The Role of MAIT Cells in Antimicrobial Resistance: Elucidating Key Mechanisms in the Control of Drug-Resistant Infections

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Abstract

Antimicrobial resistance (AMR) has emerged as a major global health threat, with the efficacy of conventional antibiotics progressively declining due to the continuous evolution of drug-resistant pathogens. While the development of novel antibiotics is essential, the human immune system likewise plays a critical role in eradicating bacterial populations. This review examines the significant role of mucosal-associated invariant T (MAIT) cells—a unique immune cell subset capable of bridging innate and adaptive immunity to synergistically combat AMR infections. We further propose that MAIT cells exert core functions in fighting multidrug-resistant (MDR) bacteria through direct killing of resistant pathogens and regulation of immune responses. MAIT cells can recognize conserved microbial metabolites and circumvent bacterial resistance mechanisms (including those that cause existing antibiotics to fail). Moreover, we discuss the potential of enhancing MAIT cell function as a novel therapeutic strategy (particularly for immunocompromised and high-risk populations) and the prospects for combining MAIT cell therapy with existing antibiotics to enhance treatment efficacy.

Full Text

The Role of MAIT Cells in Antimicrobial Resistance: Unveiling Key Mechanisms in the Control of Drug-Resistant Infections

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Antimicrobial resistance (AMR) has emerged as a major global health threat, with traditional antibiotics gradually losing efficacy due to the continuous evolution of resistant pathogens. While developing novel antibiotics remains crucial, the human immune system plays an equally vital role in clearing bacterial populations. This review explores the important function of mucosal-associated invariant T (MAIT) cells—a unique subset of immune cells that bridge innate and adaptive immunity to combat AMR infections. We further propose that MAIT cells possess core functions in fighting multidrug-resistant (MDR) bacteria through direct killing of resistant pathogens and regulation of immune responses. MAIT cells can recognize conserved microbial metabolites and overcome bacterial resistance mechanisms, including those that render existing antibiotics ineffective. Additionally, we discuss the therapeutic potential of enhancing MAIT cell function as a novel treatment strategy, particularly for immunocompromised and high-risk populations, and the prospects of combining MAIT cell therapy with existing antibiotics to improve efficacy.

Impact of Antimicrobial Resistance and Host Immune Response

The escalating crisis of AMR infections poses severe challenges to global healthcare systems. The widespread prevalence of multidrug-resistant (MDR) bacteria has weakened the efficacy of available antibiotics, while the pace of resistance development far exceeds that of new drug discovery (1). This imbalance threatens major medical procedures such as cancer therapy, surgical operations, and organ transplantation, all of which carry fatal risks without effective antibiotics (1). The misuse and overuse of antibiotics in community and hospital settings represent primary drivers of this problem, exacerbated by the scarcity of new antimicrobial agents in the development pipeline (2). Although novel antibiotics continue to emerge, bacteria rapidly develop resistance, making infection control increasingly difficult. Given the lengthy drug development cycles and the potential for rapid resistance emergence, exploring alternative strategies to combat AMR has become imperative.

Despite laboratory evidence showing bacteria can rapidly develop resistance to antimicrobial drugs, treatment failure remains relatively rare in healthy individuals. This observation suggests that the host immune system may play a more important role than anticipated in combating resistant infections—not only limiting bacterial proliferation during treatment but even promoting their clearance (3). In this process, mechanisms linking innate and adaptive immunity may become key targets for novel therapies.

Mucosal-associated invariant T (MAIT) cells have attracted increasing attention due to their unique functions. These unconventional T cells are abundant in human blood and tissues, playing a central role in anti-infectious defense by recognizing microbial metabolites (4,5). This review systematically examines how MAIT cells influence the course of bacterial infections, particularly drug-resistant ones, and elucidates their mechanisms based on evidence from human

studies and animal models. We further dissect the molecular basis of MAIT cells' potent antimicrobial activity and propose that harnessing this versatile immune defense mechanism may provide a novel and efficient strategy against AMR.

