Trends in Cancer

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Review

MAIT cells in gastrointestinal cancer: immunity to therapy

Yan-Ruide Li [1,2,3,*,#], Yuning Chen [1,2,#], Shelby Yeh [1,2], Thomas Yuen [1,2], and Lili Yang [1,2,3,4,5,6,7,*]

Mucosal-associated invariant T (MAIT) cells are emerging as important regulators of immunity in gastrointestinal (GI) cancers. Enriched in mucosal and hepatic tissues, MAIT cells recognize microbial-derived metabolites presented by MHC class I-related molecule (MR1) and rapidly exert effector functions, including cytokine production and cytotoxicity. Across GI malignancies, including hepatocellular carcinoma, cholangiocarcinoma, colorectal, gastric, pancreatic, and esophageal cancers, MAIT cells display context-dependent roles shaped by the tumor microenvironment, microbiome, and immune signaling pathways. While they can mediate antitumor immunity, they frequently exhibit functional exhaustion or adopt pro-tumorigenic phenotypes. Therapeutic strategies aim to enhance MAIT cell activity, reverse dysfunction, and integrate them into combinatorial immunotherapy approaches. Understanding MAIT cell biology may enable their exploitation as biomarkers and therapeutic targets in GI cancers.

Highlights

Mucosal-associated invariant T cells are enriched in mucosal and hepatic tissues and act as key immune sensors linking microbial-derived metabolites to gastrointestinal cancer immunity.

Across gastrointestinal cancers, mucosal-associated invariant T cells exhibit context-dependent roles, ranging from antitumor cytotoxicity to exhaustion or pro-tumorigenic inflammation.

Tumor microenvironment signals, including checkpoint pathways and microbial dysbiosis, critically shape mucosal-associated invariant T-cell function and fate.

Emerging strategies aim to enhance mucosal-associated invariant T-cell antitumor activity via cytokine priming, MHC class I-related molecule targeting, and combinatorial immunotherapy approaches.

Mucosal-associated invariant T cells hold promise as biomarkers and therapeutic targets, but their functional heterogeneity presents key translational challenges.

MAIT cells are emerging as key immune players in GI cancers

Gastrointestinal (GI) cancers comprise a heterogeneous group of malignancies arising within the digestive tract and associated organs, including the esophagus, stomach, colorectum, liver, and pancreas [1,2]. Collectively, these cancers represent a substantial global health burden, accounting for a significant proportion of cancer incidence and mortality worldwide, with colorectal, gastric, and liver cancers ranking among the leading causes of cancer-related deaths [3]. Beyond their clinical prevalence, GI malignancies are characterized by pronounced immunological complexity shaped by constant exposure to dietary antigens, **commensal microbiota** (see Glossary), and microbial metabolites within the mucosal environment [4,5]. This unique interface fosters a **tumor microenvironment (TME)** that is highly dynamic and immunologically regulated, in which host–microbe interactions play a pivotal role in tumor initiation, progression, and response to therapy [6].

In this context, mucosal-associated invariant T (MAIT) cells have emerged as important immune effectors in GI cancers. Human MAIT cells are innate-like T lymphocytes characterized by a **semi-invariant T-cell receptor (TCR)**, typically comprising a conserved TRAV1-2–TRAJ33/12/20 (TCR alpha variable 1-2–TCR alpha joining 33/12/20) α-chain paired with a limited repertoire of β chains, conferring restricted **TCR clonality** [7–9]. They recognize microbial-derived vitamin B2 (riboflavin) biosynthesis intermediates [10–12], most notably 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) and related metabolites, presented by the monomorphic MHC class I-related molecule MR1 [13–16]. This antigen specificity positions MAIT cells at the interface between microbial sensing and immune surveillance (Box 1). MAIT cells are highly enriched in mucosal and hepatic compartments, constituting ~1–10% of peripheral blood T cells, up to 20–50% of intrahepatic T cells, and a substantial fraction of T cells within the intestinal lamina propria [22,23], reflecting their specialized role in barrier tissues [24–26].

[1]Department of Microbiology, Immunology and Molecular Genetics, University of California, Los Angeles, CA 90095, USA
[2]Department of Bioengineering, University of California, Los Angeles, CA 90095, USA
[3]Goodman-Luskin Microbiome Center, Los Angeles, CA 90095, USA
[4]Molecular Biology Institute, University of California, Los Angeles, CA 90095, USA
[5]Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, University of California, Los Angeles, CA 90095, USA
[6]Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California, Los Angeles, CA 90095, USA

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[7]Parker Institute for Cancer Immunotherapy, University of California, Los Angeles, CA 90095, USA
[#]These authors contributed equally

*Correspondence:
charlie.li@ucla.edu (Y.-R. Li) and liliyang@ucla.edu (L. Yang).

Functionally, MAIT cells rapidly exert effector responses upon activation, including the production of proinflammatory cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-17 (IL-17), as well as cytotoxic mediators including granzyme B and perforin, enabling them to directly lyse infected or transformed cells [27–29]. In the TME, their roles appear context-dependent and multifaceted. On the one hand, MAIT cells can contribute to antitumor immunity through cytokine-mediated activation of other immune cells and direct cytotoxicity against MR1-expressing tumor cells [30]. On the other hand, accumulating evidence indicates that MAIT cells may also adopt pro-tumorigenic functions, for example, through IL-17 production, which can promote chronic inflammation, angiogenesis, and tumor progression, or through functional skewing driven by tumor-derived signals and microbial **dysbiosis** [31–33]. Moreover, in hepatocellular carcinoma (HCC), **tumor-associated macrophages (TAMs)** have been shown to induce MAIT cell dysfunction and exhaustion via immune checkpoint pathways, particularly through programmed death-ligand 1 (PD-L1)–programmed cell death protein-1 (PD-1) interactions, leading to impaired cytokine production and reduced cytotoxic capacity [34,35]. Collectively, these findings highlight the dual and context-dependent roles of MAIT cells in GI cancers. A deeper understanding of MAIT cell biology within the TME may therefore uncover novel mechanisms of disease progression and inform the development of targeted immunotherapeutic strategies.

In this review, we summarize current insights into MAIT cell biology and their roles in GI cancers (Table 1 and Figure 1). We discuss MAIT cell distribution, infiltration patterns, and functional states across GI malignancies, highlighting their dual pro- and antitumor activities within the TME and their crosstalk with immune and tumor cells. We also examine the clinical relevance of MAIT cells, including associations with disease progression and patient outcomes, and discuss emerging therapeutic strategies aimed at modulating MAIT cell function, underscoring their potential as biomarkers and targets for immunotherapy in GI cancers.

