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REVIEW

The Emerging Roles and Therapeutic Potential of Unconventional T Cells in Sepsis

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Abstract: Sepsis represents a dynamic, dysregulated host immune response to infection in which unconventional T cells—γδ T cells, mucosal-associated invariant T (MAIT) cells, natural killer T (NKT) cells, and double-negative T cells—actively shape the balance between early hyperinflammation and subsequent immune paralysis across time and tissues. These cells employ unique antigen recognition mechanisms to trigger rapid immune responses. γδ T cells facilitate early pathogen elimination and immune regulation, whereas MAIT cells detect microbial metabolites and modulate the systemic inflammation. NKT cells balance immune homeostasis through dual pro- and anti-inflammatory cytokine production. This review classifies these subsets and examines their sepsis-related functions alongside immunotherapies targeting them, such as cytokine manipulation, immunomodulators, and checkpoint inhibitors. Elucidating the precise mechanisms underlying sepsis could advance therapies that restore immune equilibrium and potentially improve clinical outcomes. Future studies should unravel the interactions between unconventional T cells and broader immune networks while translating the findings into practical treatments. Understanding the dynamic roles of these cells provides pathways for tailored interventions in sepsis management.

Keywords: sepsis, γδ T cells, invariant natural killer t cells, mucosal-associated invariant t cells, double-negative t cells, immunotherapy

Introduction

Sepsis is characterized by organ dysfunction that poses a threat to life, resulting from an abnormal host response to infection.[1] The key components of its pathophysiology include cytokine storm, characterized by the excessive release of pro-inflammatory cytokines, endothelial dysfunction, and immunosuppression.[2–4] A major health problem that is often underappreciated, sepsis causes a significant number of deaths around the world each year.[5] In 2017, globally, there were an estimated 48.9 million new cases of sepsis and 11.0 million deaths due to sepsis, which accounted for 19.7% of all deaths worldwide.[6]

Despite advances in supportive care, therapies targeting the underlying immunopathology remain elusive. Conventional T cells, which are central to adaptive immunity, have dominated sepsis research; however, their responses alone may not fully explain the rapid immunologic transitions of sepsis, which can be driven by innate-like activation and tissue residency typical of unconventional T cells.[7,8] Unconventional T (UTC) cells consist of γδ T cells, mucosal-associated invariant T (MAIT) cells, and natural killer T (NKT) cells, and other emerging subpopulations such as double negative T (DNT) cells, whose precise definitions and functional roles are still under investigation.[9–11] Unconventional T cells can directly recognize antigens (including non-peptide antigens). Hence, unconventional T cells combine elements of both innate and adaptive immune functions, with their enhanced "innate-like" properties, can rapidly detect and modulate pathogens and inflammatory responses, playing a pivotal role

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in early or localized immune defense.[12] Crucially, UTCs exhibit functional plasticity: pro-inflammatory in early sepsis (eg, interleukin-17 [IL-17] and interferon-γ [IFN-γ]) yet regulatory or exhausted in late phases.[13,14]

While many studies have thoroughly explored the essential function of conventional T cells in sepsis, there is a lack of research and detailed reviews on how unconventional T cells connect pathophysiological processes with therapeutic possibilities. This review focuses on the primary classifications and functions of unconventional T cells, systematically delving into their potential mechanisms of action in sepsis pathogenesis and exploring their viability as novel therapeutic targets.

Unconventional T Cells: An Overview

Unconventional T cells exhibit non-classical antigen sensing and tissue-specific roles that set them apart from traditional $CD4^+$ and $CD8^+$ subsets.[15] Conventional T cells are central players in the adaptive immune system, where they respond to peptide fragments displayed by MHC molecules on antigen-presenting cells. Rather than relying on peptide presentation via classical MHC molecules, unconventional T cells can detect alternative antigenic structures through non-traditional antigen presentation pathways.[16] By participating in both early and antigen-specific immune processes, unconventional T cells help integrate innate and adaptive immune pathways.[17–20]

Unique Activation Pathways in Response to Infection

In contrast to the MHC-dependent recognition seen in αβ T cells, γδ T cells can engage diverse antigens—including non-peptide molecules—through an unconventional T-cell receptor (TCR)-based mechanism.[21] This mode of antigen recognition by UTC is considered non-MHC restricted.[22] In many cases, unconventional T cells recognize various non-peptide antigens. Non-peptide antigens consist of phosphoantigens, vitamins, and self- and non-self-lipids.[23] In conclusion, it is noteworthy that recognition of non-peptide antigens by UTC forms the basis of their unique immunological functions.

Contribution to Innate and Adaptive Immunity

Characterized by rapid activation, pro-inflammatory cytokine release, and cytotoxic potential, unconventional T cells exhibit properties typically associated with innate immunity. Although they have innate-like qualities, unconventional T cells are also vital to adaptive immune responses. Unconventional T cells significantly contribute to immune regulation by exhibiting antigen-specific memory, modulating adaptive immune responses through cytokine secretion, and maintaining immune homeostasis.[14] Unconventional T cells contribute to adaptive immunity by managing cytokine levels. These cells exert immunoregulatory effects primarily through the secretion of cytokines such as IL-4, IL-10, and IFN-γ, which collectively shape the behavior of antigen-presenting cells and guide lymphocyte differentiation.[19,20,24] Cytokine-driven interactions are essential for orchestrating immune responses, maintaining homeostasis, and preventing immune dysregulation. Moreover, certain unconventional T cell subsets, including type II NKT cells and specific γδ T cell populations, serve as immunoregulatory mediators.[25] These cells help suppress excessive inflammatory responses and promote immune tolerance, thereby preventing pathological immune activation and contributing to the immune equilibrium.[26] In the context of sepsis, unconventional T cells contribute to immune homeostasis by bridging innate detection pathways with adaptive effector responses. The primary roles of UTCs in sepsis are outlined in Table 1 and will be discussed in the following sections.

γδ T Cells in Sepsis

Tissue-Specific Distribution of γδ T Cells

As key mediators of barrier immunity, γδ T cells preferentially localize to epithelial-rich environments such as the intestines, respiratory mucosa, and reproductive tissues. They form an essential part of intraepithelial lymphocytes (IEL) within the epidermis and mucosal tissues, representing only 1–5% of T cells found in peripheral blood.[45]

In contrast to αβ T cells composed of α and β chains, γδ T cells utilize γ and δ chains[46] and encompass a diverse range of subsets, characterized by distinct tissue distributions and effector functions. They can be categorized into three groups according to the specific TRDV genes expressed in the δ chain: the Vδ1+, Vδ2+, and Vδ3+ subsets.[47] Different subsets

Table 1 Key Evidence on the Role of Unconventional T Cells in Sepsis

Cell subset	Main Functions in Sepsis	Key Evidence
γδ T cells	Protective	Antigen-present;[27] IL-17A produced by γδ T17 cells protect against liver injury;[28] IL-22→restricts Staphylococcus;[29]
	Pro-inflammatory/pathogenic	Excess IL-17A→acute lung injury;[30,31] Excess IL-17A→acute kidney injury;[32] Excess IFN-γ→ endothelial cell damage;[33]
MAIT cells	Protective	MR1-restricted recognition of riboflavin-pathway metabolites → cytotoxicity, IFN-γ/IL-17;[34–36]
	Immunosuppressive	MAIT cell decline contribute to post-sepsis immunosuppression.[37,38]
NKT cells	Dual Role (Pathogenic/ Immunosuppressive)	Produce IFN-γ to induce tissue damage in the early stage→ suppress Treg cell formation via IFN-γ in the late stage[39,40]
	Immunosuppressive	The immune checkpoint molecule Tim-3 promotes iNKT cell apoptosis[41]
	Protective	Produce IL-10 to anti-inflammation[42,43]
DNT cells	Pro-inflammatory/pathogenic	Produce IFN-γ and IL-17A[44]

of γδ T cells exhibit significant variations in their function and tissue distribution.[48,49] Notably, Vγ9Vδ2 T cells, a subset within the Vδ2 lineage, represent the most numerically dominant γδ T cells in human peripheral circulation. This subgroup is currently recognized as the most potent class of innate-like γδ T cells.[50]