Characteristics and Immunological Functions of MAIT Cells

MAIT cells represent a unique T cell subset that plays a critical role in anti-infectious immune defense (6). These cells are abundant in the lungs, liver, and circulatory system, enabling effective defense against pathogens invading these sites (6). Unlike conventional T cells, MAIT cells possess a semi-invariant T cell receptor (TCR) that recognizes antigens presented by the MHC class Ib molecule MR1 (6). Notably, the MR1 molecule is highly conserved among placental mammals, underscoring its central role in immune defense and confirming the importance of the MR1-MAIT cell system in immune surveillance.

The uniqueness of MAIT cells lies in their ability to recognize intermediate metabolites from the bacterial riboflavin (vitamin B2) synthesis pathway (7). These antigens are presented via MR1 molecules, enabling MAIT cells to target numerous bacteria dependent on riboflavin metabolism (6). Compared to other immune cells, MAIT cells possess a special capacity to recognize bacteria that evade immune surveillance. Due to the ubiquitous nature of the riboflavin synthesis pathway in bacteria, MAIT cells can mount rapid responses to various bacterial infections, constituting the first line of defense against infection.

Upon activation, MAIT cells exert immunomodulatory functions by releasing multiple cytokines, including interferon-γ, tumor necrosis factor, interleukin-17, and interleukin-22 (8-13). These cytokines promote inflammatory responses while providing tissue protection. Additionally, MAIT cells can directly kill infected cells (14) and inhibit bacterial growth (15-17), providing multiple layers of anti-infectious defense. Both animal models and clinical studies confirm that MAIT cells play important roles in controlling bacterial infections. Particularly in the context of escalating AMR, this multifunctional characteristic positions MAIT cells as key components of the immune system against microbial threats.

Mechanisms of MAIT Cells in Antimicrobial Immunity

MAIT cells have emerged as a key target for studying immune responses to both intracellular and extracellular bacterial infections. Although these cells play important roles in defending against various bacterial infections, their protective effects often vary depending on infection type and host immune status. Animal model studies reveal differential response characteristics of MAIT cells to different bacterial species: whether intracellular infections such as *Legionella longbeachae*, *Mycobacterium tuberculosis* (Mtb), *Mycobacterium bovis*, and *Francisella tularensis*, or extracellular infections such as *Escherichia coli* and *Klebsiella pneumoniae*, MAIT cells respond rapidly by producing pro-inflammatory

factors like IFNγ (18). However, this immune response is highly complex, and its protective effects are not always consistent.

In *L. longbeachae* infection models, MAIT cells accumulate and proliferate in the lungs, significantly promoting pathogen clearance. This protective effect becomes even more pronounced when MAIT cell function is enhanced using MR1 ligands combined with cytokines (19). In contrast, in *M. bovis* infection, MR1-deficient mice show higher bacterial loads, while MAIT cell activation through MR1 ligands effectively controls infection (17). However, the role of MAIT cells in *M. tuberculosis* infection is more complex: early studies found MAIT cells recruited to the lungs exert protective effects after Mtb infection (20), yet subsequent experiments showed that even pre-treatment with MR1 ligands to increase lung MAIT cell numbers failed to enhance resistance to subsequent Mtb challenge (15). This variability in protective efficacy may stem from the chronic nature of tuberculosis infection, which may require immune responses beyond the scope of MAIT cells alone.

Notably, these differences in MAIT cell functional performance may relate to the characteristics of chronic infections like tuberculosis, and mouse models may not fully recapitulate this complex process. *Mycobacterium tuberculosis* may persist in the host through specific immune evasion mechanisms, such as infected macrophages releasing immunosuppressive cytokines like IL-10 to inhibit MAIT cell responses (17). This phenomenon suggests that while MAIT cells can effectively control acute infections, their capacity to clear chronic or latent infections where bacteria employ immune evasion strategies is relatively limited.