MAIT cells in GI cancer immunity

Hepatocellular carcinoma

MAIT cells are of particular interest in HCC due to the unique immunological environment of the liver. As a barrier organ continuously exposed to gut-derived microbial products via the portal circulation, the liver is highly enriched in MAIT cells, which can comprise 20–50% of intrahepatic T cells under physiological conditions (Table 1). This abundance, together with their capacity to sense microbial metabolites presented by MR1, positions MAIT cells as key mediators at the interface between immunity, inflammation, and tumorigenesis. HCC typically arises in the context of chronic liver inflammation, driven by viral **hepatitis**, alcohol-related liver disease, or metabolic dysfunction, making immune regulation a central determinant of disease initiation, progression, and therapeutic response [48–50].

Multiple studies have demonstrated that MAIT cells are numerically and functionally altered in HCC. A significant reduction in MAIT cell frequency was observed in both the peripheral blood and liver tissues of patients with HCC compared with healthy controls [37]. This decrease was accompanied by impaired effector function, as evidenced by reduced IFN-γ production. Phenotypically, circulating MAIT cells exhibited increased expression of activation and exhaustion markers, including human leukocyte antigen–DR isotype (HLA-DR) and PD-1, whereas intrahepatic MAIT cells displayed distinct activation profiles [37]. Notably, MAIT cells remained relatively enriched in liver compartments compared with peripheral blood, suggesting tissue-specific regulation. Single-cell transcriptomic analyses further demonstrated that intrahepatic MAIT cells in HCC undergo extensive transcriptional reprogramming. Specifically, MAIT cells exhibited increased expression of cytotoxicity- and activation-associated genes, including *GZMB*,

GZMH, *TNF*, *BIRC3*, and the inhibitory receptor *LAG3*, while genes associated with homeostatic maintenance and survival, such as *IL7R*, *PFN1*, *VIM, H1FX*, and *CD52*, were downregulated, consistent with a transition toward an activated yet dysfunctional or exhausted phenotype [37]. Gene Ontology analysis further revealed enrichment of pathways involved in translational initiation, mRNA metabolic processes, and apoptotic signaling, suggesting increased metabolic and biosynthetic activity accompanied by cellular stress and reduced functional fitness within the TME [37].

Consistent with these findings, another study demonstrated that although MAIT cells are less abundant in tumor tissues compared with adjacent liver tissue, they remain a prominent T-cell subset within the HCC microenvironment relative to other mucosal sites [35]. Tumor-infiltrating MAIT cells displayed an effector memory phenotype ($CCR7^{-}CD45RA^{-}CD45RO^{+}CD95^{+}$) but exhibited marked functional impairment. Specifically, these cells showed reduced production of key effector molecules, including IFN-γ, IL-17, granzyme B, and perforin, alongside diminished co-stimulatory capacity [35]. Instead, they were skewed toward a tumor-promoting phenotype, characterized by increased secretion of cytokines such as IL-8. This functional shift was associated with upregulation of inhibitory receptors, including PD-1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), and transcriptional reprogramming involving downregulation of cytotoxic pathways (e.g., Nuclear factor kappa B subunit 1 [NFKB1] and Signal transducer and activator of transcription 5B [STAT5B]) and upregulation of genes linked to tumor progression (e.g., IL-8, C-X-C motif chemokine ligand 12 [CXCL12], and TIM-3) [35]. Importantly, high MAIT cell infiltration in HCC tumors correlated with poorer clinical outcomes, suggesting that their functional state, rather than their abundance alone, may determine their impact on disease progression.

Further insight into the mechanisms underlying MAIT cell dysfunction in HCC has been provided by studies examining cellular interactions within the TME. High-dimensional imaging, flow cytometry, and single-cell RNA sequencing analyses of human and murine liver cancer models revealed reduced MAIT cell infiltration into tumor cores and a progressive loss of cytotoxic function within the TME [34]. A key finding was the identification of TAMs, particularly $PD\text{-}L1^{+}$ subsets, as critical regulators of MAIT cell activity. Spatial and functional analyses demonstrated that $PD\text{-}L1^{+}$ TAMs engage MAIT cells through PD-1–PD-L1 interactions, promoting exhaustion and functional impairment [34,51,52]. Importantly, disruption of this crosstalk, either through macrophage-targeted approaches or immune checkpoint blockade (anti-PD-1/PD-L1), partially restored MAIT cell effector function in experimental models [34]. Interestingly, despite evidence of dysfunction, MAIT cell gene signatures were associated with improved survival in some patient cohorts, highlighting the complexity and potential context dependence of their role in HCC.

A recent study observed a significant enrichment of MAIT cells within relapsed tumor regions, accompanied by a pronounced shift toward dysfunctional phenotypes [36]. Relapsed MAIT cells exhibited reduced expression of inflammatory and cytotoxic genes, alongside enhanced interactions with malignant hepatocytes, suggesting a role in shaping relapse-associated tumor biology. Clinically, high MAIT cell signature scores in relapsed HCC were associated with poorer overall survival (OS), reinforcing the link between MAIT cell dysregulation and adverse outcomes [36].

Collectively, these studies highlight the multifaceted and context-dependent roles of MAIT cells in HCC. One possible explanation for these contradictory findings is that MAIT cell abundance alone may not predict clinical outcomes. Rather, the balance between cytotoxic MAIT1-like and IL-17-producing MAIT17-like states, together with local microbial composition and immune checkpoint signaling, is likely to determine whether MAIT cells exert antitumor or protumor functions.

Glossary

Barrett's esophagus (BE): a premalignant condition in which normal esophageal epithelium is replaced by intestinal-like cells due to chronic acid reflux, increasing the risk of EAC.
Carcinoembryonic antigen (CEA): a glycoprotein involved in cell adhesion that is normally expressed during fetal development but becomes elevated in certain cancers (e.g., CRC), making it a commonly used tumor biomarker for diagnosis and monitoring.
Commensal microbiota: the community of non-harmful microorganisms that naturally reside in the body (e.g., the gut and skin), contributing to host metabolism, immune regulation, and the maintenance of tissue homeostasis.
Dysbiosis: an imbalance or disruption in the composition and function of microbial communities, particularly in the gut, that is associated with disease or altered host health.
Hepatitis: inflammation of the liver, often caused by viral infection, alcohol use, or metabolic disorders, and is a major risk factor for HCC.
Immune surveillance: the process by which the immune system monitors and detects abnormal or transformed cells, including cancer cells, to eliminate them and maintain tissue homeostasis.
Semi-invariant T-cell receptor (TCR): a TCR with limited variability, typically composed of a conserved α-chain paired with restricted β chains, enabling recognition of a narrow range of antigens, such as MR1-presented metabolites.
TCR clonality: the diversity or uniformity of TCR sequences within a T-cell population, reflecting the extent of antigen-specific expansion.
Tumor-associated macrophages (TAMs): a heterogeneous population of macrophages within tumors that can either promote or suppress antitumor immunity, depending on their activation state and microenvironmental cues.
Tumor microenvironment (TME): the complex cellular and molecular environment surrounding a tumor, including immune cells, stromal cells, blood vessels, and signaling molecules that influence tumor growth and immune responses.

