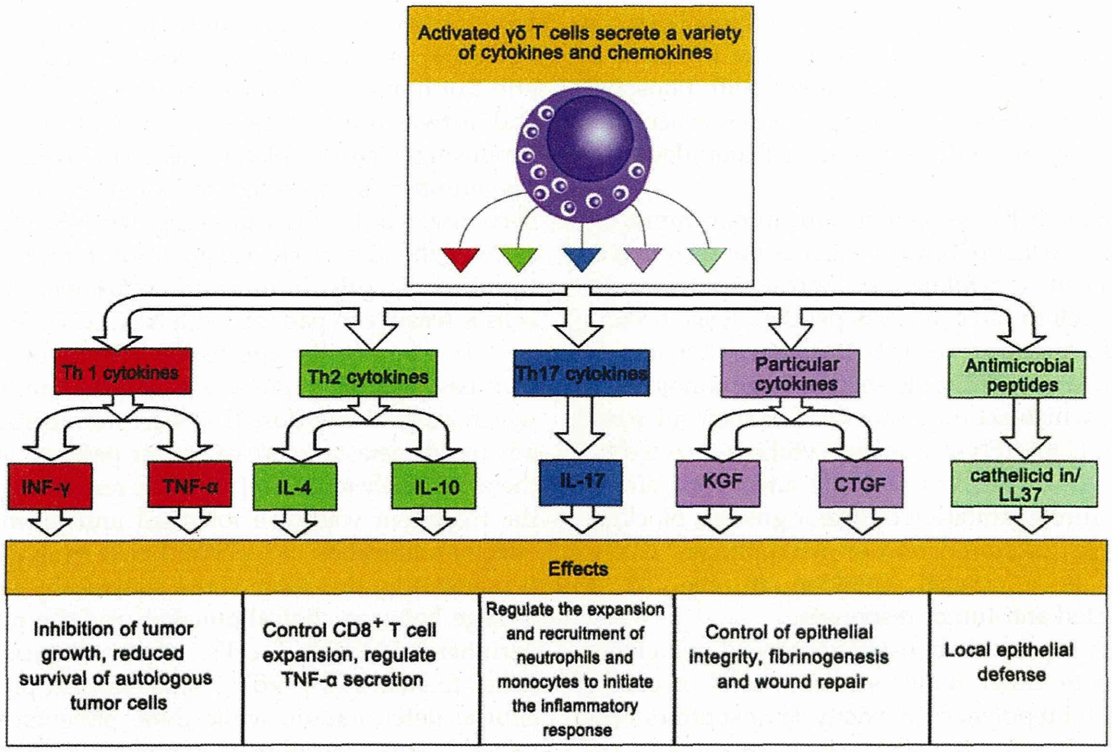

Figure 2. Secretion by activated γδ cells of multiple cytokines and their physiological roles.

Applications

γδ T-cell based cancer immunotherapy

In 1890, Paul Ehrlich proposed vaccines against cancer, which was the first suggestion using the immune system to cope with cancer. In fact, immune deficiency states, such as iatrogenic immune suppression, common variable immunodeficiency (CVID), severe combined immunodeficiency (SCID), and acquired immunodeficiency syndrome (AIDS), make patients more susceptible to various kinds of malignancies [117, 118]. The importance of immune surveillance against tumor emergence and progression was reinforced with the observation of different immune deficiency states. Targeting the immune system to combat tumors is a promising therapeutic strategy [119] although progress has been slow and success is limited.

Immunotherapeutic approaches for anti-tumor responses via stimulating the adaptive immune system rely on major histocompatibility complex (MHC)-restricted αβ T cells. Although significant advances in the adaptive immunotherapies toward tumors have been made and vaccine-based strategies have been improved, αβ T cell-mediated immunotherapies have met with limited success. Durable responses are scarce, and active immunotherapy has not achieved an established treatment modality. αβ T cells require specific tumor-associated antigens (TAAs) and suitable costimulatory molecules for activation. Once failure or loss of TAAs, MHC molecules, and/or costimulatory molecules occurs, it will render tumor cells less susceptible to αβ T-cell-mediated cytotoxicity or induce anergy in specific αβ T cells.

