Review Article

γδ T cells and their roles in immunotherapy: a narrative review

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Objective: In order to understand the activation mechanism of γδ T cells and their role in tumor immunity and autoimmune diseases.

Background: γδ T cells are a conserved population of natural lymphocytes with a variety of structural and functional heterogeneities, accounting for approximately 0.5% to 10% of total peripheral blood lymphocytes in healthy adults. As a "bridge" between innate and acquired immunity, they have an important role in tumor surveillance.

Methods: γδ T cells are considered to be effective anti-tumor effector cells, which can kill tumor cells through direct and indirect methods; γδ T cells can secrete a variety of cytokines, such as tumor necrosis factor α (TNF-α), γ-interferon (IFN-γ), perforin, etc., thus, they own the ability to kill tumor cells directly, and can also regulate other innate and adaptive immune cells, and then achieve the purpose of indirectly killing tumor cells, thereby establishing anti-tumor immunity. A unique feature of γδ T cells is that they recognize antigens in a non-major histocompatibility complex (MHC)-restricted manner, and they have strong cytotoxicity to a variety of cancer cells, which make them have important clinical application value.

Conclusions: In this review, we provide an overview of the activation mechanisms of γδ T cells and their role in tumor immunity and autoimmune diseases. These studies provide insights into γδ T cell function to facilitate more targeted approaches for tumor therapy.

Keywords: γδ T cells; antitumor immunotherapy; clinical application

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Introduction

Human T lymphocytes can be divided into two major classes, αβ T cells (e.g., CD4, CD8, etc.) and γδ T cells, according to their surface T cell antigen receptors (TCR) (1). The vast majority of αβ T cells recognize antigens through major histocompatibility complex (MHC) class I and class II molecules (2). In human peripheral blood lymphocytes, αβ T cells account for approximately 95% of the total, while γδ T cells account for only 1–10% (3). Most αβ T cells belong to the helper or cytotoxic/effector T cell subpopulation (4). In contrast, γδ T cells are usually $CD4^{-}CD8^{-}$, which do not require MHC to present antigens (3). In addition to directly recognizing and killing tumor cells in a non-MHC-restricted manner, γδ T cells can also activate other immune cells [e.g., dendritic cells (DCs), macrophages, $CD8^{+}$ T lymphocytes, etc.] by secreting various cytokines, thus acting as a bridge between natural and acquired immunity, and thus are also called "bridge cells". γδ T cells are involved in regulating various physiological functions in the human body, including immune homeostasis, immune protection, immune surveillance, inflammation and autoimmunity, etc., and have demonstrated powerful anti-tumor capabilities by recognizing and killing tumor cells of various origins (5). We present the following article in accordance with the Narrative Review reporting checklist (available at https://

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Classification of γδ T cells

γδ T cells were first identified by Brenner *et al.* (6) in 1986 in an antibody prepared by applying a peptide encoded by the TCR gene sequence, and it was not until 1990, when Zocchi *et al.* (7) were the first to isolate γδ T cells from tumor-infiltrating lymphocytes of lung cancer patients, that scholars began to focus on γδ T cells. Human γδ T cells can be subdivided into Vδ1, Vδ2 and Vδ3 T cells according to their surface antigens (8). Typically, about 50% to 75% of γδ T lymphocytes in peripheral blood express Vδ2 chains and co-express Vγ9 chains; these cells are called Vγ9Vδ2 T cells. Vγ9Vδ2 T cells are found only in humans and non-human primates (9) and represent 0.5% to 10% of healthy human peripheral blood T cells (10). Activated Vδ2 T cells express cell adhesion molecules such as CD86, CD80, and MHC-II (11), and Vγ9Vδ2 T cells have a unique characteristic of recognizing non-peptide phospho-antigen (12). These cells proliferate dramatically *in vitro* in response to stimulation by microbial or synthetic phospho-antigen (3). They play very important functions in anti-infection, anti-virus and anti-tumor (13). Activated Vγ9Vδ2 T cells can directly eliminate virus-infected or malignant transformed cells by secreting perforin and granzymes A and B. They can also be used in a similar manner to $CD8^+$ T cells, such as through cell induction of receptors (Fas/FasL) or tumor necrosis factor (TNF) related apoptosis inducing ligand receptors (TRAILR) and other pathways mediated apoptosis to kill tumor cells (14).