Box 1. Mechanisms of microbiota sensing by MAIT cells in GI cancers

The development and function of MAIT cells are critically dependent on the microbiota. Studies in germ-free (GF) mice have demonstrated markedly reduced MAIT cell numbers compared with those in SPF mice, indicating that microbial exposure is essential for MAIT cell development, particularly during thymic maturation [13,17]. Consistently, only commensal bacteria capable of riboflavin (vitamin B2) biosynthesis generate ligands that activate MAIT cells, with highly stimulatory species enriched in the *Bacteroidetes* and *Proteobacteria phyla* [18].

In GI cancers, MAIT cells sense microbiota primarily through microbial-derived metabolites, antigen presentation, and tissue accessibility. Commensal and tumor-associated bacteria produce riboflavin pathway intermediates, such as 5-OP-RU, which are potent ligands for MAIT TCRs. Multiple mechanisms enable these metabolites, or the microbes themselves, to access tumor tissues (Figure I). First, tumor-associated inflammation disrupts intestinal epithelial integrity, resulting in increased permeability ('leaky gut') that allows microbial metabolites to diffuse into the lamina propria and surrounding tissues [19,20]. Second, small metabolites can be absorbed into the circulation and transported via the portal vein, providing a direct route to liver tumors [21]. Third, microbial translocation may occur, whereby bacteria or their products cross the epithelial barrier and disseminate into local tissues or systemic circulation. Fourth, many GI tumors harbor tumor-associated microbiota, which can serve as a local and continuous source of microbial metabolites within the TME [4]. Finally, antigen-presenting cells (APCs), such as macrophages and dendritic cells, can internalize microbial products in the gut and transport them to tumor sites.

Microbiota regulate MAIT cells through both direct and indirect mechanisms. Direct activation occurs when riboflavin biosynthesis-competent bacteria generate unstable intermediates that are converted into potent MR1 ligands, such as 5-OP-RU, which are presented by APCs and recognized by the invariant MAIT TCR. In contrast, bacteria lacking the riboflavin biosynthetic pathway can indirectly activate MAIT cells by stimulating pattern-recognition receptors, including Toll-like receptors, on APCs. This promotes the release of inflammatory cytokines, particularly IL-12 and IL-18, which activate MAIT cells independently of TCR engagement and synergize with MR1 signaling to enhance effector responses. In addition, activating natural killer (NK)-cell receptors, such as NKG2D, can further modulate MAIT cell effector responses through the recognition of stress-induced ligands expressed by transformed cells. Dysbiosis may reflect both alterations in the abundance of riboflavin pathway-competent bacterial taxa, which influence MR1 ligand availability, and broader inflammatory remodeling of the microbiota that promotes cytokine-driven MAIT cell activation.

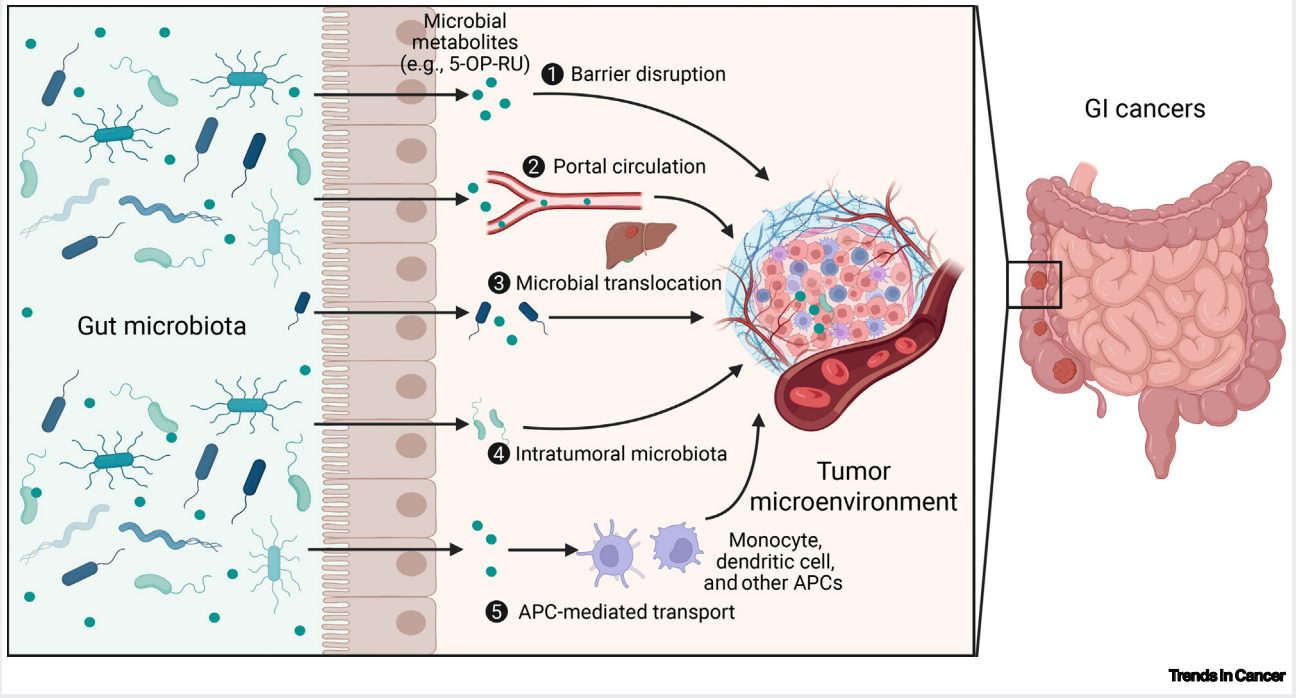

Figure I. Microbial-derived riboflavin metabolites access GI tumors via barrier disruption, circulation, or the local microbiota, are presented by MR1 on APCs, and activate MAIT cells within the TME. The figure was created using BioRender (biorender.com).