γδ T cells are considered to be a member of innate immune cells and exhibit an important role in immune-surveillance and immune defense against tumors, including melanomas [120], leukemias, lymphomas, neuroblastomas, and other types of carcinomas [102, 104, 121]. The antitumor activity of γδ T cells has been confirmed by expanding them *ex vivo* followed by infusion to cancer patients [122, 123]. Recently, *in vitro*-activated γδ T cells have been shown to target a small number of colon cancer stem cells, which had been demonstrated to be attributable to the failure of conventional therapies. In addition, γδ T cells can kill chemotherapy (imatinib)-resistant chronic myelogenous leukemia lines.

γδ T cells can be utilized for antitumor therapies in an unconventional manner [64], because they exhibit a potent MHC-unrestricted lytic activity against a wide variety of tumor cells *in vitro*. In clinical studies, γδ T cells have been shown to infiltrate into different kinds of tumors, including lung carcinomas [124], renal cell carcinomas [125], and breast carcinomas [126]. It is worthy of note that they have exhibited to specifically respond *in vitro* to tumors but not to normal cells. Moreover, a high level of γδ T cells was found in disease-free survivors of acute leukemia following allogeneic bone marrow transplantation [127]. Clinical evidence in the therapy of human malignancies using γδ T cells stimulated with phosphoantigens or bisphosphonates [128] will further support the antitumor effects of this cell population *in vivo*.

Human γδ T cells mediate anti-tumor immunity via several distinct pathways, such as the secretion of proinflammatory cytokines and pro-apoptotic molecules, and cell to cell contact-dependent lysis through an NK-like pathway or a TCR-dependent pathway [129]. Activated γδ T cells secrete large amounts of cytokines, which act on tumor cells or their microenvironment [130]. IFN-γ, a major cytokine secreted by activated γδ T cells, has multiple anti-tumor effects including direct inhibition of tumor growth, blocking angiogenesis, or stimulation of macrophages. IFN-γ, therefore, is a crucial cytokine in the γδ T cell–mediated anti-tumor responses.

Many reports demonstrate that γδ T cell clones derived from either tumor sites or blood of cancer patients exhibit potent cytotoxicity against tumor cells *ex vivo* [20]. In addition, γδ T cells have a unique capacity to present antigens to both CD8 and CD4 cells and potentially elicit strong adaptive anti-tumor responses [131]. Furthermore, γδ T cells can respond to stress stimuli originated from transformed cells and exhibit MHC-unrestricted antigen recognition. Activated γδ T cells can exert an immediate and robust direct cytotoxic effect, and simultaneously induce secondary inflammation which attracts tumor specific effector T cells [132]. Adoptive transfer of large number of activated γδ T cells, either alone or along with $CD8^+$ tumor specific T cells, therefore, can potentially boost the dysfunctional host immune system in many ways.

Several clinical trials including patients with advanced diseases refractory to conventional treatments have been performed to test the safety and efficacy of γδ T-cell–based immunotherapy. Consequently, up to 50% efficacy has been observed in a most recent clinical trial using phosphostim™ for expanding the autologous γδ T cells in patients with metastatic renal cell carcinomas [133].

Dokouhaki and his colleagues [134] have built a xenograft model of human non-small cell lung cancer (NSCLC) to study the *in vivo* function of γδ T cells, and found that the lung cancer progression was remarkably inhibited after the infusion of γδ T cells in the absence of cytokine co-administration. The results indicate that the interaction between NKG2D and its ligand (s) may partially contribute to the anti-tumor effect of human γδ T cells. Treatment with expanded and activated γδ T cells for NSCLC is especially promising. Firstly, γδ T cells reside in lung tissues and the number is increased in patients with NSCLC. Secondly, γδ T cells can recognize NSCLC cells in spite of the loss of HLA expression found in 69% of the cases. Thirdly, infusion of *ex vivo* expanded γδ T cells is feasible in patients with NSCLC [135].