Another subset of γδ T cells has a Vδ1 chain. V δ1 T cells are mainly found in mucosa-associated lymphoid and epithelial tissues. Most tissue-associated γδ T cells protect against epithelial tissue injury or infection, as well as epithelial cell carcinogenesis (15).

Peripheral blood Vδ2 T cells can be amplified by phospho-antigen. Anti-γδ antibodies are a strong source of stimulation and can be used to amplify Vδ1 and Vδ2. Anti-CD3 antibodies or concanavalin A (16) can also be used to amplify Vδ1 and Vδ2 T cells.

In addition to Vδ1 and Vδ2 cells, there is a very small subpopulation of Vδ3 T cells. Little is known about this human γδ T cell population, except for evidence that Vδ3 T cells play a very important function in fighting cytomegalovirus (CMV) and human immunodeficiency virus (HIV) (17).

γδ T cells in the immune response

γδ T cells play multiple roles in the immune response. They are not only able to promote immune responses by interacting with other immune cells, but also secrete different cytokines, chemokines and growth factors to perform the functions of macrophage recruitment and cytolysis (18).

Cytotoxicity is one of the important roles of γδ T cells. The cytotoxicity of Vγ9Vδ2 T cells can be achieved in many ways, the most important of which is the production of a variety of cytokines, such as perforin, granzyme, TNF and γ-interferon (IFN-γ) etc. (19). Mattarollo and his colleagues found that the combination of Vγ9Vδ2 T cells and chemotherapeutic drugs, diphosphonate drugs, and zoledronic acid exhibited high levels of killing effects on cells of solid tumor origin (19,20). It is reported that γδ T cells have a role as a key early effector cell providing an early source of cytokines (21), and their study showed that γδ T cells are a major source of IFN-γ after Listeria monocytogenes infection and a major source of IL-4 after *Nocardia brasiliensis* infection. γδ T cells produce inflammatory cytokines that can directly attack infected cells, such as IFN-γ, and establish a memory response to eliminate pathogens after re-exposure (22). It is evident that γδ T has powerful cytotoxic effects.

Second, another major role of γδ T cells is antigen presentation. DCs are the most efficient antigen presenting cells (APCs) (23). However, the limited ability of DCs to expand and recognize antigen makes the adoptive immunotherapy of DCs severely limited. These limitations can be overcome by finding alternative sources of APCs (24). Activated γδ T cells have the functions and properties of APCs. They can present specific antigens via MHC or MHC-related molecules (23). In addition, activated γδ T cells have the ability to induce antigen-specific $CD4^+$ and $CD8^+$ T cells (2,25). γδ T cells exhibit both cytotoxic functions and antigen-presenting capabilities, and they are characterized by both innate and adaptive immunity (26). When appropriately stimulated, phosphine antigen-activated γδ T cells can induce antigen-specific immune responses in αβ T cells. The role of γδ T cells in the immune response are summarized in *Table 1*.

In addition, γδ T cells can regulate the immune response by interacting with other cells. They can assist B cells to produce IgA, IgM and IgG antibodies, and play a regulatory role in humoral responses (27). *In vitro*, activated Vγ9Vδ2 T cells provide B cells with surface

Table 1 Anti-tumoral effect of γδ T cells

Anti-tumoral effect	Method	Concrete content
Directly anti-tumor	Cytokines	Cytokine-mediated cytotoxicity, such as TNF-α and IFN-γ
		Perforin and granzyme mediated target cell apoptosis
	Surface marker	FasL and TRAILR mediated target cell apoptosis
		Antibody-dependent cell-mediated cytotoxicity
	Antigen presenting	Interacting with professional antigen presenting cells, and also directly processing and presenting antigens
Indirectly anti-tumor	Cell interaction	Interacting with B cells, DCs, NK cells and αβ T cells

TNF-α, tumor necrosis factor α; IFN-γ, γ-interferon; FasL, Fas ligand; TRAILR, tumor necrosis factor-related apoptosis inducing ligand receptors; DCs, dendritic cells; NK, natural killer.

marker like CD40L, and cytokines such as IL-10 and IL-4 to support the function of B cells (26). In addition, γδ T cells activate immature DCs. When immature DCs are co-cultured with phosphine antigen-stimulated γδ T cells, DC cells show a significant increase in the expression of CD86 and MHC-I-like molecules and acquire the characteristics of activated DCs (28).