In stark contrast, MAIT cells demonstrate significant protective effects against acute infections caused by Gram-negative bacteria such as *E. coli* and *K. pneumoniae* (21,22). In MR1-deficient mice lacking functional MAIT cells, such infections lead to more severe outcomes, including increased bacterial loads and mortality (23). These findings reveal the complexity of MAIT cell immune responses: their antimicrobial efficacy depends on both pathogen species and infection course (acute versus chronic). Different pathogens may have evolved strategies to counteract or evade MAIT cell activity, adding a new dimension to MAIT cell functional research.

As our understanding of MAIT cells deepens, we recognize that while these cells are powerful immune effectors, harnessing their full potential in chronic infection treatment may require developing more targeted regulatory strategies. This insight points future research toward establishing more precise infection models and exploring synergistic mechanisms between MAIT cells and other immune cells.

Insights from Human Immunodeficiency Diseases on Antimicrobial Functions of MAIT Cells: Key Revelations

Congenital immunodeficiency diseases provide a unique perspective for understanding the core role of MAIT cells in anti-bacterial defense (4). These genetic defects often impair immune system function, thereby highlighting the critical value of specific immune components like MAIT cells in infection defense.

A typical case involves immunodeficiency caused by MR1 gene mutation: a patient carrying a rare MR1 mutation exhibited complete absence of MAIT cells due to abnormal MR1 protein structure and transport defects, resulting in severe recurrent bacterial pneumonia and refractory *Campylobacter* gastroenteritis (24). The lack of MAIT cells likely represents a key factor in increased infection susceptibility, strongly confirming the protective role of MAIT cells against bacterial pathogens. Notably, this patient's immune system compensated by increasing $\gamma\delta$ T cell numbers, which share antimicrobial functions similar to MAIT cells (24). This discovery demonstrates both the plasticity of the immune system and the irreplaceable role of MAIT cells in resisting specific bacterial infections.

Another genetic study in Vietnamese adults identified an association between MR1 single nucleotide polymorphisms (SNPs) and tuberculosis susceptibility (25). This SNP may impair MAIT cell function by interfering with MR1 gene expression, thereby increasing infection risk (25). This finding reveals how genetic factors can influence infection susceptibility through effects on MAIT cell activity.

The clinical manifestations of STAT3 deficiency patients provide additional evidence for MAIT cell importance: these patients exhibit not only reduced MAIT cell numbers but also impaired IL-17 production capacity in residual MAIT cells (26,27). Since IL-17 plays a critical role in resisting pathogens such as *Staphylococcus aureus* and *Candida albicans*, these patients often struggle to control such infections (26,27). The defective IL-17 response indicates that MAIT cells participate not only in direct pathogen clearance but also in coordinating broader immune responses to suppress bacterial growth.

Mutations in the RORC gene, which encodes a key transcription factor for MAIT cell development, can lead to complete absence of functional MAIT cells, significantly increasing susceptibility to infections including *Candida albicans* and *Mycobacterium tuberculosis* (28). This lack of MAIT cells highlights their critical role in controlling specific infections and raises important scientific questions regarding interactions between MAIT cells and other immune cells such as invariant natural killer T (iNKT) cells (26,27). While iNKT cells are less abundant and their partial deficiency in these patients may exacerbate infections, the core defect remains the absence of MAIT cells (6).

These genetic findings also apply to diseases such as cystic fibrosis. For example, a cystic fibrosis patient with recurrent bacterial lung infections showed

near-complete absence of MAIT cells (29). Despite receiving potent antibiotic therapy and showing no other clear immune deficiencies, persistent infections were likely attributable to the lack of MAIT cell-driven immune responses. This case powerfully demonstrates that MAIT cells play an irreplaceable role in resisting bacterial pathogens even when other immune functions appear normal.