Mechanisms of γδ T Cells Activation During Sepsis

When an infection occurs, microorganisms invade the human body and serve as antigens that activate γδ T cells, as summarized in Figure 1. Antigen-presenting γδ T cells (γδ T-APCs) can directly detect conserved molecular patterns, including lipopolysaccharide (LPS) and lipoteichoic acid (LTA), in various microbes through pattern recognition receptors.[51] γδ T-APCs use their T cell receptors (TCRs) to directly detect phosphoantigens,[52] thereby initiating a rapid immune response against pathogens. γδ T cells can specifically recognize the phosphoantigens (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP) and isopentenyl pyrophosphate (IPP),[53] as summarized in Figure 1. Vγ9Vδ2 TCR activation requires Butyrophilin 3A1–Butyrophilin 2A1 interaction (BTN3A1-BTN2A1) complex formation upon phosphoantigen binding, which is a microbial sensing mechanism distinct from peptide-MHC recognition.[54] The activation of Vγ9Vδ2 T cells in microbial contexts is heavily dependent on HMB-PP, despite its lack of direct interaction with the T cell receptor. Cytokines like IL-12, IL-18, and type I interferons may fine-tune the activation status of γδ T cells, thereby reinforcing their antiviral capabilities.[55,56] γδ T cells also exhibit memory-like responses during certain infections.[57] For example, in *Staphylococcus aureus* infection, memory γδ T cells undergo expansion after initial infection and provide enhanced protection upon reinfection.[58]

Involvement in Modulating Early Immune Response During Sepsis

The cytotoxic response of γδ T cells involves the activation of apoptosis-inducing cascades in infected cells, mediated by molecules such as perforin and granzyme released upon stimulation.[59] This cytotoxic response has been implicated in the host defense against pathogens that evade extracellular detection, including many viruses and intracellular bacteria.[60] γδ T cells have been shown to fulfill antigen-presenting roles under certain conditions, highlighting their immunological versatility beyond innate-like cytotoxicity. This function is particularly evident when they interact with opsonized target cells, which can license them for antigen presentation.[61] Through their antigen-presenting capabilities, γδ T cells help facilitate communication between the innate and adaptive arms of the immune system. Subsequently, $CD4^+$ T cells activated through this pathway can activate B cells via co-stimulatory signals.[24] However, during the immunosuppressive phase in patients with sepsis, γδ T-APCs exhibit significant impairment in their antigen-presenting function.[27] Moreover, γδ T cells can influence dendritic cell (DC) function during infection by promoting DC maturation through IFN-γ and