To examine the anti-tumor activity of γδ T cells in breast cancer, a phase I trial was conducted, in which Zol and low-dose IL-2 were administered to 10 advanced metastatic breast cancer patients who were therapeutically terminal [136]. The results suggest that the treatment was well tolerated and promoted the effector maturation of Vγ9Vδ2 T cells in all patients. It is noteworthy that there was a statistically significant linkage between clinical outcome and the number of peripheral Vγ9Vδ2 T cells, as seven patients who failed to sustain Vγ9Vδ2 T cells showed progressive clinical deterioration, while three patients who sustained robust peripheral Vγ9Vδ2 cell populations displayed one instance of partial remission and two of stable disease, respectively. Consistent with the earlier clinical trial in prostate cancer, there was a strong correlation of Vγ9Vδ2 T cell status with reduced carcinoma progression, and Zol plus low-dose IL-2 provided a novel, safe, and feasible strategy to treat refractory patients with advanced breast cancer [136]. It has been reported that the treatment of patients with Vγ9Vδ2 T cells plus Zol could efficiently enhance the lysis of MCF-7 breast tumor cells and PC-3 prostate carcinoma cells in a γδ TCR-dependent manner at the effector to target ratios of 30:1 to 7.5:1 [126].

Recently, Kobayashi and his colleagues have reported a complete remission (CR) in a patient with advanced renal cell carcinomas who underwent 6 monthly cycles of autologous γδ T cell therapy, in which the activation and expansion of γδ T cells were performed *in vitro* using 2-methyl-3-butenyl diphosphate plus IL-2, followed by the infusion of the expanded γδ T cells, Zol (4 mg) plus low-dose IL-2 (1.4×10^6 IU) [137]. The clinical responses were associated with a sharp increase in the number of IFN-γ-producing adoptively transferred Vγ9Vδ2 T cells. The CR patient has been disease free for more than 3 years without any additional treatment. Some important clinical trials on γδ T-cell-based cancer immunotherapy are summarized in Table 1.

Table 1. Examples of the important clinical assays about γδ T-cell-based cancer immunotherapy.

Cancer Immunotherapy	Cancer Type	Results	Ref.
Treated with zoledronate+IL-2	Malignant melanomas	γδ T cells and the cancer's stage are negatively correlated, result in target cell lysis and death	[120]
Treated with zoledronate+IL-2	Hormone-refractory prostate cancer	Partial remission and stable disease, aggregate increases in γδ T cell numbers	[66]
Pretreated with pamidronate and zoledronate	MCF-7 breast tumor	Tumor cells were efficiently lysed, depended on the perforin-granzyme pathway.	[126]
Bone marrow grafts depleted of αβ T cells	Acute lymphoblastic leukemia (ALL), Acute myeloid leukemia (AML)	Have a significant improvement in disease-free survival, a post-BMT absolute increase in γδ T cells was significantly associated with αβ T-cell depletion.	[127]
Autologous γδ T cells infusion alone or with IL-2	Renal cell carcinoma (metastatic)	The maximum-tolerated dose and safety of γδ T cells is 8×10^9 cells.	[128]
Inoculation without cytokines	Non-small cell lung cancer	Progression is remarkablely inhibited.	[134]
In vitro proliferation of γδ T cells with pamidronate/IL-2	Non-Hodgkin lymphoma (relapsed and/or refractory) or multiple myeloma	Pamidronate/IL-2 was well tolerated, and no dose-limiting toxicity was observed.	[138]
Autologous γδ T cells	Colon carcinoma	Recognition and efficient killing of autologous and allogeneic CCCL (Colon Carcinoma Cell Lines)	[139]
Treated with zoledronic acid	Pancreatic carcinoma	Tumor cells treated with zoledronic acid are more vulnerable against γδ T cell attack.	[140]

Applications of γδ T cells to treatment of patients with infectious diseases

Infectious diseases are a serious threat to human health and gradually increase in global morbidity and mortality in recent years. Current strategies to control infections mainly focus on the pathogens themselves, but neglect the host factors which may regulate the progression of the diseases. The frequent appearance of drug resistance in infectious pathogens often leads to costly but ineffective therapy. In addition, the efficiency of vaccines inducing adaptive immune responses could be impaired by the rapid immune evasion of pathogens through their frequent mutations. In conclusion, innate immune cells that recognize the conserved structural components of pathogens and elicit rapid responses against infections have great potential in anti-infection immunotherapy.

Human γδ T cells are vital components of the innate immune system and play important roles in the early responses to invasive pathogens. Besides, some γδ T cells, such as IL-17-producing γδ T cells, have been demonstrated to be involved in the pathogenesis of transplantation rejection, autoimmune disease [141], inflammatory diseases [142] and allergy [143] in humans. The quality and quantity of human γδ T cells with dynamic variation affects the initiation, progression and prognosis of infectious diseases.