Genetic mutations that impair MAIT cell function have significant implications for human health, providing direct evidence for the central position of MAIT cells in anti-bacterial defense and suggesting that therapeutic strategies targeting MAIT cell activity may represent a new direction for addressing immunodeficiency and improving outcomes in patients with chronic bacterial infections.

Multidimensional Regulatory Role of MAIT Cells in Human Infection Response

Recent clinical studies demonstrate that the role of MAIT cells in infection extends far beyond simple pathogen response, exhibiting highly dynamic functional characteristics. During systemic bacterial infections, MAIT cells are rapidly activated with a significant decline in peripheral blood numbers (23,30-32). This reduction reflects both their directed migration to infection sites and implies their important function in fine-tuning immune responses during bacterial infection (33-38). Analysis of MAIT cell exhaustion and activation patterns in severe infections such as sepsis provides crucial clues about their interactions with the immune system (39). Notably, in critically ill patients, failure of MAIT cells to recover after initial infection often predicts significantly increased risk of secondary infection (35), highlighting the irreplaceable value of MAIT cells not only in immediate immune defense but also in preventing infectious complications.

Tissue-Specific Protection and Immunoregulatory Mechanisms: In localized infections such as community-acquired pneumonia, the enrichment of respiratory MAIT cells correlates inversely with disease severity (40), indicating that their tissue-localized activity is crucial for controlling bacterial dissemination and alleviating clinical symptoms. Controlled challenge experiments using *Salmonella Typhi* and *Shigella flexneri* confirm that MAIT cells exhibit dynamic responses during infection: they can recognize pathogens and initiate immune responses, then undergo numerical expansion and functional enhancement following bacterial stimulation (41-43). Particularly noteworthy is that strong MAIT cell activation correlates significantly with resistance to *Streptococcus pneumoniae* nasopharyngeal colonization, revealing a unique mechanism by which they reduce secondary infection risk by blocking bacterial colonization (40).

Clinical Translation Prospects: These findings collectively portray MAIT cells as multifaceted "regulatory hubs" of immune response: they dynamically adjust their numbers and activity according to infection stage and severity; provide bidirectional protection by participating in both acute defense and sec-

ondary infection prevention; exhibit tissue-specific patterns with differential protection modes at different infection sites; and may participate in establishing protective responses against reinfection. This understanding provides a theoretical basis for developing novel infection control strategies targeting MAIT cells, particularly for vulnerable high-risk patient populations with compromised immune function, where precise modulation of MAIT cell function may become a breakthrough for improving outcomes in bacterial infections.

Multidimensional Mechanisms of MAIT Cell Antimicrobial Immunity: Beyond Direct Killing

The antimicrobial functions of MAIT cells exhibit surprising complexity, extending far beyond simple pathogen clearance to encompass critical aspects of immune regulation and overall immune response coordination. While their cytotoxic effects have long been a research focus, emerging evidence indicates that MAIT cells are essentially highly adaptable immune modulators that manage infection progression through dual synergy of direct and indirect mechanisms.

Multimodal Features of Direct Killing Mechanisms: The core of MAIT cell antimicrobial function lies in their ability to directly attack infected cells, a process dependent on release of potent cytolytic proteins such as granzyme B (GrzB) and perforin (Prf) (14,42-45). However, compared to conventional cytotoxic cells like CD8+ T cells and natural killer (NK) cells, MAIT cells possess a unique antimicrobial protein expression profile—particularly their capacity to produce granulysin (Gnly) (46-49). This molecular configuration endows MAIT cells with dual killing advantages: clearing infected host cells and directly killing intracellular bacteria (such as *Mycobacterium tuberculosis*) through pore formation and membrane disruption mechanisms.

Molecular Cascade of Bacterial Clearance: The direct antimicrobial action of MAIT cells triggers an exquisite molecular cascade: initial membrane disruption by perforin forming transmembrane pores; penetration of effector molecules like GrzB into bacterial cytoplasm; lethal strikes destroying essential bacterial survival mechanisms such as energy metabolism and DNA repair; and synergistic clearance where dead bacteria are phagocytosed by other immune cells (51,52). This multilayered killing strategy not only improves bactericidal efficiency but also reduces opportunities for bacteria to develop resistance.