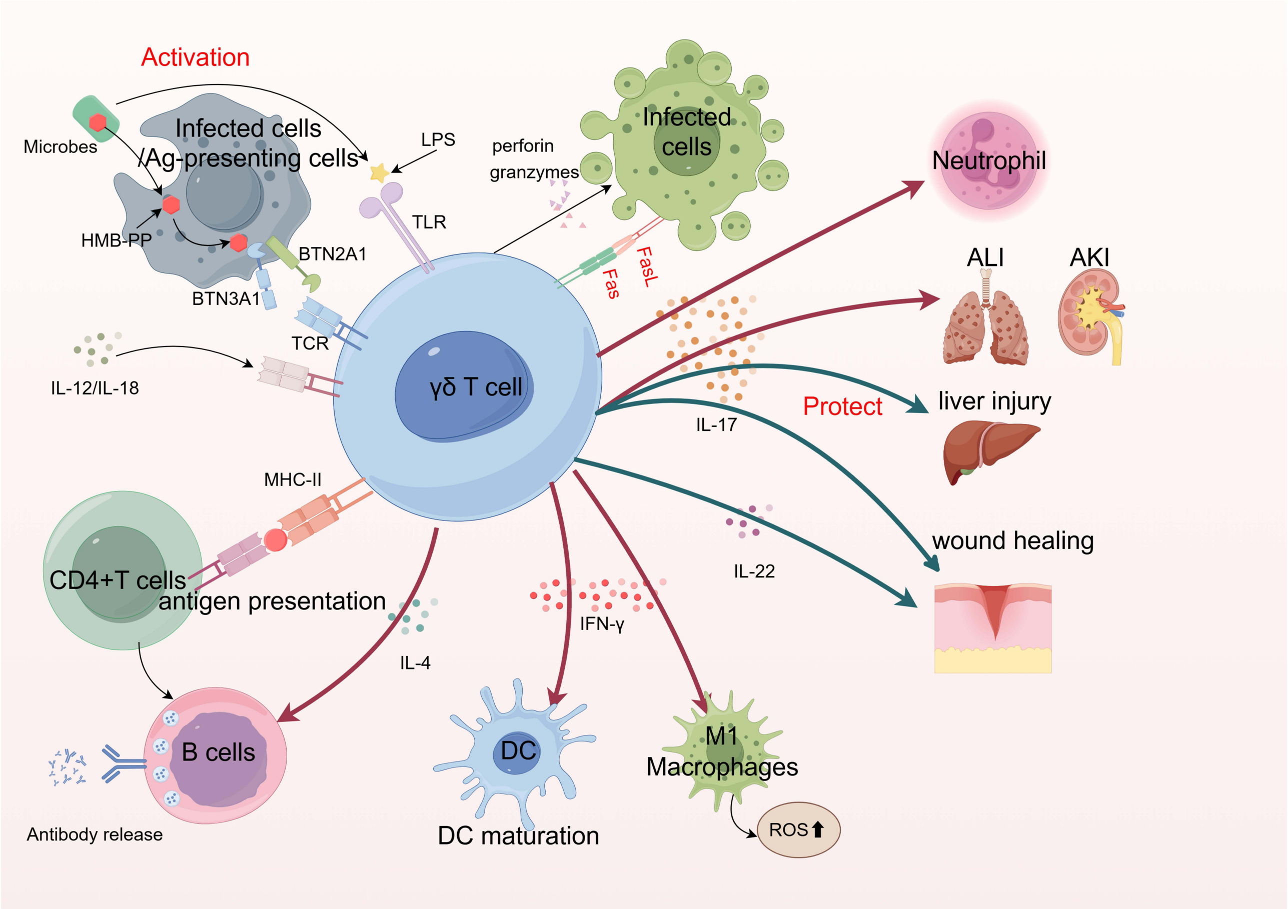

Figure 1 Schematic illustration of γδ T cell activation pathways and effector functions during sepsis.The diagram illustrates key pathways involved in γδ T cell activation during infectious challenges, along with their subsequent immune effector functions. Red arrows indicate pro-inflammatory or pathogenic effects, whereas green arrows represent protective or homeostatic functions. Created by Figdraw Activation pathways: (1) Phosphoantigens act as direct ligands for γδ T-cell receptors, triggering immediate immune responses.(2) Specific phosphoantigens, including (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP) and isopentenyl pyrophosphate (IPP), induce γδ T cell activation via a butyrophilin-dependent mechanism. HMB-PP/IPP first attaches intracellularly to BTN3A1, which induces a shape change that permits BTN2A1 to engage with the Vγ9 chain of Vγ9Vδ2 T-cells.(3) γδ T cells can be activated independently of TCR signaling, with inflammatory mediators such as IL-12 and IL-18 playing a pivotal role in this process.Effector functions:Cytotoxicity: Activated γδ T cells eliminate infected cells via the Fas-FasL pathway or by releasing perforin and granzyme. IL-17 production: IL-17 secreted by γδ T cells promotes neutrophil activation, granulopoiesis, and accumulation, contributing to acute kidney and lung injury during sepsis. However, IL-17 produced by liver-infiltrating γδ T17 cells plays a protective role against sepsis-induced liver injury. IL-17 and IL-22 also facilitate tissue and wound healing.Antigen presentation and bridging innate–adaptive immunity: By acquiring and processing soluble antigens, γδ T cells may facilitate the priming of αβ T cells, contributing to the initiation of adaptive immune responses. Activated CD4 + T cells subsequently provide costimulatory signals to B cells.Support of humoral immunity: IL-4 produced by γδ T cells facilitates early B cell activation and guides their maturation into antibody-secreting cells.IFN-γ production: IFN-γ enhances macrophage activation and bactericidal activity, promotes oxidative stress, contributes to endothelial cell damage, and supports dendritic cell maturation.

Abbreviations: Ag, Antigen; HMB–PP, (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate; BTN3A1, Butyrophilin3A1;BTN2A1, Butyrophilin2A1; LPS, Lipopolysaccharide; TLR, Toll -like receptor;IL, Interleukin; TCR, T-cell receptor; MHC – II, Major Histocompatibility Complex class II; IFN-γ, Interferon–gamma; DC, Dendritic cell; ALI, Acute Lung Injury; AKI, Acute Kidney Injury; ROS, Reactive Oxygen Species.

other mechanisms.[62] Recent studies have demonstrated that unlike conventional dendritic cells, patients with sepsis have γδ T cells that show high expression of HLA-DR molecules.[27] These findings highlight the therapeutic relevance of γδ T cells and support their potential exploitation in future immunotherapy strategies.

By producing cytokines such as IFN-γ, IL-17, IL-4, and IL-22, γδ T cells actively participate in shaping immune responses against infections.[24] IL-17 is central to the immune response, as these cytokines are important for recruiting and activating other immune cells to eliminate pathogens. It can drive neutrophil activation, granulopoiesis, and neutrophil accumulation.[63] During infection, IL-17 derived from γδ T cells supports host protection by coordinating innate immune responses, including neutrophil mobilization, antimicrobial peptide induction, and improved barrier resistance to pathogens. However, in sepsis patients, the overproduction of IL-17 also results in excessive inflammation and is a significant contributor to acute lung injury.[30,31] In the pathogenesis of sepsis, in addition to lung-resident γδ T17 cells,[64] γδ T17 cells originating from the gut are also major producers of IL-17.[64,65] Xue-Wei Yang et al discovered that memory γδ T17 cells formed in the small intestine are capable of homing to the lungs and mediating immune-driven inflammation. The increase in these cells is correlated with the severity of lung injury.[66,67] And within the kidney, IL-17A produced by γδ T cells is also a key factor contributing to sepsis-associated acute kidney injury.[32] However, IL-17A, produced by γδ T17 cells that infiltrate the liver, is crucial for protection against liver injury resulting from sepsis.[28] γδ T cell-derived IL-17 exacerbates lung/kidney injury but protects the liver during sepsis, highlighting the organ-specific pathophysiology. Therapeutic IL-17A blockade improves survival in murine lung injury models[68] yet requires cautious organ-targeted delivery to avoid compromising hepatic defense. IFN-γ produced by γδ T cells can activate macrophages, enhance bactericidal activity, induce oxidative stress, and cause endothelial cell damage.[69,70] Mechanical disruption of the skin triggers IL-22 secretion, primarily from γδ T cells, which contributes to wound healing and epithelial regeneration. γδ T cells have been demonstrated to enhance IL-22 expression in CD4+ T cells in the intestinal environment.[71] This activity contributes to epithelial homeostasis and supports mucosal immune surveillance by maintaining barrier integrity and promoting local immune signaling. γδ T cell–derived IL-22 is instrumental in mounting an effective immune response against Staphylococcus aureus, particularly by promoting barrier integrity and host defense.[29] And IL-4 produced by γδ T cells facilitates early B cell activation and guides their maturation into antibody-secreting cells.[24,72]

Furthermore, γδ T cells modulate immune responses partly by engaging αβ T cells and NK cells through cytokine-mediated signaling and physical interactions,[24] as summarized in Figure 1. These interactions create an intricate immune network that strengthens both innate and adaptive responses, enabling rapid and effective elimination of pathogens.

γδ T Cell-Based Immunotherapy for Sepsis

Zoledronate, a clinically approved phosphatase activator, is extensively used to treat both malignant and nonmalignant bone resorption disorders.[73] In the presence of γδ T cells, zoledronate stimulates human CD14+ monocytes in peripheral blood mononuclear cells to express inflammatory cytokines.[74,75] Loïc Raffray demonstrated that zoledronate could reverse monocyte immunosuppression during acute sepsis, potentially improving clinical outcomes in severe infections.[76] Furthermore, IL-7 administration can enhance IL-17 production by γδ T cells, aided by CXCR3 expression on these cells.[77] Regrettably, our analysis revealed a paucity of current therapeutic research targeting γδ T cells for sepsis management. Notably, future investigations may explore adoptive transfer strategies and precise modulation (activation/inhibition) of γδ T cell functionality as innovative therapeutic approaches for this critical condition.

Mucosal-Associated Invariant T (MAIT) Cells

Tissue-Specific Distribution of MAIT Cells

MAIT cells are a distinct T cell lineage defined by recognition of riboflavin-derived antigens presented by the MHC class I-related molecule MR1. Upon activation by microbial metabolites, they mount innate-like immune responses. These antigens are produced from intermediate metabolites formed during the biosynthesis of riboflavin (vitamin B2).[78] MAIT cells are a diverse and functionally rich group of innate-like T cells whose classification can be further refined based on dimensions such as surface markers, functional status, tissue distribution, antigen reactivity, and disease association.[79] MAIT cells preferentially localize to sites such as the liver and gut, where constant antigen exposure necessitates rapid immune surveillance. They typically comprise a minor fraction of peripheral blood T cells (1–10%) but are far more abundant in intestinal (up to 10%) and liver tissues (up to 40%).[80–82]

Recognition of Bacterial Metabolites and Activation

MAIT cells detect microbial infections through MR1-presented 5-OP-RU,[83–86] a riboflavin (vitamin B2) biosynthesis derivative synthesized by bacteria and fungi, but not humans.[87–89] These vitamin B2-derived antigens (VitBAgs) serve as conserved microbial signatures, enabling MR1-dependent MAIT activation via TCR recognition (Figure 2).[90] Antigen-presenting cells (APCs) bind intracellular VitBAgs to MR1, triggering MAIT effector responses such as direct cytolysis and inflammatory release (eg, IFN-γ and IL-17).[91–93] While MAIT cell activation primarily relies on MR1-TCR interactions, it can also be partially triggered by cytokine signaling pathways, especially IL-12 and IL-18,[94] as summarized in Figure 2.