Viral infections

Although the mechanism underlying γδ T cell-mediated immune responses against viruses remains to be delineated, their protective roles have been confirmed in some acute and chronic viral infections. The activation and cytokine secretions of γδ T cells are considered as indicators of early viral infection.

Recently, the beneficial effects of human Vγ9Vδ2 T cells against influenza virus infection have been re-ported. Vγ9Vδ2 T cells can control infection of several strains of influenza viruses, such as pandemic H1N1, human seasonal H1N1, and the avian H5N1 and H9N2 viruses [144]. A study has suggested that Vγ9Vδ2 T cells expressed both type 1 cytokines and chemokine receptors during influenza virus infection, and IPP-activated cells had a higher capacity to produce IFN-γ [145]. It is worth noting that IPP-activated γδ T cells also can inhibit seasonal and pandemic H1N1 viruses in a noncytolytic manner, mainly through IFN-γ production [145]. Avian H5N1 and H9N2 viruses can induce higher CCL5 production in Vγ9Vδ2 T cells, which may mediate the migration of Vγ9Vδ2 T cells toward influenza virus-infected cells [145].

In addition, Pam activated human Vγ9Vδ2 T cells could kill influenza virus-infected cells and suppress viral replication *in vitro*. Tu et al. [146] demonstrated that Pam-expanded Vγ9Vδ2 T cells by themselves can control influenza virus infection effectively *in vivo*. Regarding H1N1 viruses, the inhibition of the virus replication by the Vγ9Vδ2 T cells may rely on direct killing of virus-infected cells and secretion of IFN-γ, but, for H5N1 infection, mainly by direct killing.

The antiviral mechanisms elicited by Vγ9Vδ2 T cells during different viral infections are diverse. For example, human Vγ9Vδ2 T cells can kill Epstein-Barr virus (EBV)-, and herpes simplex virus

(HSV)-infected target cells in an HLA-unrestricted manner *in vitro* [147]. IPP-activated Vγ9Vδ2 T cells can kill human immunodeficiency virus (HIV)-infected target cells and inhibit viral replication by releasing certain CCR5 ligand chemokines to block the HIV entry co-receptor CCR5. Furthermore, phosphoantigen-activated Vγ9Vδ2 T cells can induce noncytolytic inhibition of hepatitis C virus (HCV) replication by IFN-γ secretion [148]. It was revealed that simian γδ T cells could produce β-chemokines, such as macrophage inflammatory protein-1α [MIP1-α], MIP1-β, and RANTES. These factors are known to block virus attachment to the CCR5 co-receptor [149], thus preventing SIV infection.

Furthermore, γδ T cells can induce the maturation of dendritic cells (DCs) to promote the establishment of protective adaptive immunity against West Nile virus [150]. The protective roles of γδ T cells have also been confirmed in some chronic infectious diseases. During human cytomegalovirus (HCMV) infection [151], $V\delta2^-$ T cells, a minor population of peripheral blood γδ T cells, have been found to expand significantly, showing a potent 'virus-specific' cytotoxicity and increased elimination of pathogens [152]. Similarly, γδ T cells in HIV-infected patients have been found to exhibit beneficial roles in controlling HIV infection [153] through their cell-lytic functions and cytokine secretions. γδ T cells are potent effectors in antibody-directed cell cytotoxicity [154], which is important for HIV inhibition [155], although the quantity and quality of γδ T cells are generally decreased with the advancement of HIV infection [156]. γδ T cells also help control the infection caused by Epstein-Barr virus [157] and human hepatitis virus C [158].

More recently, Yin's group found negative correlation between the ratios of Vδ2 T cells to Th17 (IL-17-producing $CD4^+$ T) cells and liver damage in HBV-infected immune-activated patients and provided experimental evidence that Vδ2 T cells suppressed Th17 cytokine production through cell contact-dependent and IFN-γ-dependent mechanisms [116].

The applications of γδ T cells in the antiviral immunity are summarized in Table 2.

Bacterial infections

The discovery that γδ T cells expanded in the peripheral blood of patients with bacterial infections raised the possibility that the T cell subset can be utilized for the control of bacterial infections. Mounting evidence indicates that γδ T cells are of importance in human bacterial infections. Human γδ T cells can recognize HMBPP derived from various bacteria and provoke adaptive immunity in various ways. They expand during bacterial infections such as tuberculosis (mean, 14%), salmonellosis (mean, 18%), tularemia (mean, 31%), brucellosis (mean, 29%), listeriosis (mean, 12%), and ehrlichiosis (mean, 57%). Activated and expanded $V\gamma2V\delta2^+$ T cells might directly participate in antimicrobial immune responses. They recognize HMBPP in a TCR-dependent, MHC-, and CD1-unrestricted manner [6], then kill bacteria-infected cells and bacteria.