The mechanism of γδ T cell activation and anti-tumor function regulation

According to the structure of the heterodimeric TCRs chains, T cells are mainly divided into γδ T cells and αβ T cells. Although the proportion of γδ T cells in the human body is trivial, they play important roles in cancer immunity (29). γδ T cells share similarities with αβ T cells such as their ability to secrete cytokine, induce tumor cytotoxicity, etc. Nevertheless, γδ T cells do not rely on MHC molecules for antigen recognition. In the peripheral blood of healthy humans, γδ T cells (Vγ9Vδ2-T cells) that carry the Vδ2 gene and co-expressed with the Vγ9 chain are the most abundant whereas other subtypes exist in various tissues (30); γδ T cells behave as the immune effector cells in cancer immunity. The tumor infiltrated γδ T cell has been considered as one of the best markers for patient prognosis (31). Studies have shown their involvement in cancer immunity of hepatocellular and colorectal carcinoma (32), lymphoma, myeloma (31), and lung (33), prostate (34), breast (35), colon (36), and ovary cancers (37).

In cancer immune surveillance, the anti-tumor activity of γδ T cell mainly includes: (I) induction of stimulus signals in a non-MHC-restricted manner; (II) a large number of effector molecules are produced to directly or indirectly kill tumor cells; (III) a distinctive recognize manner. A distinctive feature of Vγ9Vδ2 T cells is the TCR-dependent recognition of phospho-antigens. Vγ9Vδ2 TCR recognizes the phospho-antigens when cells undergo stressful conditions. The levels of these phospho-antigens are too low to be detected as a dangerous signal by Vγ9Vδ2 T cells in normal cells. Tumor cell metabolic dysfunction can lead to the accumulation of endogenous phosphorylated antigens recognized by Vγ9Vδ2 T cells (38). In addition, another distinctive characteristic of γδ T cell is the expression of natural killer cell receptors (NKRs), such as NKG2D, and therefore exhibiting similar recognition patterns (39). NKG2D can recognize its ligands (40), such as MICA/B and ULBP-1, -2, -3, and -4, which are expressed in different tumors, including leukemia, lymphoma, ovarian, and colon carcinoma (38).

Notably, γδ T cells require direct contact with target cells and form immune synapses to initiate the subsequent killing. The formation of early immune synapses is facilitated by the interaction between lymphocyte function-associated antigen 1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) (41). After the initial contact and following TCR activation, γδ T cells kill tumor cells in a variety of ways, such as antibody-dependent cell-mediated cytotoxicity (ADCC), cytokines (like TNF-α and IFN-γ) and releasing effector molecules (for example granzyme family molecules and perforins) (39). Moreover, they could also trigger target cell apoptosis through Fas/FasL, TNF-related apoptosis-inducing ligand (TRAIL), and TNF-α pathways. Lastly, chemokine receptors (including CCR5) control the ability of γδ T cells to migrate to the tumor site (39) and cytokines (such as IL-2 and IL-15) determine

the survival and proliferation of γδ T cells (42).

γδ T cells in tumors

Antitumor function of cytotoxic γδ T cells

There are many reports on the anti-tumor activity of Vγ9Vδ2 T cells (43). Their antitumoral activity mostly relies on the recognition of phospho-antigens and stressed molecules by TCRγδ (44) and other cellular receptors, like NKG2D (45). These receptors can respond to "danger signals" that appear during cell stress and malignant transformation. Apart from the direct cytotoxicity of Vγ9Vδ2 T cells, these cells can also stimulate and regulate other immune components to establish the antitumoral activity (46). Therefore, it has become a new research hotspot in cellular immunotherapy. In the last decade, a large number of studies on autologous γδ T cells against tumors have been conducted and their safety and efficiency have been proved. γδ T cells have shown good therapeutic effects on different types of cancer, such as lung cancer (47), prostate cancer (34), melanoma (48), breast cancer (35), etc. At present, most of the γδ T cell adoptive immunotherapy reported in the literature at home and abroad uses autologous cells, but there are few reports on allogeneic γδ T cell therapy. In 2017, our research group conducted a phase I clinical trial in 132 patients with advanced cancer in which a total of 414 cells were infused, which clearly verified the clinical safety of allogeneic Vγ9Vδ2 T cells. Among these 132 patients, the survival time of 8 patients with liver cancer and 10 patients with lung cancer who received ≥5 cell infusions was greatly prolonged, preliminarily verifying the efficacy of allogeneic Vγ9Vδ2 T cell therapy (49). The clinical research emphasizes the safety and effectiveness of allogeneic Vγ9Vδ2 T cell immunotherapy, which will stimulate further clinical research and ultimately benefit cancer patients.