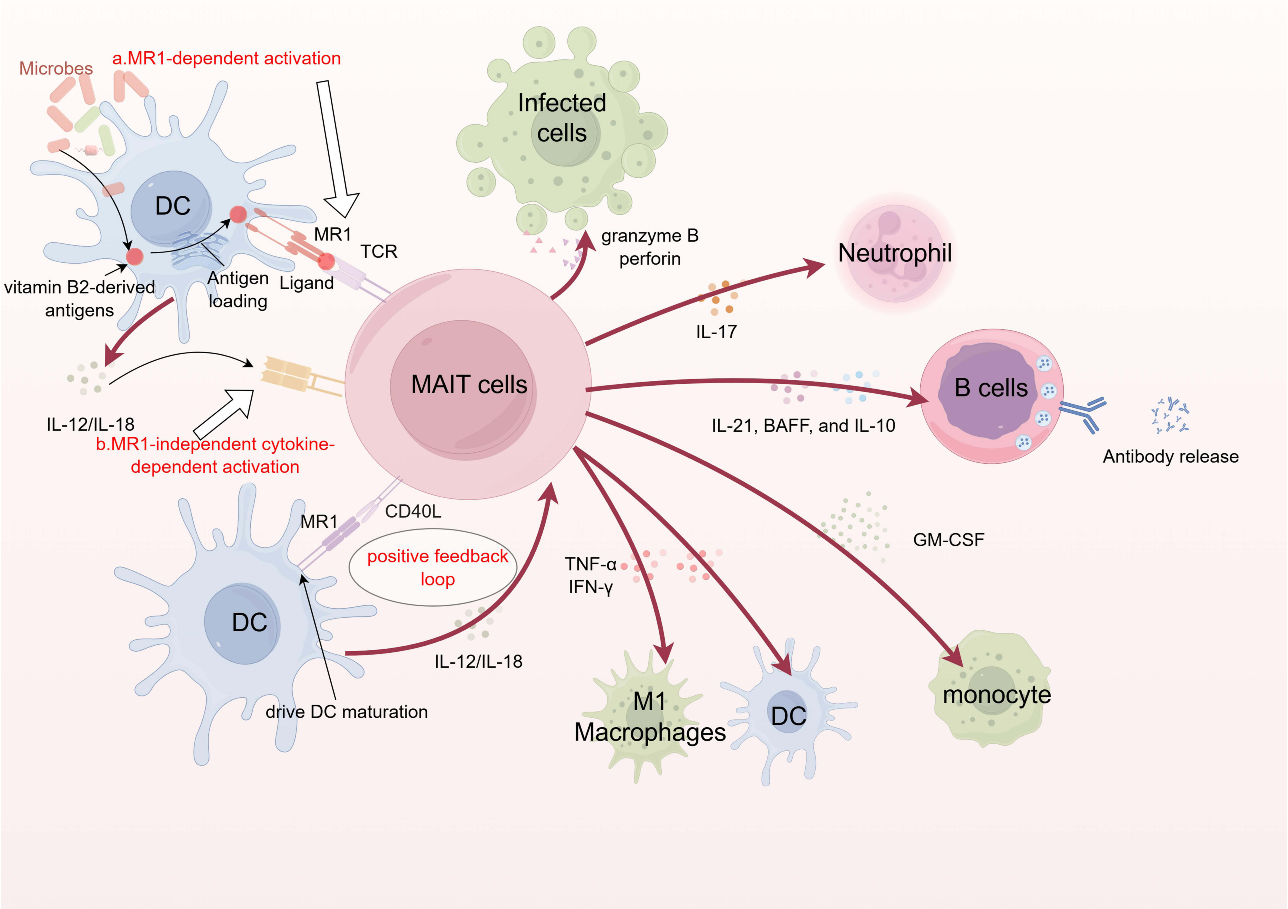

Figure 2 Schematic illustration of mucosal-associated invariant T (MAIT) cell activation pathways and effector functions during sepsis.The chart depicts the activation processes and immune functions of MAIT cells when responding to microbial infections in sepsis. Red arrows indicate immunostimulatory or pro-inflammatory effects, while green arrows represent protective or regulatory roles. Created by Figdraw. Activation pathways: (1) MR1-dependent activation: MAIT cells detect microbial vitamin B2 (riboflavin) metabolites through their semi-invariant T cell receptor (TCR) when presented by MHC class I-related molecules (MR1).(2) MR1-independent activation: Infected cells secrete IL-12 and IL-18, which engage cytokine receptors on MAIT cells and initiate activation through a TCR-independent signaling cascade.Effector functions: Cytotoxicity: Once MAIT cells are activated, they attack infected cells or pathogens by releasing granzyme B and perforin. Neutrophil recruitment: IL-17 secreted by MAIT cells promotes neutrophil chemotaxis to sites of infection. Support of humoral immunity: MAIT cells facilitate plasmablast differentiation and antibody secretion by producing B cell-activating cytokines such as IL-21, BAFF, and IL-10, thereby promoting B cell proliferation and immunoglobulin class switching. Activation of antigen-presenting cells and macrophages: The secretion of TNF-α and IFN-γ by MAIT cells is thought to facilitate dendritic cell maturation and support M1-type macrophage responses during inflammation. Monocyte recruitment: Activated MAIT cells secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), promoting monocyte recruitment and activation. Feedback amplification via the CD40L-MR1 axis: Upon stimulation with the cognate antigen 5-A-RU/MG, MAIT cells upregulate CD40L expression, promoting DC maturation through the CD40L-MR1 costimulatory axis. Mature DCs, in turn, enhance IL-12 production, establishing a positive feedback loop that amplifies MAIT activation and supports cytotoxic T lymphocyte (CTL) priming.

Abbreviations: DC, Dendritic cell, MR1,MHC class I-related molecules; TCR, T-cell receptor; IL: Interleukin; TNF-α, Tumor Necrosis Factor; IFN-γ, Interferon–γ; BAFF, B-cell–activating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Pro-Inflammatory and Antimicrobial Functions

Although their role complements conventional adaptive immunity, MAIT cells may become indispensable in immunocompromised hosts or during overwhelming infections, where mobilizing every available defense mechanism is essential for survival. Notably, in critically ill patients, a reduced frequency of circulating MAIT cells correlates with an increased severity of acquired infections, further emphasizing their importance in host immunity.[95]

Activated MAIT cells can directly target and kill infected cells or pathogens by releasing granzyme B and perforin.[34] Upon activation by superantigens such as streptococcal superantigens, human MAIT cells elicit a potent pro-inflammatory response by producing high levels of IFN-γ, IL-17, and tumor necrosis factor-alpha (TNF-α),[96] as summarized in Figure 2. MAIT cells facilitate neutrophil recruitment via IL-17 production,[97] and the proportion of MAIT17 cells correlates with how severe sepsis is.[98] The secretion of TNF-α and IFN-γ by MAIT cells contributes to the immunological priming and functional maturation of dendritic cells and concurrently facilitate the activation of M1 macrophages, thereby orchestrating key processes in the innate immune response and bridging it with adaptive immunity.[99] Excessive cytokine secretion has been implicated in the development of hyperinflammatory syndromes that threaten host viability.[35,36] Human MAIT cells respond to 5-A-RU/MG by upregulating CD40L, engaging a CD40L-MR1 axis that supports the functional maturation of dendritic cells.[100] Mature DCs subsequently enhance IL-12 production, thereby establishing a positive feedback loop that amplifies MAIT cell activation while synergistically facilitating cytotoxic T lymphocyte (CTL) priming.[101] Human MAIT cells enhance humoral immune responses by secreting IL-21, B-cell–activating factor (BAFF), and IL-10. These cytokines not only promote plasmablast differentiation and antibody production in vitro but also directly facilitate B cell proliferation and immunoglobulin class switching, particularly following microbial activation.[100,102] Furthermore, the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), secreted by activated MAIT cells, plays a key role in promoting monocyte activation and facilitating their migration to sites of inflammation.[103]