Tabel 2. Applications of γδT-cell in the antiviral immunity.

Virus Type	The Functions of γδ T Cells	Ref.
Influenza virus	Cytotoxic and noncytolytic antiviral activities	[144]
Simian immunodeficiency virus (SIV)	Produce β-chemokines, block virus attachment to the CCR5 co-receptor	[149]
West Nile virus	Induce the maturation of dendritic cells (DCs)	[150]
Human Cytomegalovirus (HCMV)	Have 'virus-specific' cytotoxicity	[151]
Human immunodeficiency virus (HIV)	Cell-lysis and cytokine secretion	[153]
Hepatitis C virus (HCV)	Mediate non-(MHC)-restricted killing of primary hepatocytes, produce Th1-like cytokine	[158]

Pontiac fever-like disease, which is caused by *Legionella micdadei*, was found to be related to a significant and long-lasting expansion of Vγ9Vδ2 T cells, implying that the subset may also be pathophysiologically important in a mild and transient form of intracellular bacterial diseases. Surprisingly, patients with the Pontiac fever-like disease showed an early depletion of Vγ9Vδ2 T cells from the circulation, followed by a sharp increase and subsequently, a slow decline over the next 6 months [159]. The ability of the γδ T cells to secrete IFN-γ and TNF-α seemed to be down-regulated after the acute phase of the disease. These results support the assumption that Vγ9Vδ2 T cells are pathophysiologically important in intracellular bacterial infections, including a mild and transient condition such as Pontiac fever.

Moreover, some intracellular bacterial pathogens, such as *Mycobacterium tuberculosis*, can specifically expand and activate Vγ9Vδ2 γδ T cells by inducing the production of metabolites (e.g., IPP) in infected cells, which strongly demonstrates that γδ T cells are crucially important in infection control [33]. Consistent with this finding, the suppression of γδ T cells by chronic tuberculosis infection can contribute to a disastrous outcome.

Other pathogen infections

γδ T cells not only play protective roles in viral and bacterial infections, but also control infections by protozoas such as *Leishmania* [160] and *Toxoplasma gondii* [161], whereas the γδ T cell-mediated inflammation may cause some unwanted destruction of surrounding tissues. Similarly, the protective roles of γδ T cells during malaria infection have been confirmed in several independent studies [162].

Applications of γδT-cell in autoimmune diseases

In recent years, γδ T cells have been shown roles in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). γδ T cells, by bridging innate and adaptive immunity, may display different functions similar to those of $CD4^+$ T-cell subsets such as CTLs, Th1/Th2 cells, Tregs, Th17 cells, and APCs depending on specific microenvironment [163].

Rheumatoid arthritis (RA) is an autoimmune disease that primarily affects the limbs, but the pathogenic mechanism is still unclear. Research has demonstrated that γδ T cells can function as antigen-presenting cells and are related with rheumatoid arthritis development. During the development of rheumatoid arthritis, γδ T cells can aggravate immune dysfunction and produce abnormal immune damage by the secretion of cytokines (such as IFN-γ and IL-17) and induction of inflammatory cells to participate in synergistic inflammatory responses [164].

Systemic lupus erythematosus (SLE) is a common autoimmune disease with severe dysregulation of the immune system. Research suggested that the $CD27^+CD45RA^-$ γδ T cells (a subset constitution of the peripheral blood γδ T cells) were significantly decreased in SLE patients and the numbers of $CD27^+CD45RA^-$ γδ T cells was negatively correlated with the SLE disease activity. In inactive SLE patients following glucocorticosteroid and cyclophosphamide treatment, Vδ1 cells were significantly increased. This research group also suggested that $CD27^+CD25^{high}$ Vδ1 T cells had immunoregulatory activities through cell-to-cell contact, which could express Foxp3 similar to $CD4^+Foxp3^+$. These regulatory γδ T cells decreased in the peripheral blood of active SLE patients could be generated *in vitro* under the stimulation with anti-TCR γδ in the presence of TGF-β and IL-2 [165]. This finding provides a theoretical basis and feasibility for employing γδ Tregs as a potential therapeutic target in autoimmune disease immunotherapy.