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a highly aggressive malignancy arising from the epithelial cells of the intrahepatic and extrahepatic bile ducts. It is characterized by late diagnosis, limited treatment options, and poor prognosis [53,54]. Although immunotherapy has demonstrated efficacy in several solid tumors, its success in CCA has been relatively modest, reflecting the complex and

Table 1. Biology and immunity of MAIT cells in GI cancers

Cancer type	Sample source	MAIT cell frequency	Phenotype	Functionality	Clinical correlation	Refs
HCC	Tumor tissues, including tumor core and adjacent liver tissues	~2% of T cells in tumor core and ~20% in adjacent liver	Upregulated PD-1, CD25, and HLA-DR, with reduced CD56 expression in the tumor core	Impaired cytotoxicity; tumor-induced dysfunction with aberrant activation; interaction with $CSF1R^+$ $PD\text{-}L1^+$ TAMs contributes to MAIT cell dysfunction	MAIT cell gene signature is associated with better survival in patients with HCC	[34]
	PBMCs, adjacent tissues, and tumor tissues	~0.5% of T cells in PBMCs, ~20% in adjacent liver, and ~3% in tumors	Tumor-derived MAIT cells exhibit a $CCR7^-CD45RA^-CD45RO^+CD95^+$ effector memory phenotype, with upregulated inhibitory receptors including PD-1, CTLA-4, and TIM-3	Reduced costimulatory and effector functions; decreased secretion of IFN-γ and IL-17; minimal production of granzyme B and perforin; increased production of tumor-promoting cytokines such as IL-8, indicating functional reprogramming toward a tumor-promoting phenotype	High MAIT cell infiltration in HCC is associated with unfavorable clinical outcomes	[35]
	Tumor samples from primary and relapsed patients with HCC	~6% of T/NK cells in primary tumors, and ~13% of T/NK cells in relapsed tumors	Relapsed tumor-derived MAIT cells exhibit an upregulation of CXCR4, CCR6, TGFB1, and WNT1 compared with primary tumor-derived MAIT cells	Relapsed tumor-derived MAIT cells exhibited a decrease in inflammation related pathways and effector functions compared with primary tumor-derived MAIT cells; there was a marked decrease in *GNLY*, *TNF*, *IFNG*, *CD40LG*, and *GZMH* levels	High relapsed MAIT cell signature scores are associated with a reduced overall survival	[36]
	Peripheral blood samples and liver-associated mononuclear cells extracted from liver perfusions of donors and patients with HCC	~3% of total T cells in healthy controls, and less than 1% of total T cells in patients with HCC	MAIT cells from peripheral blood samples of patients with HCC express higher levels of PD-1, IL-6, GM-CSF than healthy controls	After IL-12 +IL-18 stimulation, HCC MAIT cells exhibited reduced IFN-γ, IL-1b, TNF-α levels compared with the healthy controls, indicating impaired MAIT cell function in patients with HCC	The proportion of perfusate MAIT cells was significantly associated with aspartate aminotransferase and alanine aminotransferase levels, which may correlate with poor clinical outcome	[37]
CCA	PBMCs, normal liver, tumor margin, and tumor tissues	~0.9% of total cells in blood, ~20% in normal liver, ~10% in tumor margin, and ~5% in tumor	Tumor-infiltrating MAIT cells express high levels of tissue-residency markers (CD69 and CD103); no significant differences in PD-1, CD25, HLA-DR, or granzyme B compared with peripheral MAIT cells; reduced expression of CD56, CCR6, and CXCR6 in tumor MAIT cells	Tumor-infiltrating MAIT cells exhibit increased proliferative capacity compared with liver-resident counterparts, as indicated by higher Ki-67 expression	High MAIT cell abundance in CCA livers is associated with favorable prognosis, including improved long-term survival and a beneficial antitumor immune signature	[38]

(continued on next page)

Table 1. (continued)

Cancer type	Sample source	MAIT cell frequency	Phenotype	Functionality	Clinical correlation	Refs
CRC	Healthy colon and tumor tissues	~1% of T cells in healthy colon and ~2.5% in tumors	Increased MAIT cell density and proportion among tumor-infiltrating T cells, with notable interpatient variability	Not reported	Higher MAIT cell infiltration is associated with poorer survival in patients with CRC	[32]
	Colon adenocarcinomas and unaffected colon lamina propria	~1% of $CD45^+CD3^+CD4^-TCR\gamma\delta^-$ T cells in unaffected colon lamina propria and ~2.5% in tumors	Colonic MAIT cells displayed an activated memory phenotype with expression of CCR6 and CCR9. In unaffected colon, most MAIT cells produced IFN-γ, while only a few produced IL-17; they also produced TNF-α, IL-2, and granzyme B.	Tumor-infiltrating MAIT cells exhibited significantly reduced IFN-γ production compared with unaffected colon, whereas production of TNF-α, IL-2, IL-17, and granzyme B was largely unchanged. Tumor-derived soluble factors suppressed MAIT cell IFN-γ production *in vitro*, indicating functional inhibition by the TME.	MAIT cells infiltrate colon tumors but exhibit impaired IFN-γ production, suggesting that although they have antitumor potential, the TME suppresses their effector function.	[39]
	PBMCs, adjacent tissues, and tumor tissues	~2% of T cells in PBMCs, ~2% in adjacent tissues, and ~2% in tumor	Presence of a tumor-infiltrating MAIT cell subset expressing CD4 and Foxp3, with elevated CD39 expression	Tumor-infiltrating MAIT cells exhibit phenotypic and functional exhaustion; high bacterial infiltration in CRC tumors can activate MAIT cells in a TCR-dependent manner	MAIT cell responses to microbial antigens in CRC highlight potential opportunities to modulate MAIT cells or the microbiome for therapeutic benefit	[33]
	Murine tumor samples	Not reported	Upregulated levels of CD69 and eotaxin-1 after *in vitro* stimulation with 5-A-RU/MGO compared with unstimulated MAIT cells	Increased IFN-γ, IL-17, and GM-CSF were observed from MAIT cell-treated tumor samples compared with controls; *in vitro* validation of stimulated MAIT cells upheld these results.	Associated with increased production of proinflammatory and eosinophil-modulating cytokines	[40]
	Peripheral blood, serum, and tumor tissues	~12% of T cells in the peripheral blood in patients with colon cancer, and ~6% of T cells in the peripheral blood in healthy patients	Increased expression of CD161 in tumor tissues compared with non-tumor tissues; KLRB1, the coding gene for CD161, is positively associated with *CTLA4*, *PDCD1*and *CD274*	Increased levels of IL-17A and IFN-γ were detected in the serum	MAIT cells could be used as a biomarker for deciding if patients could be treated with immune checkpoint inhibitors	[41]
	Tumor tissues, including samples from the center and peripheral regions; tissue samples from unaffected regions of the colon	~1% of T cells in unaffected colon, colon tumors, and peripheral blood	Among $PD\text{-}1^+$ MAIT cells, tumor-derived cells had more PD-1 than unaffected tissue-derived MAIT cells; tumor-derived MAIT cells also had higher levels of Tim-3.	Significantly reduced levels of IFN-γ production in MAIT cells from tumor tissues compared with those from unaffected tissues	Reduced effector functions correlate with impaired patient outcome	[42]
	Whole blood collection and tissue samples from healthy liver	~30% of T cells in healthy tissues, and ~20% of T cells in tumor tissues	Not reported	Tumor-infiltrating MAIT cells have a dramatic decrease in IFN-γ production	MAIT cells are not rendered dysfunctional because of chemotherapy, and	[43]