Potential Role in Post-Sepsis Exhaustion

Despite growing interest in sepsis research, studies on the role of MAIT cells in sepsis remain relatively scarce. According to Trivedi et al, the absence of MAIT cells causes a rise in bacterial burden and mortality in sepsis experiments. Furthermore, during clinical sepsis, MAIT cells exhibit heightened activation but ultimately become dysfunctional. However, they also mediate tissue-specific cytokine responses that help mitigate sepsis-related mortalities.[37] Similarly, Choi et al described a distinct post-sepsis immunosuppressive pattern involving a prolonged decline in MAIT cell functionality and abundance, even though their phenotypic characteristics remained largely unchanged. This dysfunction makes individuals more susceptible to secondary infections. These findings suggest that MAIT cell impairment is essential in post-sepsis immune suppression.[38] Future research on the specific mechanisms of MAIT cells in sepsis is expected to enhance our understanding of the disease and facilitate the development of effective therapeutic strategies.

MAIT Cell-Targeted Therapies: Promises and Challenges in Sepsis

Evidence from Barber et al indicates that MAIT cell activity may delay the activation of CD4$^+$ T cells in tuberculosis, highlighting the potential relevance of inhibitory ligands in modulating MAIT cell function during infection.[104] Similarly, in the context of Helicobacter pylori infection, pathological outcomes like gastritis and mucosal damage—partly driven by MAIT cell-derived IL-17A—may be attenuated through targeted IL-17A neutralization.[105] In sepsis, where MAIT cells may contribute to immune pathology, interventions aimed at modulating their cytokine release or cytolytic activity could represent a novel treatment option, as observed in other infections like TB and H. pylori. Bacterial superantigens have been shown to hyperactivate MAIT cells, potentially triggering a dysregulated cytokine response that contributes to systemic inflammatory damage.[35] Therapeutic strategies targeting MAIT cell activity have explored inhibitory ligands like 6-FP[106] and Ac-6-FP,[107] particularly in contexts requiring immune suppression. This approach has been researched for treating tumors,[108] inflammatory bowel disease,[109] and other conditions. However, more research is required to explore the application of this therapy in cases of sepsis.

Invariant Natural Killer T (iNKT) Cells

Tissue-Specific Distribution of NKT Cells

NKT cells uniquely co-express T cell receptors and markers commonly associated with NK cells, reflecting their hybrid functional identity. Type I, type II, and NKT-like cells are the three main subsets of NKT cells, categorized by TCR usage and lipid antigen specificity.[110] CD1d-restricted NKT cells encompass two distinct populations—type I and type II. Type I NKT cells, commonly referred to as invariant NKT (iNKT) cells, are characterized by the use of a conserved TCRα chain—Vα24-Jα18 in humans—together with a narrowly restricted set of TCRβ chains that shape their antigen specificity.[19] And iNKT cells, a subset of NKT cells, are primarily responsible for immune functions and are generally seen as the most functionally and clinically relevant. Type II NKT cells have unique TCRα and TCRβ chains, indicating that their TCR shows increased ligand specificity.[111] Some cells do not exhibit CD1d dependency and are referred to as NKT-like cells.[110] In the livers of adult mice, NKT cells constitute the majority, making up approximately 12–30% of hepatic lymphocytes.[112] In adult humans, the peripheral distribution of NKT cells appears to closely parallel that observed in adult mice. NKT cells are predominantly located in the liver, accounting for 20–30% of hepatic T cells; however, they remain rare in the peripheral blood, constituting only approximately 0.2% of circulating T cells.[112,113]

Activation of Lipid Antigen Sensing in Sepsis

iNKT cells, as CD1d-restricted T cells,[114,115] recognize lipid antigens, including endogenous glycosphingolipids (GSLs), that regulate immune homeostasis and pathogen responses.[116,117] Their activation primarily occurs through two distinct pathways: (1) TCR-dependent mechanisms, where CD1d-antigen complexes trigger broad cytokine secretion (eg, IFN-γ and IL-4), activating diverse immune effectors, such as NK cells and macrophages,[19] and (2) LPS-induced IL-12 and IL-18 signaling can activate immune cells independently of TCR stimulation, leading to a cytokine-mediated surge in IFN-γ production.[118] Certain gram-positive pathogens, including *Staphylococcus* and *Streptococcus*, are capable of activating iNKT cells, likely via superantigen exposure or direct interaction with microbial-associated molecular patterns (PAMPs). Sepsis-induced tissue injury may promote iNKT cell activation through CD1d-mediated presentation of self-glycolipid antigens. Once activated, they eliminate infected targets through direct cytotoxic mechanisms, including Fas-FasL interaction and secretion of perforin and granzymes.[119]

Staphylococcus and Streptococcus, as major contributors to Gram-positive bacterial sepsis, can produce superantigens that engage iNKT cells and potentially amplify systemic inflammation.[120] It is also plausible that bacterial PAMPs are directly recognized by iNKT cells. Additionally, through iTCR engagement, iNKT cells can be activated by CD1d-presented endogenous glycolipids, which are often released or structurally modified following septic tissue damage. After activation, iNKT cells can kill infected cells through the Fas-FasL pathway or by releasing perforin/granzymes.

Cytokine Networks and Cellular Crosstalk in Sepsis

Different subsets of mouse iNKT cells can produce distinct types of cytokines upon activation, contributing to immune processes.[121] For instance, NKT1 cells resemble Th1 cells and group 1 ILCs (ILC1s) due to their elevated levels of the transcription factor T-bet (encoded by TBX21) and their capacity to produce IFN-γ and TNF-α when activated.[122] Notably, iNKT cell-induced damage is primarily mediated by IFN-γ. Compared with other iNKT subsets, NKT1 cells exhibited stronger cytotoxic activity. Th1-Type pro-inflammatory cytokines enhance M1-macrophage activation, neutrophil recruitment and improve bacterial clearance. NKT2 cells, on the other hand, primarily secrete IL-4 and IL-13, aligning them functionally with Th2 cells.[123] Th2-Type anti-inflammatory cytokines regulate immune responses, prevent excessive inflammation, and enhance B cell activation for antibody production. Meanwhile, NKT17 cells share similarities with Th17 cells in their cytokine secretion profile, particularly in their production of IL-17.[124] Th17-Type inflammatory cytokines enhance inflammatory responses, promote neutrophil recruitment, and improve immunity against bacterial infections. Additionally, the anti-inflammatory role of iNKT cells is partly mediated through IL-10, which limits the activity of APCs and NK cells.[42,125–127]However, in humans, the classification of iNKT subsets is less clearly defined than in mice. Upon activation, human DN and CD8$^+$ iNKT cells demonstrate enhanced IFN-γ output and potent cytotoxic responses, aligning functionally with murine NKT1 cells.[128] Human iNKT cells are capable of secreting both pro- and anti-inflammatory cytokines—such as IL-17 and IL-10—reflecting their dual role in modulating immune responses during infection.[42,129]

Beyond cytokine secretion, iNKT cells modulate immune function by engaging in direct cellular interactions that shape the behavior of other immune populations. Through their interactions with dendritic cells and B lymphocytes, these cells facilitate communication across the innate and adaptive immune systems. A crucial aspect of their role in adaptive immunity is facilitation of DC maturation into APCs. Upon recognizing CD1d-presented lipid antigens on DCs, iNKT cells upregulate CD40L and secrete cytokines, triggering DC maturation into potent APCs.[125] This process enhances MHC class II expression, co-stimulatory markers (CD80/CD86), and IL-12 production, thereby optimizing T cell priming.[130,131] For example, in vivo administration of α-GalCer activates iNKT cells, which subsequently stimulate dendritic cells to promote robust activation of CD4$^+$ and CD8$^+$ T cells in an antigen-specific manner.[132] Furthermore, iNKT cells support cytotoxic immunity by licensing dendritic cells, thereby enhancing CD8$^+$ T cell activity, and also shape the CD4$^+$ T cell response through promoting Th1/Th2 differentiation pathways.[133,134]

Notably, iNKT cells balance the immune activation and homeostasis. They eliminate pro-inflammatory APCs via CD1d-dependent cytotoxic granule release,[135,136] while supporting humoral immunity through dual mechanisms.