In addition, in an experimental autoimmune encephalomyelitis (EAE) model of the human CNS autoimmune disease multiple sclerosis, γδ T cells had been shown to regulate CNS inflammation and promote disease recovery through Fas/FasL-induced apoptosis of encephalitogenic T cells [166].

Applications of γδT-cell in allergic diseases

Some researches have suggested that γδ T cells may serve as effectors and immunoregulatory cells in allergic disease. Atopic dermatitis (AD), a chronic relapsing inflammatory disease of the skin, is associated with allergic bronchial asthma. Cairo et al. [167] have observed that the circulating Vγ9Vδ2 T cells were significantly increased in AD patients, which is positively correlated between their expansion and the severity of the disease.

Zhang et al. demonstrated that γδ T cells play a proinflammatory role in the development of ovalbumin-induced allergic airway inflammation [168]. Svensson et al. indicated that γδ T cells promote allergic airway inflammation by enhancing the systemic IgE response and local antibody reactivity without a specific role in the shift of the immune response towards Th2 [169]. $IL-17^+$ γδ T cells, belonging to the Vγ4 subset, have been recently shown to downmodulate central features of allergic reaction in airway inflammation, including Th2 response and lung eosinophilia [143]. When activated, γδ T cells are able to produce a number of cytokines and chemokines, with a unique plasticity to produce Th1, Th2, and Th17 cytokines, contributing to the development and regulation of immune responses [170].

Furthermore, Pawankar et al. have observed an important role for the oligoclonally expanded nasal mucosal gamma delta T cells in the pathogenesis of perennial allergic rhinitis (PAR), with the increase of δ1 T cells and able to produce mainly interleukin such as IL-4, IL-5 and IL-13 [171, 172].

Summary

In the previous paragraphs, we have elaborated on the mechanism of ligand recognition, activation, cytokine secretion, and applications of γδ T cells. To be understood better, we summarized the above-mentioned contents in Fig 3.

Obstacles

Clinical applications mentioned above provide enormous opportunities for accelerating the establishment of novel approaches to disease treatment and control, slowing disease progression, reducing comorbidities, and reducing or modifying requirements for antiretroviral therapy. People, however, envisage that some specific obstacles have to be overcome for the development of γδ T cell immunotherapies.

Firstly, clinical trials have demonstrated that repeated administration of phosphoantigens might cause anergy, exhaustion or even death of effector γδ T cells. For instance, a macaque study showed that declining responses occurred after repeated BrHPP/IL-2 injections compared to the first treatment [173]. A similar pattern of declining responses was reported for Zol and IL-2 treatment in prostate cancer patients [66]. Thus, therapies targeting γδ T cells produce short-term responses for a long-term, chronic disease. If we can extend the duration of elevated γδ T cell levels and functions following treatment, repetitive dosing may not be necessary or the detrimental anergizing effect may not occur. Pauza and his colleagues [22] defined the protocol for γδ T cell activation, including adding immunomodulators such as rapamycin that increase the yield of the cells and potentially modulate the onset of anergy [18].

Secondly, immunostimulatory treatments may elicit significant adverse events (SAEs). For instance, activated γδ T cells will produce proinflammatory cytokines that may cause SAEs. People, therefore, must minimize or manage the potential consequences of immune reconstitution. These potential obstacles, the risk for SAEs and anergy, have to be addressed by definitively controlled human clinical trials.

Thirdly, although the activation of Vγ2Vδ2 T cells can contribute to the rapid acquisition of APC characteristics (γδ T-APCs), dominant Vγ2Vδ2 T-cell subset capable of recognizing microbial phosphoantigen exist only in primates. Therefore, current task is to find an analogue to evaluate the characteristics and clinical potential (including side effects) in murine systems, which may be overcome by the development of a humanized mouse model. This is another current key barrier for the application of γδ T cells based immunotherapy.

Outlooks

Although great progress has been made in γδ T cell-based immunothearpies, many aspects need to be improved in future clinical trials.