Table 1. (continued)

Cancer type	Sample source	MAIT cell frequency	Phenotype	Functionality	Clinical correlation	Refs
	cells and tumors			after stimulation with rIL-12/rIL18, SEB, or Klebsiella lysate; a reduced proportion of GZMB$^+$ MAIT cells in tumor samples, indicating impaired effector function and responsiveness to stimuli	therefore, they may be attractive therapeutic options to combine with chemotherapeutic agents	
GC	PBMCs	~0.3% of total cells in blood	Reduced frequency of circulating MAIT cells in peripheral blood of patients	Preserved production of proinflammatory cytokines, including IFN-γ, IL-17, and TNF-α	Decreased circulating MAIT cell levels are associated with disease progression in GC	[44]
	PBMCs	~2% of T cells in the peripheral blood of healthy patients ~1% of T cells in the peripheral blood of patients with GC	Decreased proportions of CD4$^-$CD8$^+$ MAIT cells compared with healthy controls	Decreased levels of GZMB in cancer patients compared with healthy controls	MAIT cells may conduct immune surveillance of GC. However, they did not correlate well with biomarkers for GC progression	[45]
Pancreatic cancer	Tumor tissues from patients with PDAC	~19/HPF in patients with stage I or stage II tumor differentiation ~15/HPF in patients with stage III tumor differentiation	Display CD161^{high}CD8$^+$ phenotype	CD161$^+$CD8$^+$ T cells have higher levels of TNF-α, IFN-γ, granzyme B, and perforin, compared with the CD161$^-$CD8$^+$ subset	CD161$^+$CD8$^+$ T cells significantly associate with tumor differentiation, perineural invasion, and serum CA19-9 levels. Data may be combined with CA19-9 data to predict survival and response to adjunctive chemotherapy	[46]
Esophageal cancer	Esophagogastric tissues samples and whole blood collections	~3% of whole blood in healthy patients, ~1% of whole blood in patients with BE, ~2% of whole blood in patients with EAC, and MAIT cells are enriched in tumor samples compared with blood	Across all tissue types, PD-1 levels were significantly elevated in oesophageal tissue compared with the blood; NKG2D expression was reduced in EAC tumor tissues compared with BE or control groups.	Decreased levels of IFN-γ and TNF-α when exposed to tumor-conditioned media	MAIT cells show an inverse relationship with circulating IP-10 levels and are found at higher levels in tumors of node-negative patients, though they are not significantly linked to other clinical parameters	[47]

HPF: high power field in immunofluorescence; CSF1R : colony-stimulating factor 1 receptor-positive; Foxp3: forkhead box P3; GM-CSF: granulocyte-macrophage colony-stimulating factor; GZMB: granzyme B; IP-10: interferon gamma-induced protein 10; MGO: methylglyoxal; rIL-12/rIL-18, recombinant interleukin-12/recombinant interleukin-18: SEB: staphylococcal enterotoxin B; TGFβ1: transforming growth factor beta 1; Tim-3: T-cell immunoglobulin and mucin domain-containing protein 3; WNT1: Wnt family member 1.

often immunosuppressive TME. MAIT cells are strategically positioned near the biliary epithelium, where they are exposed to microbial-derived metabolites and may contribute to **immune surveillance** in this tissue.

Recent studies have provided important insights into the distribution, phenotype, and clinical relevance of MAIT cells in CCA (Table 1). Comprehensive analyses of patient samples, including peripheral blood, normal liver tissue, tumor margins, and tumor cores, revealed a progressive