Molecular Barrier Function in Extracellular Bacterial Clearance: MAIT cells play a critical role in combating extracellular bacterial infections by releasing high concentrations of granulysin (Gnly) and granzyme B (GrzB) into surrounding tissues (53). This extracellular mode of action enables MAIT cells to form an "immune barrier" in the tissue microenvironment, effectively clearing free-living pathogens, and enhancing antimicrobial efficacy through IL-26 (an IL-10 family cytokine) (11,12). Notably, IL-26 can disrupt bacterial membrane structure similarly to Gnly, though its synergistic mechanisms with other immune molecules remain to be fully elucidated (54,55). This dual

mechanism of direct bacterial killing and cytokine regulation confers significant antimicrobial synergistic effects on MAIT cells.

Immune Microenvironment Reprogramming Function: The core value of MAIT cells extends far beyond direct pathogen clearance. At mucosal surfaces, IL-17/IL-22 production can stimulate antimicrobial peptide release, maintain mucosal barrier integrity, and enhance defense capabilities at portals such as the respiratory and digestive tracts (9,13,15,56). Through promoting dendritic cell maturation, MAIT cells bridge innate and adaptive immunity by inducing B cell differentiation into plasma cells and recruiting neutrophils and conventional CD4+ T cells (11,57). Recent research reveals that the immunobiological characteristics of MAIT cells endow them with unique capacity to recognize broad-spectrum microorganisms, hub functions in regulating multiple immune responses, and dual potential against both antibiotic-resistant bacteria and antifungal-resistant pathogens. This multitarget, multilayered defense characteristic positions MAIT cells as an important direction for developing novel therapeutic targets against drug-resistant bacterial infections.

The Growing Threat of Carbapenem-Resistant Enterobacteriaceae: A Global Health Crisis

Carbapenem-resistant Enterobacteriaceae (CRE) have become a major global health threat as multidrug-resistant Gram-negative pathogens. These pathogens have developed resistance to carbapenem antibiotics—once the last line of defense for treating severe bacterial infections. Carbapenems, as potent β-lactam antibiotics, target bacterial cell wall synthesis, but CRE renders these drugs completely ineffective through mechanisms including carbapenemase production, efflux pump activity, and altered cell membrane structure preventing antibiotic entry (58).

The danger of CRE lies in its ability to rapidly disseminate resistance genes among strains via mobile plasmids. This characteristic allows carbapenemase-producing Enterobacteriaceae to spread rapidly in hospital and community settings, causing infections that are extremely difficult or sometimes impossible to treat with existing antibiotics (58). CRE infections are often critically severe, with mortality rates far exceeding those caused by non-resistant bacteria, posing serious challenges to available treatment options.

Treatment options for CRE infections are worrisome. Last-resort antibiotics such as polymyxin B and polymyxin E (colistin) are frequently used despite significant toxicity. However, with the emergence of polymyxin-resistant CRE strains, treatment options are further limited, forcing physicians to rely on a few novel or experimental antibiotics—which are not always effective against these resistant pathogens (59,60). The widespread dissemination of CRE and its resistance to nearly all existing antibiotics urgently demand the development of completely new treatment and prevention strategies.

This crisis reflects the larger challenge in combating AMR: as bacteria continue

to evolve, our countermeasures are gradually becoming obsolete. The emergence of CRE highlights the deadly combination of bacterial adaptive evolution, healthcare-associated infections, and slow development of new antibiotics (14). As CRE continues to spread globally, we must prioritize coordinated efforts in rational antibiotic use, resistance surveillance, and rapid development of novel antimicrobial agents. Without these measures, we face a future where even common infections could become fatal.