Pro-tumorigenic effects of human γδ T cells

In recent years, it has been reported that IL-17-producing γδ T cells have pro-tumorigenic effects in human cancers (50). $Vδ1^+$ T cells are the main source of IL-17 involved in chronic inflammation in colorectal cancer. In addition, IL-17-producing γδ T cells are involved in the development of myeloid-derived suppressor cells (MDSCs) into the malignant microenvironment, further driving inflammation at the tumor site. Importantly, the degree of infiltration of IL-17-producing γδ T cells was positively correlated with the clinical stage of the disease, suggesting a potential pro-cancer role for IL-17-producing γδ T cells in human intestinal cancer (50). Notably, unlike mice, human γδ T cells do not differentiate into IL-17-producing subtypes under normal physiological conditions, but require a highly inflammatory environment. For example, a large accumulation of IL-17-producing Vγ9Vδ2 T cells has been observed in children with bacterial meningitis (40).

γδ T cells in autoimmunity

Autoimmune disease (AID) is an abnormal immune function in which the body treats its own tissues as foreign and produces antibodies (called autoantibodies) or immune cells that attack the body's own cells or tissues, leading to inflammation and tissue damage. γδ T also plays an important role in the development and progression of AIDs due to its wide distribution and multiple functional phenotypes. Psoriasis (psoriasis) is a chronic inflammatory skin disease with the clinical manifestations are characteristic scales or red plaques that can appear on any part of the body, especially the elbows, knees, and scalp. Studies have shown that the immune imbalance of T cells plays a key role in the pathogenesis of psoriasis (51). The complex interaction between genetic and environmental factors, such as microbial infections and physical trauma will trigger a series of processes leading to the activation of DCs to produce IFN-α, IL-12, and IL-23 to activate and polarize γδ T cells toward the γδ T17 (γδ T cells that produce IL-17A) subset, leading to immune imbalance of T cells (51,52). The release of pro-inflammatory cytokines by activated T cell subsets contributes to the excessive proliferation of keratinocytes and the production of chemokines and defensins by keratinocytes, which leads to the recruitment of leukocytes and amplifies the immune response in psoriatic plaques. Clinical studies have shown that blocking IL-23 or IL-17A is very effective for patients with psoriasis. This indicates that Th17 and γδ T17 cells with IL-17A as the main cytokine are essential for the pathogenesis of psoriasis (53). Skin γδ T cells have been shown to constitutively express IL-23R and RORγt, and produce large amounts of IL-17 under the stimulation of IL-23, which promotes the development and progression of psoriasis (53). Intradermal injection of IL-23 will cause $CCR6^+$ γδ T cells to accumulate in the epidermis and express increased amounts of IL-17A and IL-22, resulting in severe psoriatic dermatitis (54). Therefore, better understand the development and function of γδ T17 cells will provide

Table 2 γδ T cells in autoimmunity

Disease	Pathogenic mechanism
Psoriasis	The complex interaction between genetic factors and environmental factors, such as microbial infection and physical trauma, will trigger a series of processes that will activate dendritic cells and produce IL-12, IL-23 and other cytokines, making γδ T cells Polarization towards a subpopulation of γδ T17 (γδ T cells that produce IL-17A) leads to immune imbalance of T cells (11,12). The activated γδ T cells release pro-inflammatory cytokines, which promote the excessive proliferation of keratinocytes, and the keratinocytes produce chemokines and defensins, which leads to the recruitment of neutrophils and amplifies the immune response of psoriatic plaques
Inflammatory bowel disease (IBD)	γδT cells are involved in the disease progression of IBD patients, and the chronic inflammatory response with IBD characteristics is related to the obvious changes in the number, distribution, composition and function of mucosal γδ T cells (16). However, the specific role of γδ T in the intestinal mucosal immune balance and the occurrence and development of IBD and the role of cytokine balance are still unclear, and further research is needed

important insights and new targets for the treatment of psoriasis. In the study of psoriasis, the γδ T quantity distribution and cytokine release levels in the peripheral blood and skin inflammation areas of patients are worthy of further exploration.