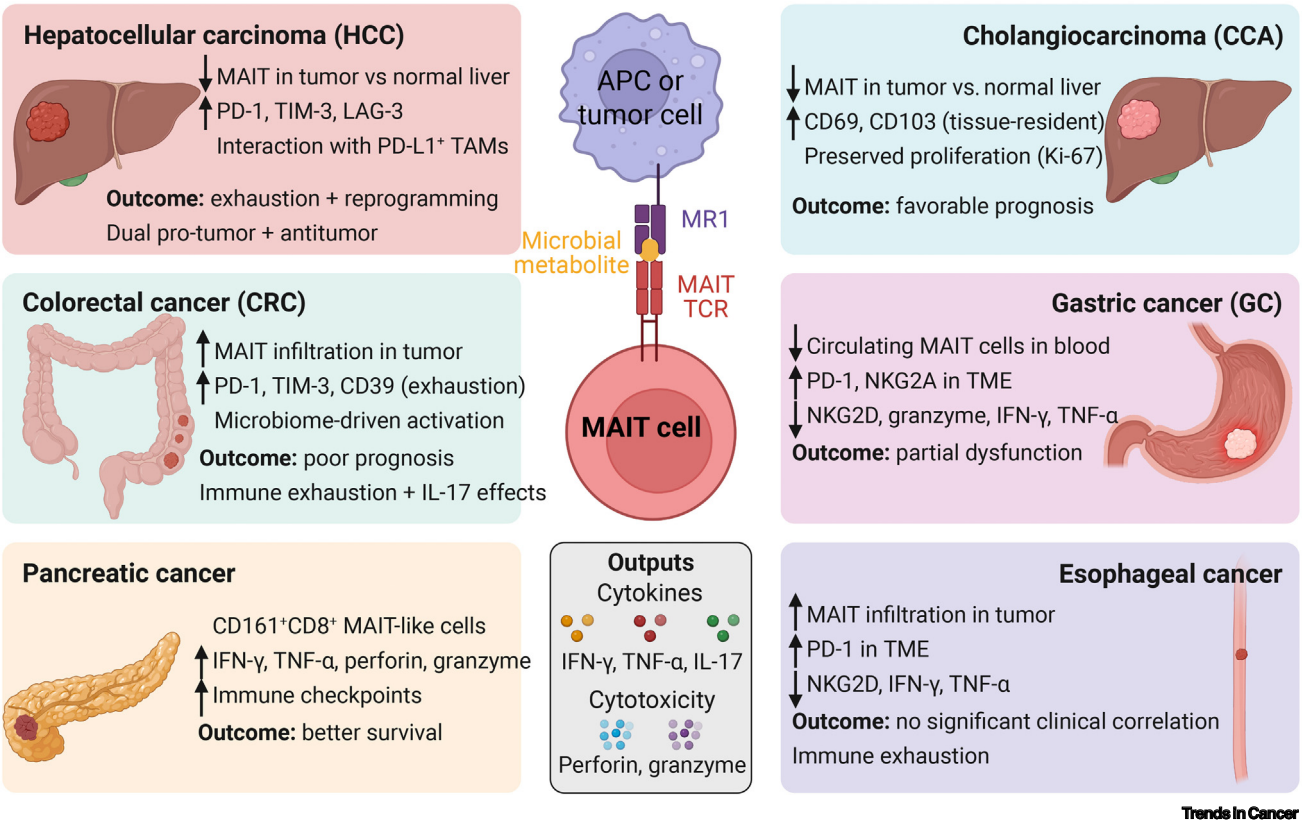

Figure 1. Context-dependent roles of MAIT cells across GI cancers. MAIT cells recognize microbial-derived metabolites presented by MR1 and exert effector functions, including cytokine production (IFN-γ, TNF-α, and IL-17) and cytotoxicity (granzyme B and perforin). Their roles vary across GI cancers depending on the TME. In HCC, MAIT cells are abundant but exhibit exhaustion driven by PD-1–PD-L1 interactions with tumor-associated macrophages. In CCA, MAIT cells display tissue-resident features and are associated with a favorable prognosis. In CRC, they are enriched but functionally exhausted and linked to poor outcomes, partly driven by the microbiota. In GC, circulating MAIT cells decrease due to tumor recruitment and show partial dysfunction. In PDAC, $CD161^{+}CD8^{+}$ MAIT-like cells retain cytotoxicity and predict better survival. In EAC, MAIT cells infiltrate tumors but exhibit checkpoint-mediated inhibition. Overall, MAIT cell function is shaped by microbial signals, inflammation, and immune checkpoint pathways. The figure was created using BioRender (biorender.com). APC: antigen-presenting cell; CCA: cholangiocarcinoma; CRC: colorectal cancer; EAC: esophageal adenocarcinoma; GC: gastric cancer; GI: gastrointestinal; IFN-γ: interferon-gamma; IL-17: interleukin-17; MAIT: mucosal-associated invariant T; MR1: MHC class I-related molecule; PD-1: programmed cell death protein 1; PDAC: pancreatic ductal adenocarcinoma; PD-L1: programmed death-ligand 1; TAMs: tumor-associated macrophages; TCR: T-cell receptor; TIM-3: T-cell immunoglobulin and mucin domain-containing protein 3; TME: tumor microenvironment; TNF-α: tumor necrosis factor-alpha; LAG-3: lymphocyte activation gene 3; NKG2A: natural killer group 2 member A; NKG2B: natural killer group 2 member B.

decline in MAIT cell frequency from normal liver (~20%) to the tumor margins (~10%) and tumor tissue (~5%) [38]. This reduction suggests either impaired recruitment or local depletion of MAIT cells within the tumor site. One proposed mechanism underlying this observation is chronic microbial stimulation, as CCA tumors exhibit increased bacterial presence alongside preserved MR1 expression, potentially leading to sustained antigen exposure and subsequent MAIT cell exhaustion or attrition [25,38,55,56].

Phenotypically, tumor-infiltrating MAIT cells in CCA display features consistent with tissue residency, including elevated expression of CD69 and CD103, supporting their localization within the tumor niche. Interestingly, unlike in HCC, these cells do not exhibit substantial upregulation of classical exhaustion markers such as PD-1, CD25, or HLA-DR [38]. However, they do show reduced expression of chemokine receptors such as C-C chemokine receptor type 6 (CCR6) and C-X-C chemokine receptor type 6 (CXCR6), which may influence their migratory capacity

and positioning within the TME [38]. Functionally, CCA-associated MAIT cells demonstrate preserved or even enhanced proliferative potential, as indicated by increased Ki-67 expression, suggesting that they retain a degree of responsiveness despite changes in their frequency and phenotype.

Importantly, the clinical implications of MAIT cells in CCA appear to differ from those observed in HCC. High intratumoral MAIT cell abundance has been consistently associated with favorable clinical outcomes, including improved long-term survival, particularly in patients with intrahepatic CCA (Table 1). This positive prognostic association is further supported by the observation that MAIT cell-rich tumors exhibit immune signatures indicative of active antitumor responses. These findings suggest that, in contrast to the frequently dysfunctional or tumor-promoting roles described in HCC, MAIT cells in CCA may contribute to effective immune surveillance and tumor control.

Colorectal cancer

Beyond liver malignancies, colorectal cancer (CRC) represents one of the most extensively studied contexts for MAIT cell biology, largely due to the intimate relationship between the intestinal mucosa, the microbiome, and immune regulation (Figure 1) [57–59]. The colon harbors a dense and diverse microbial community, providing continuous antigenic stimulation that is highly relevant for MAIT cells, which recognize microbial riboflavin metabolites presented by MR1. This unique microenvironment positions MAIT cells as important mediators at the interface between host immunity and microbial signals in CRC pathogenesis.

Accumulating evidence indicates that MAIT cells are enriched in CRC tumors and that their presence is associated with disease progression. A significant, though variable, increase in MAIT cell infiltration in tumor tissue compared with adjacent healthy mucosa has been reported [32]. This increase was observed both in absolute density and as a proportion of total tumor-infiltrating lymphocytes. Importantly, higher intratumoral MAIT cell abundance was associated with poorer clinical outcomes, as demonstrated by survival analyses and multivariate models [32]. These findings suggest that MAIT cells may serve as a prognostic biomarker in CRC and that their inclusion in immune profiling of tumor-infiltrating lymphocytes could enhance disease monitoring and risk stratification.