Cognate interactions with CD1d$^+$ B cells drive rapid antibody responses against lipid antigens, whereas non-cognate assistance via follicular helper T (TFH) cell activation sustains long-term memory against antigens.[137] Additionally, iNKT cells regulate broader immune networks through cytokine signaling.

Dual Roles in Sepsis: Exacerbation and Protection

iNKT cells play dual roles in sepsis pathogenesis, acting as both amplifiers of early immunopathology and mediators of late immunosuppression. Their functional outcomes depend on the infection stage (early hyperinflammation vs late immunosuppression), pro- versus anti-inflammatory balance, and crosstalk with the immune cells (Figure 3).

During the hyperinflammatory phase, iNKT cells exacerbate tissue damage through excessive IFN-γ production,[39] which drives cytokine storms and hyperactivates NK cells via mTORC1 (Mammalian Target of Rapamycin complex 1)

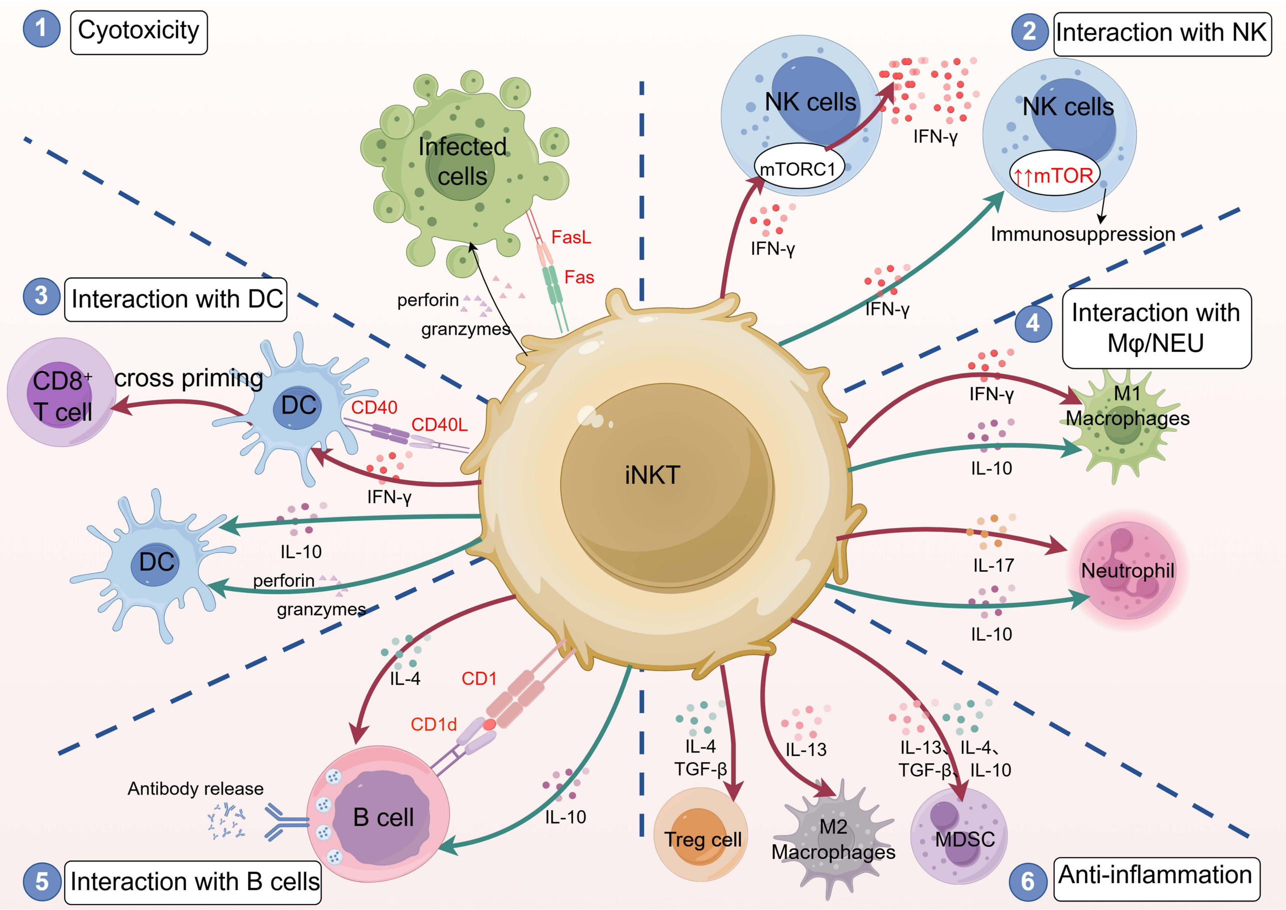

Figure 3 Schematic illustration of the major functions of invariant natural killer T (iNKT) cells following activation during sepsis.Upon activation, iNKT cells engage in complex interactions with various immune cells, exerting both pro-inflammatory and anti-inflammatory effects. Red arrows indicate stimulatory functions, while green arrows denote inhibitory functions. Created by Figdraw. 1.Cytotoxicity: iNKT cells directly kill infected cells via the Fas-FasL pathway or by releasing perforin and granzymes. 2.Interaction with NK cells: Through mTORC1 signaling, iNKT cells modulate NK cell function, leading to increased IFN-γ production. However, iNKT-derived cytokines may also suppress NK cell function during sepsis via the upregulation of the mTOR pathway. 3.Interaction with dendritic cells (DCs): iNKT cells rapidly produce cytokines and upregulate CD40L, which binds to CD40 on DCs and enhances their maturation. This process induces the upregulation of IL-12, along with key antigen-presenting components including MHC class II and the co-stimulatory molecules CD80 and CD86, thereby promoting antigen presentation and T-cell priming. iNKT cells contribute to CD8$^+$ T cell activation via cross-priming mechanisms and shape CD4$^+$ T cell responses toward Th1 and Th2 lineages. Additionally, iNKT cells regulate DC function through cytokines: IFN-γ enhances DC activity, IL-10 inhibits it, and cytolytic killing of inflammatory DCs helps restore immune homeostasis. 4.Interaction between macrophages and neutrophils: IFN-γ enhances M1 macrophage activation, while IL-17 promotes inflammation and neutrophil recruitment. Conversely, IL-10 from iNKT cells suppresses the pro-inflammatory activities of both M1 macrophages and neutrophils. 5. Interaction with B cells: iNKT cells support humoral immunity through both cognate (CD1d-mediated) and non-cognate (via TFH activation) B cell help. IL-4 enhances B cell activation and antibody production, while IL-10 inhibits B cell function to limit inflammation. 6.Anti-inflammatory regulation: iNKT cells contribute to immune suppression by secreting Th2-associated cytokines (IL-4 and IL-13) and regulatory cytokines (IL-10 and TGF-β) as well as by activating anti-inflammatory cell types, including M2 macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs).