Inflammatory bowel disease (IBD) includes ulcerative colitis and Crohn's disease. It is caused by chronic inflammation in the intestinal epithelial tissue that destroy the tissues and causes mucosal dysfunction due to the down-regulation of the immune response, but the exact cellular mechanism of induction is not yet clear (55). It has been reported that γδ T cells are involved in the disease progression of IBD and the chronic inflammatory response with IBD characteristics is related to the obvious changes in the number, distribution, composition and function of mucosal γδ T cells (56). At present, the specific role of γδ T in the balance of immune homeostasis in the intestinal mucosa and the occurrence and progression of IBD and the role of cytokine balance still need to be further studied. Experiments have found that colitis induced by dextran sulfate sodium (DSS) in TCR-$\delta^{-/-}$ knockout mice is more severe than TCR-$\alpha^{-/-}$ knockout mice. It shows that γδ T plays an important role in intestinal mucosal immunity and homeostasis regulation (57). At the same time, it has also been reported that IL-17-producing γδ17 T cells promote Th17 cell differentiation and the development of T cell-mediated colitis (58). γδ17 T cells can also cause damage after tissue infiltration or accumulation. The secretion of IL-17 by γδ17 T cells plays an important role in the homeostasis of intestinal immune balance. Studies have shown that the regulation of γδ17 T by Treg cells can affect the occurrence and progression of colitis (59). In the colitis model, depletion of T helper cells or αβ T cells has no effect on survival, or myeloperoxidase activity after colitis is induced. The colitis in the γδ T cell depletion group was histologically more severe and the consumption of γδ T cells led to a significant increase in mortality (60). Studies have evaluated the frequency and phenotype of γδ T cells in tissue infiltrating lymphocytes from healthy donors and IBD patients. After functioning, it was found that Vδ1 T cells are the main γδ T cell population in healthy tissues, while Vδ2 T is significantly abundant in chronic IBD (61). In chronic inflammatory IBD, Vδ2 T cells produce more IFN-γ, TNF-α and IL-17 than Vδ1 T cells. Analysis in the intestinal mucosa of patients with early-onset or long-term IBD found that γδ T cells are significantly related to clinical status. Infiltrating Vδ2 T cells have the main effect memory and terminally differentiated phenotype and produce elevated levels of TNF-α and IL-17. The frequency of tissue Vδ2 T cells is related to the degree of inflammation and the severity of IBD (62). At present, the role of γδ T in the occurrence of IBD and the relationship between γδ T and intestinal flora still need further research. The role of γδ T cells in autoimmunity are summarized in *Table 2*.

Clinical application and prospect of γδ T cells

γδ T cell immunotherapy has gained increasing attention in recent years due to its anti-tumor efficacy and relatively easy *in vitro* expansion. Studies mainly focused on understanding the tumor cytotoxicity of γδ T cells in both *in vitro* and *in vivo* models. Lately, a series of clinical trials on the anti-tumor effect of γδ T cells have been carried out. Merely in 2020, there are seven γδ T cells clinical trials, 5 out of 7 are about its anti-tumor effect. Among numerous γδ T cell subtypes, Vγ9Vδ2 subtype is the main one adopted in clinical settings. Besides the relatively large number and convenient sampling due to its presence in human

peripheral blood, its excellent anti-tumor effects (63) also attract the attention among researchers.

Furthermore, activated Vγ9Vδ 2 T cells can play the equivalent role of mature DC cells to induce the activation of peptide-specific T cells (64). Specifically, they can self-express high levels of antigen-presenting molecules as well as co-stimulatory molecules for antigen presentation (23).