Consistent with these observations, alterations in circulating MAIT cells have also been described in patients with CRC. There was an increased frequency of multiple MAIT cell subsets ($CD4^+$, $CD8^+$, and double-negative populations) in the peripheral blood of patients with colon cancer than healthy controls [41]. In tumor tissues, elevated expression of CD161, a canonical MAIT cell marker encoded by *KLRB1*, was observed, with *KLRB1* expression positively correlating with immune inhibitory molecules such as PD-1, CTLA-4, TIM-3, and PD-L1 [41]. These associations suggest that MAIT cells in CRC are linked to immunosuppressive signaling pathways. Additionally, correlations between circulating MAIT cells and serum IFN-γ and **carcinoembryonic antigen (CEA)** levels further support their involvement in systemic immune responses in CRC [41].

Despite their increased presence, tumor-infiltrating MAIT cells in CRC frequently exhibit features of functional exhaustion. A recent study identified a population of MAIT cells within colon tumors characterized by a PD-1^{high} Tim-3^+ $CD39^+$ phenotype, indicative of terminal exhaustion [42]. These cells displayed reduced polyfunctionality, including diminished production of key effector cytokines and cytotoxic mediators. Notably, blockade of PD-1 signaling partially restored MAIT cell activation *in vitro*, suggesting that immune checkpoint pathways play a central role in regulating their dysfunction [42]. This aligns with broader observations that the CRC TME drives exhaustion not only in conventional T cells but also in innate-like T-cell populations such as MAIT cells.

The functional impairment of MAIT cells is further influenced by their spatial localization within the tumor and metastatic niches. A recent study examined MAIT cells in colorectal liver metastases and demonstrated that their effector capacity is strongly determined by their proximity to tumor lesions [43]. Tumor-infiltrating MAIT cells exhibited markedly reduced IFN-γ production in response to both TCR-dependent and cytokine-mediated stimulation, whereas MAIT cells in tumor-adjacent regions retained partial functionality. Importantly, these defects were independent of prior chemotherapy, indicating that the local TME, rather than treatment exposure, is the primary driver of MAIT cell dysfunction [43]. These findings highlight the spatial heterogeneity of MAIT cell responses in CRC and suggest that restoring their function could have therapeutic relevance.

Gastric cancer

Gastric cancer (GC) is a major cause of cancer-related mortality worldwide and develops within a complex mucosal environment shaped by chronic exposure to dietary antigens, microbiota, and pathogens such as *Helicobacter pylori* [60,61]. Given their enrichment in mucosal tissues and their ability to recognize microbial metabolites, MAIT cells are increasingly implicated in GC immunity.

Studies consistently report a reduction in circulating MAIT cells in patients with GC. MAIT cell frequencies in peripheral blood are significantly decreased in patients with mucosa-associated cancers, including GC, and this reduction correlates with disease progression markers such as lymph node involvement and CEA levels [44]. Despite their reduced numbers, circulating MAIT cells retain the ability to produce key cytokines, including IFN-γ, IL-17, and TNF-α, suggesting preserved functional potential [44]. This apparent discrepancy may be explained by the recruitment of MAIT cells from the circulation into tumor tissues, supported by elevated expression of chemokine receptors such as CCR6 and CXCR6 and their ligands within the TME [44].

However, evidence also indicates partial functional impairment of MAIT cells in GC. A recent study reported not only reduced frequency and absolute numbers of circulating MAIT cells but also altered subset composition, including decreased $CD8^+$ MAIT cells [45]. Importantly, MAIT cells from patients with GC exhibited lower levels of granzyme B, suggesting diminished cytotoxic capacity [45]. Compared with other GI cancers, correlations between MAIT cell levels and tumor biomarkers were less consistent, highlighting a complex and context-dependent role.

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive GI malignancies, characterized by late diagnosis, a highly immunosuppressive TME, and poor responsiveness to immunotherapy [62–65]. Unlike other GI cancers, the role of MAIT cells in PDAC is less well defined, with most studies focusing on $CD161^+CD8^+$ T-cell populations, which may include or overlap with MAIT-like cells. Given that CD161 is a canonical marker of MAIT cells, these findings provide important indirect insights into MAIT cell-associated immunity in PDAC (Figure 1).

Tumor-infiltrating $CD161^+CD8^+$ T cells are closely associated with key clinicopathological features, including tumor differentiation, perineural invasion, and serum carbohydrate antigen 19-9 (CA19-9) levels [46]. Notably, higher infiltration of these cells was significantly correlated with improved OS and recurrence-free survival, and multivariate analyses confirmed their role as an independent prognostic factor. Furthermore, combining $CD161^+CD8^+$ T-cell levels with CA19-9 enhanced the predictive accuracy for patient outcomes, with low $CD161^+CD8^+$ T-cell infiltration and high CA19-9 levels identifying patients with the poorest prognosis [46].

Functionally, $CD161^+CD8^+$ T cells in PDAC exhibit a distinct phenotype characterized by elevated production of cytotoxic mediators, including IFN-γ, TNF-α, granzyme B, and perforin, suggesting

preserved or enhanced effector capacity [46]. At the same time, these cells express increased levels of immune checkpoint molecules, indicating a state of activation that may be restrained by inhibitory signaling pathways. This dual phenotype reflects a balance between antitumor activity and immune regulation within the PDAC microenvironment [46].

Interestingly, lower levels of tumor-infiltrating $CD161^{+}CD8^{+}$ T cells were associated with a better response to adjuvant chemotherapy, suggesting that immune contexture may influence treatment sensitivity. Collectively, these findings highlight $CD161^{+}CD8^{+}$ T cells as a functionally active and clinically relevant immune subset in PDAC [46]. Although their precise relationship to canonical MAIT cells requires further clarification, they represent a promising biomarker for prognosis and therapeutic response, as well as a potential target for immunomodulatory strategies in pancreatic cancer.

Esophageal cancer

Esophageal adenocarcinoma (EAC) is an aggressive malignancy with poor prognosis, often arising from the chronic inflammatory condition **Barrett's esophagus (BE)**. This inflammation-driven progression highlights the importance of immune regulation within the esophageal microenvironment [66,67]. Given their role in microbial sensing and mucosal immunity, MAIT cells have emerged as a relevant immune population in EAC (Figure 1).

Circulating MAIT cells are reduced in patients with BE and EAC compared with healthy controls, while being relatively enriched within tumor tissues, suggesting active recruitment to the TME [47]. Tumor-infiltrating MAIT cells predominantly exhibit a $CD8^{+}$ phenotype and express elevated levels of inhibitory receptors such as PD-1 and natural killer group 2 member A (NKG2A), alongside reduced expression of the activating receptor NKG2D [47].

