta$ T cells in inflammation induced by different antigens [105], the $\gamma\delta$ TCR repertoire changes in response to infections [106], the constant $\gamma\delta$ TCR triggering of $\gamma\delta$ T cells in vivo [107], the relationship between intestinal microbiota and $\gamma\delta$ T cell functions [108], and the observation that the repertoire of intraepithelial $\gamma\delta$ T cells is not biased toward thymic antigens [109].

A recent study demonstrated an additional $\gamma\delta$ T cell characteristic that can be influenced by an individual's IgG repertoire. It was described that an $\gamma\delta$ TCR's repertoire shifts the $V\gamma$ - and $V\delta$ -usage upon aging [110]. Considering that an individual's IgG is certainly permissive to repertoire shifts with aging if IgG can indeed act as a ligand of $\gamma\delta$ TCRs, IgG will influence the frequency of γ and δ chain expression and modulate $\gamma\delta$ T cell-mediated mechanisms, as suggested in Figure 2.

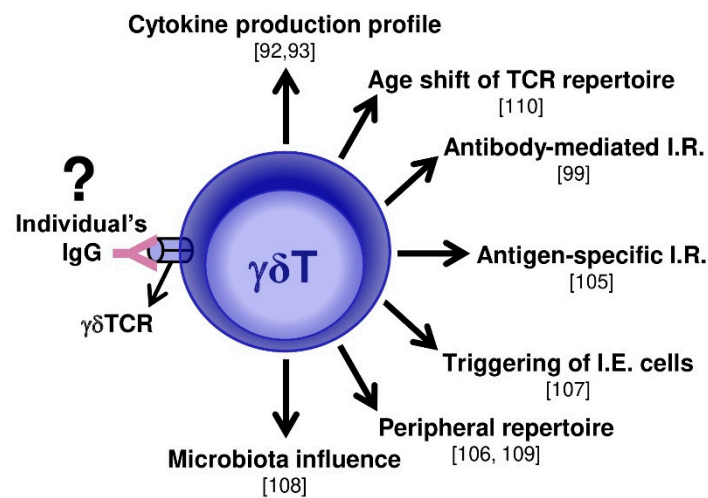


Figure 2. Possible $\gamma\delta$ T cell-mediated mechanisms that can be influenced by IgG. The main immunologic mechanisms mediated by $\gamma\delta$ T cells described in the literature, where IgG can be an influence by specifically interacting with $\gamma\delta$ TCRs, are illustrated with their respective references in brackets. ? = proposed non-evidenced ligand; I.R. = immune response; I.E. = intraepithelial.

4. Concluding Remarks

Here we discuss one of the most intriguing unanswered questions of the immune system; indeed, the long period of searching for an efficient response reflects the high degree of difficulty in identifying the natural ligands of $\gamma\delta$ TCRs. Despite the problem, $\gamma\delta$ T cells already represent a versatile immunoregulatory tool, since they can also be activated through cytokines without TCR engagement, allowing a faster response compared to $\alpha\beta$ T cells. Moreover, they were able to kill target cells via death receptor-mediated apoptosis or the release of cytolytic granules. In this discussion, we seek a broader and philosophical approach about possible $\gamma\delta$ TCR ligands, not restricted to the physicochemical characteristics of molecular interactions, but considering the complexity of knowledge about the operating range of the immune system. The lack of biological evidence represents the primary limitation on our suggestion about the potential of IgG to answer this “immunological mystery”, but if confirmed, IgG molecules acting as a specific ligand of $\gamma\delta$ TCRs can influence several immune mechanisms.

Based on these observations, we can speculate that all the in vivo immunological mechanisms that involve $\gamma\delta$ T cells are subject to influence by the IgG repertoire.

At this point, and maybe still for some years, we cannot be sure that each IgG repertoire has more affinity toward $\gamma\delta$ TCRs. However, considering some breakthrough works in the literature demonstrating the differential effects of IgG repertoires on $\gamma\delta$ T, $\alpha\beta$ T, and B cells, we can observe a common characteristic that yields some additional speculation about this mechanism. The main described functional effects of IgG repertoires were obtained from chronic pathophysiological conditions

including allergies [92,93,95,96], atopic dermatitis [94,97], or HIV-1-infected patients [111]. Considering those observations, we suggest that the $\gamma\delta$ TCR/IgG affinity determination results form a complex, long-term, and not yet clarified, process.

If confirmed, these can be additional reasons for why such controversial observations about $\gamma\delta$ T cell functions in the development of several diseases can be observed in the literature. Additionally, the verification of IgG as a ligand of $\gamma\delta$ TCRs will probably bring this molecule to a position of evidence in studies that aim to investigate immunoregulatory mechanisms involving $\gamma\delta$ T cells, but under a new perspective where its recognition diversity starts to be considered.

Thus, we hope that the discussed aspects of $\gamma\delta$ T cell biology can contribute to the future development of advances in antibody-based immunotherapies and vaccines.

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