Regarding tumor cells, it is necessary to explore the adjuvant effect of Toll-like receptor (TLR) stimulation, because *in vitro* treatment of tumor cells with TLR3 and TLR7 agonists could enhance cytotoxicity of γδ T cells isolated from cancer patients [174]. As for γδ T cells, it will be of great importance to evaluate the clinical effects of synthetic TCR agonists such as phosphostim (BrHPP) and picostim (an analog of HMBPP). Another interesting feature is the use of phosphoantigens combined with therapeutic antibodies, as suggested by the improved leukemia and/or lymphoma *in vitro* killing after co-administration of BrHPP and rituximab [175]. In addition, it is important to evaluate the safety of TCR-independent killing strategy by comparing the NKG2D-mediated cytotoxicity against transformed and healthy tissues by NKG2D+ γδ T cells.

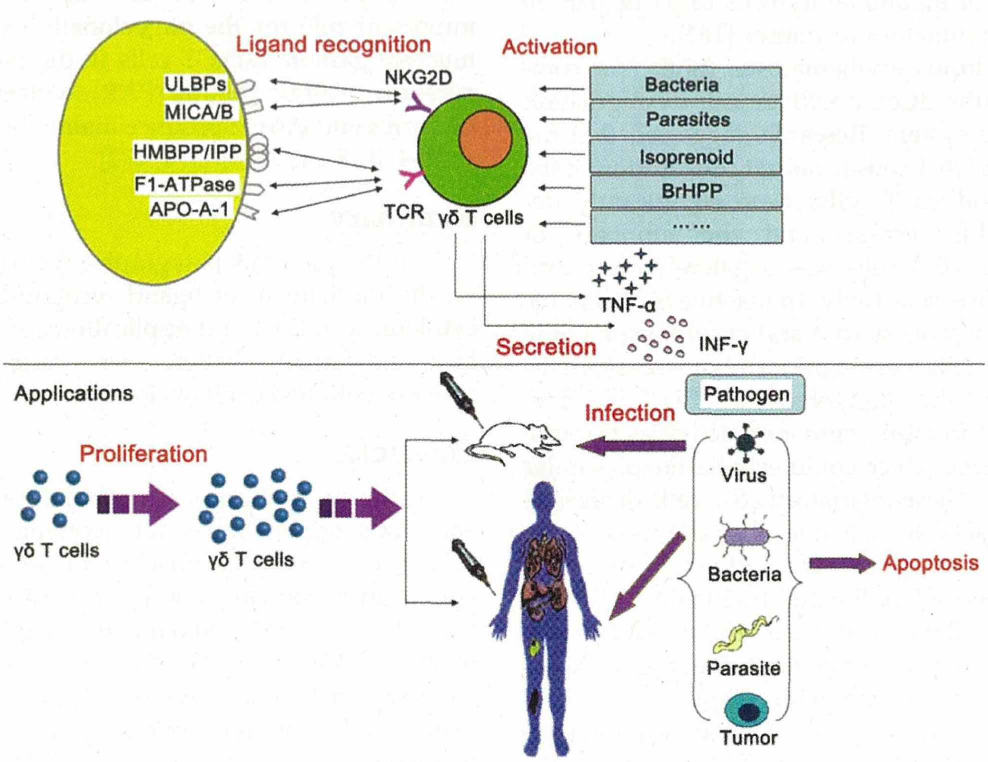

Figure 3. Mechanism underlying γδ T cell recognition of nonpeptide antigens and clinical applications.

Finally, the identification of biomarkers to predict clinical outcome is crucial for patient selection. A recent study, for example, has identified a panel of 10 genes which encode cell surface proteins that segregated "γδ-susceptible" from "γδ-resistant" hematologic tumors [121]. Equivalent markers could be promptly characterized in multiple cancer types, and their predictive value should be accessed in γδ T cell-based clinical trials. The combination of "susceptible" tumor profiles with improved strategies for γδ T -cell activation *in vivo* may be the way forward for γδ T cell-based cancer immunotherapy.

γδ T cells are attractive targets for cellular immunotherapy, but protocols for their therapeutic use need to be optimized. In addition, it is necessary to explore better antigens which help us stimulate γδ T cell expansion *in vitro* for the preparation of a large number of cells for adoptive cell transfer. Future studies should focus on the possible advantages of combining γδ T cell-based immunotherapy with conventional chemotherapy or other therapeutic approaches, such as antiangiogenic drugs.

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Competing Interests

The authors have declared that no competing interest exists.

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