Novel Strategies Using MAIT Cells to Combat CRE Infections

The unique ability of MAIT cells to recognize highly conserved microbial antigens makes them a powerful weapon against various drug-resistant bacteria, including CRE (14). By targeting conserved components of the bacterial riboflavin biosynthesis pathway, MAIT cells hold promise against resistant strains that are even unresponsive to last-resort antibiotics like carbapenems. Recent studies demonstrate that MAIT cells from healthy individuals can effectively recognize and respond to carbapenem-resistant *E. coli* (CREC) strains isolated from hospitalized patients, providing strong evidence that MAIT cells maintain robust antimicrobial defense capabilities even amid escalating antibiotic resistance (14).

The role of MAIT cells extends beyond recognition of CREC. Through MR1-dependent mechanisms and cytotoxic proteins such as granulysin (Gnly) and granzyme B (GrzB), they can effectively clear CREC-infected epithelial cells and significantly reduce bacterial loads. Critically, MAIT cells can also eliminate free-living CREC, which is essential for blocking infection transmission. These findings indicate that although CREC exacerbates clinical challenges of carbapenem resistance, they have not evolved mechanisms to escape MAIT cell killing and thus remain susceptible to the potent antimicrobial effects of MAIT cells.

This discovery provides important implications for developing novel immunotherapeutic strategies against CRE infections: enhancing or modulating MAIT cell function may open a new avenue to overcome current antibiotic resistance dilemmas. Particularly in cases where traditional antibiotic therapy fails, MAIT cell therapy could provide a crucial complementary treatment option.

An especially exciting highlight among these findings is that MAIT cell activity may synergize with carbapenem antibiotics. Studies show that granulysin (Gnly) and granzyme B (GrzB) secreted by MAIT cells can significantly enhance the bactericidal effect of carbapenems against CREC strains, reducing minimum inhibitory concentration (MIC) by 4-8 fold (14). This synergistic effect may arise from Gnly disrupting bacterial cell walls to facilitate carbapenem penetration, combined with direct bacterial killing by GrzB. This innovative mechanism for restoring antibiotic efficacy opens a new path for treating multidrug-resistant

infections—through MAIT cell action, antibiotics rendered ineffective by resistance can regain therapeutic value.

Overall, MAIT cells from healthy individuals exhibit robust and flexible antimicrobial responses against CREC, bringing new hope for fighting drug-resistant bacterial infections. Their ability to enhance carbapenem efficacy suggests an innovative therapeutic strategy: by activating host immune defense mechanisms, existing antibiotics can be revitalized to curb the spread of resistant infections. This breakthrough discovery paves the way for developing MAIT cell-based therapies or adjuvant treatments combining them with existing antibiotics, offering a promising new direction for future management of CRE and other resistant pathogens.

New Therapeutic Approaches Against CRE Infections

The emergence of CRE highlights the urgent need for novel treatment methods, especially for high-risk populations such as transplant recipients or chronically immunocompromised individuals (61). These patients often exhibit reduced MAIT cell numbers or impaired function, potentially increasing their susceptibility to resistant bacterial infections (5,6). This immunocompromised state, combined with disruption of normal flora due to long-term antibiotic use, creates conditions for resistant bacterial colonization and significantly elevates the risk of severe CRE infection.

Given the critical role of MAIT cells in antimicrobial defense, a highly promising strategy is to prevent CRE infection by restoring or enhancing MAIT cell activity in high-risk populations. Rather than relying solely on antibiotics, using MR1 ligands combined with cytokine stimulation to optimize MAIT cell populations may reverse immune defects and enhance their capacity to control bacterial growth. This approach could complement antibiotic therapy by both suppressing resistant bacterial proliferation and reducing CRE colonization. Recent evidence indicates that robust MAIT cell function in healthy populations correlates with protection against bacterial colonization, suggesting that enhancing MAIT cell responses may produce similar protective effects against CRE infection.