Abbreviations: DC, Dendritic cell; IL, Interleukin; IFN-γ, Interferon–γ; mTORC1, mammalian target of rapamycin complex 1; Mφ, Macrophages; NEU, Neutrophil; TGF-β, Transforming growth factor – beta; Treg cell, Regulatory T cell; MDSC, Myeloid - derived suppressor cells.

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signaling,[40] correlating with increased mortality in preclinical and clinical studies.[138] Across various experimental models, iNKT cell-driven damage in sepsis has consistently been associated with excessive IFN-γ production.[139,140] In the early stages of viral infection, NK cells contribute to host defense by eliminating infected cells and secreting immune-regulatory cytokines that influence downstream responses.[141,142] Notably, following NKT cell activation, NK cells emerge as the predominant producers of IFN-γ. Conversely, iNKT cells mitigate inflammation through two mechanisms: (1) The secretion of IL-4, IL-10, and TGF-β helps to polarize anti-inflammatory Th2/M2 responses and recruit regulatory cells, including M2-polarized macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs); and (2) elimination of hyperactivated APCs via cytolysis, restoring immune balance.[43,135]

In late sepsis, prolonged activation depletes iNKT cells and upregulates exhaustion markers (eg, Tim-3), leading to apoptosis and impaired bacterial clearance—a hallmark of immunosuppression.[41,143,144] Upregulation of the mTOR (Mammalian Target of Rapamycin) signaling cascade, driven by cytokines released from NKT cells, has been implicated in the suppression of NK cell-mediated immune responses during sepsis.[40] Therapeutic strategies targeting Tim-3 to inhibit iNKT cell apoptosis or modulating mTORC1 signaling may reverse late-phase immune paralysis. Thus, iNKT cells embody a double-edged sword: their early pro-inflammatory responses enhance pathogen clearance but risk collateral damage, while their late exhaustion perpetuates immunosuppression. Harnessing their phase-specific rolesvia timed cytokine blockade or checkpoint modulation could optimize sepsis immunotherapy.

Modulation of iNKT Cells to Prevent Cytokine Storms and Immunosuppression

Anti-Inflammatory Targeting (Early Phase)

iNKT cells are pivotal therapeutic targets in sepsis because of their dual role in driving hyperinflammation and immunosuppression. IL-30 therapy suppresses IFN-γ and TNF-α via the iNKT/IL-10 axis, thereby reducing mortality in LPS- and CLP-induced sepsis models.[145] Treatment with IL-30 can slow down the inflammatory response through the NKT cell pathway in sepsis. Moreover, TIM-3 blockade using α-lactose was found to prevent iNKT cell apoptosis and attenuate cytokine storms in septic mice, thus providing a novel therapeutic approach.[146] Furthermore, graphene oxide also holds potential for positive effects in the treatment of sepsis. Graphene oxide was found to polarize iNKT cells toward an anti-inflammatory phenotype by enhancing TGF-β production, reducing cytokine storms in sepsis models.[147]

Immune Restoration (Late Phase)

During the period of immunosuppression, the treatment targeting iNKT cells lies in activating the activity of iNKT cells. Among them, α-GalCer, as an effective activator for iNKT cells, is widely used in experiments.[148] However, its repeated use can lead to immunological unresponsiveness of iNKT cells.[140] Because activated iNKT cells mainly lean towards the Th1 type, which inhibits Treg cell differentiation and reduces effector function by decreasing Nr4a1 expression in the late stage of sepsis. The biphasic role of Treg cells in sepsis progression underscores the therapeutic relevance of iNKT cell regulation, particularly for mitigating late-stage immune suppression.[39] Joshua Choi's two-step treatment regimen, involving the sequential administration of various glycolipid agonists, successfully prevented iNKT cell anergy. Restoration of iNKT cell plasticity during polymicrobial sepsis has been achieved through a two-step regimen involving [(C2S,3S,4R)-1-O-(α-d-galactopyranosyl)-N-tetracosanoyl-2-amino-1,3,4-nonanetriol] (OCH), a TH2-biased ligand, administered prior to α-galactosylceramide, thereby promoting IFN-γ-driven immune recovery.[149] IFN-γ is a significant factor in the initial immunopathology of sepsis, but its managed release during the immunosuppressive phase could help in immune recovery.[138] Tailoring iNKT cell-based interventions to distinct disease stages may represent an effective strategy against sepsis, meriting continued exploration in future studies.

Double-Negative T (DNT) Cells

An Emerging Player in Inflammation and Sepsis

Double-negative T (DNT) cells are mature $CD3^+$ T lymphocytes that lack both CD4 and CD8 co-receptors and constitute a heterogeneous, functionally active subset of the T-cell compartment.[150,151] By phenotype, the DNT gate can include both $TCR\alpha\beta^+$ and $TCR\gamma\delta^+$ cells.[152] Notably, most γδ T cells are naturally $CD4^-CD8^-$ and would fall within this gate; nevertheless, γδ T cells are generally treated as a distinct unconventional T-cell lineage discussed earlier in this review.

To maintain conceptual clarity, we focus on describing TCRαβ$^+$ DNT cells in the subsequent several sections regarding DNT cells. In peripheral blood, DNT cells comprise 1–3% of total T lymphocytes.[150,153] Beyond the circulation, they are present in secondary lymphoid organs and multiple tissues (eg, intestine, liver, lung, skin, and reproductive tract), where tissue-resident DNT populations have been described.[150,154,155] Their contribution to sepsis is less well defined than that of other unconventional T cells; however, emerging evidence implicates DNT cells as important mediators of inflammatory responses in sepsis.[18,156]

Activation and Pro-Inflammatory Function

During infection, TCRαβ$^+$ double-negative T (DNT) cells are activated through two principal routes. First, TCR-dependent signals derive from peptide–MHC (pMHC) complexes displayed by professional antigen-presenting cells (APCs);[157] DNT cells can also acquire pMHC via trogocytosis, enabling antigen-specific recognition and effector function outside the APC niche.[158] Second, an inflammatory cytokine milieu—classically IL-12 with IL-18 and type I/II interferons—drives cytokine-mediated bystander activation that heightens DNT responsiveness in the relative absence of TCR ligation.[156,159] Human DNT cells express activating receptors such as NKG2D; when ligands are up-regulated on infected or stressed tissues, their regulatory or cytotoxic activity is augmented and can be associated with the emergence of induced DNT subsets.[160] In mucosal infections of the respiratory tract, DNT cells may constitute prominent responders that produce IFN-γ and IL-17A and contribute to pathogen control (eg, *Francisella tularensis*, influenza).[44] Leishmania-reactive TCRαβ$^+$ DNT cells can activate macrophages, thereby enhancing anti-parasite effector functions.[161] Depending on the pathogen and tissue context, DNT cell frequency and activation state correlate with disease severity, positioning these cells as sentinels of inflammatory activity.