However, normal human γδ T cells only account for about 1–10% of the human peripheral blood T cells, with such a limited amount, it is difficult to execute its active anti-tumor function. Therefore, the successful clinical application of γδ T cells is faced with the problems of how to activate and expand Vγ9Vδ2 T cells effectively. Because of the unique TCR-dependent reactivity of Vγ9Vδ2 T cells towards phosphoantigens, which can be increased by the administration of nitrogenous bisphosphonates (zoledronate or pamidronate) (65), there are three main strategies to expand and activate Vγ9Vδ2 T cells to exert their antitumor effects. The first strategy is to expand γδ T cells *in vitro* and then adoptively infuse them to cancer patients. Specifically, combining aminobisphosphonate with IL-2, which can rapidly expand and activate γδ T cells extracted from patients' peripheral blood, is then followed by the transfusion of γδ T cells back to patients. Another less utilized strategy is to isolate αβ T cells from the peripheral blood of patients, followed by high affinity Vγ9Vδ2 TCR transduction into αβ T cells, and then transfuse it back to patients after *in vitro* expansion. This strategy solves the problems of impaired activation status or low persistence of Vγ9Vδ2 T cells in advanced cancer patients (66). In addition, by subcutaneous or intravenous injection of aminobisphosphonate, γδ T cells can proliferate and potentiate cancer cell cytotoxicity in patients. Notably, clinical studies have shown that zoledronic acid and IL-2 can induce the safe differentiation and expansion of Vδ2 T cells *in vivo* (35,67). Another method involves modifying the patient's own γδ T cells to express chimeric antigen receptors (CAR) to treat advanced cancers, especially those that are ineffective to conventional therapeutic agents (68). The use of CAR γδ T will be a promising immunotherapy strategy. Engineered γδ T cells will become a new platform for adoptive γδ T cell cancer therapy. CD19-directed CAR-γδ T cells show high effectiveness against $CD19^+$ cell lines *in vitro* and *in vivo*, which indicates that CAR-γδ T cells produces cytokines, directly targets and kills and eliminates bone marrow leukemia cells in the NSG model (68). Multiple injections of CAR-γδ T cells and immunization of mice with zoledronate can enhance tumor reduction *in vivo*. Unlike standard CD19 CAR-T cells, CAR-γδ T cells can target CD19 antigen-negative leukemia cells. This effect is enhanced after zoledronate is used to prime the cells (68).

Besides the above strategies, immune checkpoint antibodies T lymphocyte antigen 4 (CTLA4) have been used to overcome the immune suppression and exhaustion nature in the tumor microenvironment (TME) (69). However, in a recent study, it has been shown in the mouse model of methylcholanthrene (MCA)-induced tumors that mice treated with anti-PD-1 and anti-CTLA4 displayed little change in the infiltration and effector functions of γδ T cells (70), indicating the complex nature of TME. Moreover, since patient-derived Vγ9Vδ2 T cells are functionally defective, literature has reported that autologous monocyte-derived DCs (moDCs) or tyrosine kinase inhibitor ibrutinib (approved for clinical application) could be used to co-activate patient-derived γδ T cell and to enhance its anti-tumor ability. Ibrutinib, a drug that has been clinically used to treat chronic lymphocytic leukemia, has a direct effect on Vγ9Vδ2 T cells. Particularly, it can bind to IL-2-inducible T cell kinase (ITK) and promote the differentiation of IFNγ producing T cells. Last but not the least, stimulation of γδ T cells with bispecific HER2/Vγ9 antibodies (71) [(Her2)2 × Vγ9] trimers (72) and new bisphosphonates (73) is also one of the important research directions to further enhance the anti-tumor ability of Vγ9Vδ2 T cells.

Although clinical outcomes of γδ T cells treatments have been promising and their safety has been demonstrated, how to further strengthen the anti-tumor ability of γδ T cells, suppress the function of regulatory T cells, down-regulate immunosuppressor molecule expression, and prevent premature exhaustion in γδ T cells deserve further in-depth study. Most of the clinical studies focused on Vδ2 T cells. Nonetheless, Vδ1 T cell, mainly found in mucosal and subcutaneous tissues, also deserves closer attention due to their distinctive properties and functions (74). Finally, how to use the γδ T cells in the treatment of other diseases, such as hepatitis and tuberculosis, is also at the heart of its future clinical applications.

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Footnote

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