Preclinical studies confirm that MR1-presented agonists combined with IL-7 or Toll-like receptor (TLR) ligands can increase MAIT cell numbers and enhance their antimicrobial capacity, thereby effectively defending against bacterial infections (18,19,62). This provides potential intervention options for high-risk populations, particularly when combined with antibiotics. The ability of IL-7 to boost MAIT cell numbers in vivo further supports the clinical potential of cytokine therapy. Therefore, combined use of MR1 ligands and IL-7 may become an innovative therapeutic approach against resistant pathogens such as CRE (6).

However, when MAIT cells become persistently depleted or functionally impaired during acute infection, more direct intervention is required—adoptive

MAIT cell transplantation therapy. This therapy provides an "off-the-shelf" solution independent of patients' own immune reconstitution by infusing functional MAIT cells into MAIT cell-deficient patients. Due to their lack of donor restriction, MAIT cell therapy offers broader applicability than conventional T cell treatments. When combined with antibiotics such as carbapenems, adoptive MAIT cell transplantation can effectively address antibiotic resistance in CRE and significantly enhance the efficacy of existing treatment regimens (14).

Overall, treating CRE infections through enhancing or supplementing MAIT cells represents a breakthrough paradigm shift in antimicrobial therapy. Although related research remains in early stages, the combination of MAIT cell function enhancement with existing antibiotics holds promise for developing into innovative treatments against CRE infections and curbing the spread of AMR.

Challenges and Future Opportunities

The role of MAIT cells in antimicrobial immunity, particularly against multidrug-resistant (MDR) bacterial infections, has gained increasing attention. Growing evidence demonstrates that MAIT cells can not only recognize and respond to various bacterial pathogens but also effectively clear resistant strains, potentially bypassing some resistance mechanisms. Their cytotoxic effects mediated through proteins such as granulysin (Gnly) and granzyme B (GrzB) provide new avenues for direct killing of MDR bacteria. However, the key question is whether their efficacy will gradually diminish as bacteria evolve immune evasion capabilities.

Bacteria may counteract MAIT cell activity through various strategies, such as altering the riboflavin synthesis pathway, interfering with MR1 molecule transport, or producing superantigens/immunosuppressive cytokines to weaken MAIT cell function (63,64). These evasion mechanisms suggest that although MAIT cells are powerful weapons against resistant bacteria, their long-term efficacy may be limited by bacterial adaptive evolution. Urgent investigation is needed to determine whether bacteria will develop such immune evasion mechanisms under selective pressure from MAIT cells—especially considering bacteria's remarkable adaptive capacity.

Furthermore, the microenvironment of bacterial growth significantly influences MAIT cell function. Factors such as riboflavin availability and bacterial survival capacity under harsh conditions may alter the efficiency of MAIT cell recognition and pathogen killing. Future therapeutic applications must clarify how these environmental factors regulate MAIT cell activity and the stability of their antimicrobial effects across different infection scenarios.

Looking ahead, whether MAIT cells can overcome bacterial resistance to non-carbapenem antibiotics or effectively target atypical/intracellular pathogens remains unknown. Given their broad-spectrum antimicrobial potential against multiple bacteria, comprehensive exploration of their functional boundaries is essential. This may spur novel combination therapies that activate MAIT cells

to enhance existing antibiotic efficacy, thereby revolutionizing treatment strategies for resistant infections.

However, potential risks must be noted: in certain infections, MAIT cells may exacerbate immunopathological damage, limiting their therapeutic application. Therefore, a balance must be struck between antimicrobial benefits and tissue damage risk—particularly critical for drug-resistant infections. Preclinical studies and clinical trials are needed to validate their safety and efficacy while optimizing treatment regimens to maximize benefits and minimize harm. Ultimately, deeply dissecting the immune mechanisms by which MAIT cells combat resistant bacteria will become a central component in the fight against AMR. By synergistically applying MAIT cells with other therapeutic modalities, we may develop innovative treatments to address this globally urgent health challenge.

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Note: Figure translations are in progress. See original paper for figures.