Clinical Correlation with Sepsis

A 2025 clinical study reported a direct association between circulating DNT-cell frequency and sepsis severity within a defined infectious context.[156] Expansion of DNT cells was strongly associated with the development of septic shock, and their frequencies tracked clinical severity. These data suggest that DNT cells are not passive bystanders but active participants in the immunopathology of severe sepsis. Their pronounced cytokine output likely fuels the cytokine storm and systemic inflammation that characterize septic shock8. Given their emerging links to severe disease,[11,162] DNT cells warrant focused investigation as both biomarkers for early identification of patients at risk of shock and therapeutic targets to attenuate hyperinflammation.

Prospects, Challenges and Opportunities

The Sepsis-3 criteria, while distinguishing sepsis from uncomplicated infections,[163] inadequately address patient heterogeneityranging from hyperinflammatory to immunosuppressive endotypes.[164] Precision medicine[165] frameworks integrating genomic, transcriptomic, and proteomic profiling of peripheral blood leukocytes have begun to stratify patients into immune subtypes with distinct outcomes and therapeutic responses.[166–168] Categorizing sepsis based on distinct immune characteristics can enhance the effectiveness of tailored immunotherapeutic approaches for different patient subtypes.[169] However, a consensus classification system remains elusive, hindering the development of tailored immunotherapy.[170]

Owing to their innate-like characteristics, unconventional T cells can initiate immune responses more rapidly than their conventional counterparts during infection. In the early stages of sepsis, when the infection progresses swiftly, this rapid response could be particularly beneficial, as timely intervention is critical for patient survival.[171] These T cells might be integrated into combination therapies, alongside antibiotics, anti-inflammatory agents, and immune modulators, to enhance overall therapeutic efficacy. Their distinct mechanisms of action could complement traditional sepsis treatments, potentially improving patient recovery. Therefore, future research should focus on interventions during the early stages of infection to enhance the immunologic capacity of unconventional T cells.

Several innovative interventions for sepsis are being evaluated, including hemoadsorption,[172,173] gut microbiota modulation,[174,175] and immunoadjuvant therapy.[176,177] Hemadsorption mitigates excessive immune-mediated injury in sepsis by modulating the systemic inflammatory response via the clearance of endotoxin (Polymyxin B) and excess inflammatory mediators, particularly cytokines (HA330/HA380).[172,178,179] The removal of endotoxin (LPS) could reduce the direct activation of γδ T cells and attenuate the indirect,[51] cytokine-driven activation of iNKT cells.[118] Concurrently, the broad adsorption of inflammatory cytokines like IL-12 and IL-18 could dampen the TCR-independent activation of γδ T cells, MAIT cells, and iNKT cells, thereby mitigating the cytokine storm and potentially preventing their functional exhaustion.[20,110] Therefore, future research on hemadsorption techniques should include immunophenotyping of unconventional T cells to elucidate these interaction mechanisms. Therapeutic modulation of the gut microbiota reduces microbial translocation and dampens systemic inflammation, leading to less organ injury in sepsis.[180,181] And the function of protective, liver-infiltrating γδ T cells in sepsis is regulated by gut commensal microbes.[28] This link is even more direct for MAIT cells, whose development is "imprinted" by the microbiota and whose activation is directly triggered by metabolites produced by bacteria and fungi.[87–89] Therefore, modulating the gut microbiota through therapies like probiotics or fecal microbiota transplantation offers an indirect yet powerful pathway to "tune" the function of UTCs in sepsis, potentially mitigating their pathogenic hyperactivation or bolstering their protective roles. Immunoadjuvant therapies encompass pharmacological modulation to enhance unconventional T-cell responses, including cytokine adjuvants or adoptive transfer of ex vivo expanded T-cell populations. Harnessing their early effector functions may accelerate pathogen clearance and avert progression to sepsis-associated organ failure. During the subsequent immunosuppressive phase, rapidly restoring UTC function is a priority for investigation.[13] Reactivation or replenishment of these cells may interrupt disease trajectories and improve clinical outcomes.

A significant challenge in utilizing unconventional T cells for sepsis therapy is the risk of immune exhaustion. Unconventional T cells may also become exhausted, diminishing their ability to manage the infection or modulate inflammation effectively. Moreover, given their scarcity in peripheral blood, obtaining sufficient numbers of these cells remains a practical challenge for therapeutic applications. Expanding these cells in vitro for therapeutic applications is both technically challenging and costly.[182] To improve the efficiency and specificity of generating unconventional T cells, researchers have explored stem cell engineering techniques—including gene editing of HSPCs and iPSCs—followed by lineage-directed differentiation.[183,184] While these strategies can enhance yield and purity, their clinical translation remains limited.

Although unconventional T cells show promise, their precise mechanisms of action in sepsis remain unknown. Unlike the well-understood developmental pathways and markers of αβ T cells, UTC development is complex and not fully understood.[14,185] Grasping how these cells engage with other immune elements, manage pro-inflammatory and anti-inflammatory reactions, and control their function during sepsis is vital for maximizing their therapeutic benefits.

The application of integrative omics and data-driven systems approaches is anticipated to enhance our capacity to resolve immune heterogeneity in sepsis with greater resolution. This perspective is particularly crucial for individualized and precise administration of immunotherapy. Multi-omics technologies offer novel perspectives and tools for sepsis research, enhancing our understanding of its complex pathophysiology and providing a solid scientific basis for the advancement of novel diagnostic and therapeutic approaches.[186,187]

Conclusion

Among the key players in the immune landscape of sepsis are γδ T cells, MAIT cells, and NKT cells—several types of unconventional T cells that collectively contribute to both antimicrobial defense and immunoregulation. Their ability to recognize non-peptide antigens and rapidly respond to infections highlights their potential as key therapeutic targets. Current research underscores the dual nature of their functions, as these cells can either enhance immune defense or contribute to immune dysregulation, depending on the stage and severity of sepsis.

Modulating the activity of unconventional T cells (UTCs) presents a novel immunotherapeutic approach for sepsis. Specifically, this involves targeting γδ T cells for their antimicrobial and tissue-reparative functions, MAIT cells for their capacity to regulate systemic inflammation, and NKT cells for their cytokine-modulatory roles. The clinical application of these concepts may be realized through strategies such as immunomodulation, immune checkpoint inhibition, and cytokine-based therapies, which aim to potentiate the beneficial functions of these cells while counteracting their detrimental effects. Effective translation of these approaches into clinical practice is contingent upon the development of biomarkers to stratify patients into distinct immune endotypes, thereby enabling personalized interventions. Accordingly, early and sequential immune profiling, including the assessment of UTC subsets and their activation or exhaustion markers at baseline and again at days three to five post-admission, is advisable.

Future clinical trials should be strategically designed to target specific phases of the septic response. For instance, during the initial hyperinflammatory phase, interventions could focus on neutralizing pathogenic cytokines like IL-17A and IFN-γ. Conversely, during the subsequent immunosuppressive phase, the objective would shift to restoring host immune competence. Promising therapeutic candidates for investigation include immune checkpoint inhibitors targeting molecules such as Tim-3 to prevent NKT cell apoptosis, or agents like zoledronate to reverse immune paralysis. Ultimately, the integration of precise patient stratification with temporally targeted immunomodulatory interventions holds the greatest potential for improving survival outcomes in patients with sepsis.

However, significant challenges remain, including the need for a deeper mechanistic understanding of their activation pathways, functional plasticity, and their interactions with other immune components. Future research should focus on elucidating the optimal therapeutic windows for modulating these cells in sepsis as well as developing personalized immunotherapy approaches based on patient-specific immune profiles. By advancing our knowledge of unconventional T cells in sepsis, we may unlock novel therapeutic strategies that restore the immune balance and improve patient survival.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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