Functionally, these MAIT cells show impaired effector responses, with decreased production of IFN-γ and TNF-α when exposed to tumor-conditioned media, indicating suppression by the TME. Nevertheless, they retain intrinsic cytotoxic potential, as expanded MAIT cells can reduce tumor cell viability *in vitro*. Clinically, higher MAIT cell infiltration has been observed in node-negative tumors, although broader prognostic associations remain unclear [47]. Overall, MAIT cells in EAC display a balance between cytotoxic capability and checkpoint-mediated inhibition, suggesting potential for therapeutic targeting.

MAIT cells and GI cancer therapy

Strategies to enhance antitumor MAIT cell functions

The emerging recognition of MAIT cells as context-dependent regulators of tumor immunity has spurred growing interest in their therapeutic manipulation. As mentioned earlier, unlike conventional T cells, MAIT cells integrate signals from microbial-derived antigens presented by MR1, inflammatory cytokines, and tissue-derived cues, making them uniquely positioned to be both targets and effectors of immunotherapy. Features such as donor-unrestricted antigen recognition, tissue-homing capacity, and reduced risk of alloreactivity further support their potential in adoptive cell therapies [68]. Current strategies to therapeutically target MAIT cells broadly fall into three categories: enhancing antitumor effector functions, mitigating pro-tumorigenic or inflammatory programs, and incorporating MAIT cells into combinatorial immunotherapy frameworks (Figure 2 and Box 2).

One approach to enhance MAIT cell antitumor functions is to augment their cytotoxicity and effector cytokine production. MAIT cell activation is not strictly dependent on TCR signaling but can be potently induced by inflammatory cytokines, particularly IL-12 and IL-18, which synergistically drive IFN-γ production and cytotoxic programs [74,75]. This characteristic has led to interest in

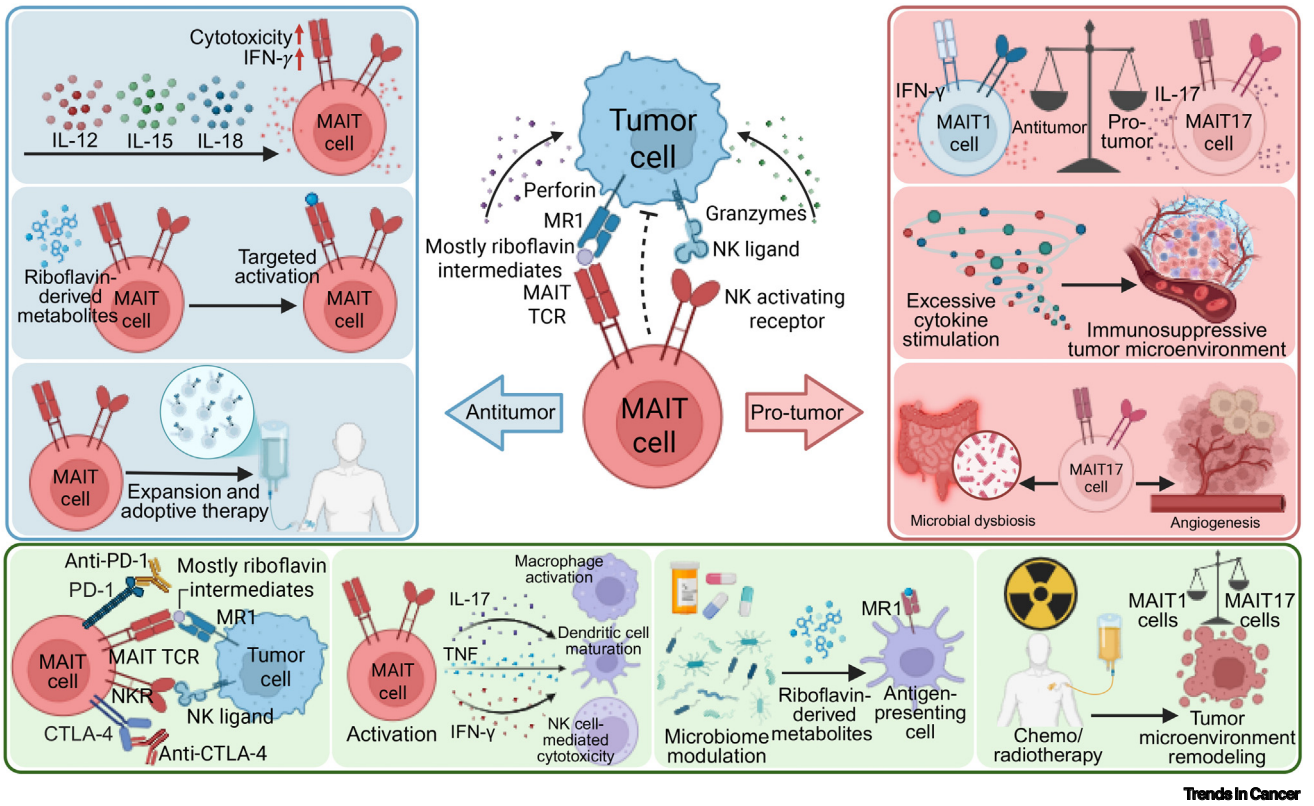

Figure 2. Therapeutic targeting of MAIT cells in GI cancers. MAIT cells integrate signals from key regulators, including the microbiome, cytokines, TME, checkpoint pathways, and target cells. Central to their activation is MR1–TCR recognition of microbial-derived metabolites (e.g., 5-OP-RU), leading to cytotoxic outputs (granzyme B, perforin) and cytokine production (IFN-γ, TNF-α, and IL-17). Their function exists along a spectrum from antitumor immunity to pro-tumor inflammation. Strategies to enhance MAIT cell function include cytokine priming (IL-12, IL-18, and IL-15), MR1 ligand targeting, and adoptive cell therapy. However, functional plasticity poses risks, including skewing toward IL-17-producing MAIT17 cells, excessive inflammation, and tumor-promoting effects. Combinatorial approaches aim to optimize therapeutic efficacy, including immune checkpoint blockade (PD-1 and CTLA-4) to restore function, modulation of myeloid and innate immune crosstalk, microbiome-targeted interventions, and integration with conventional therapies such as chemotherapy or radiotherapy to reshape the TME. In the context of human MAIT cells, the terms MAIT1 and MAIT17 are used only to describe functionally polarized MAIT cell states characterized by predominant IFN-γ or IL-17 production, respectively, rather than distinct lineage-defined subsets. In humans, MAIT cells exhibit considerable functional plasticity, and these phenotypes likely represent dynamic activation states shaped by the local microenvironment. The figure was created using BioRender (biorender.com). GI: gastrointestinal; IFN-γ: interferon-gamma; IL-17: interleukin-17; MAIT: mucosal-associated invariant T; MR1: MHC class I-related molecule; NK: natural killer cell; NKR: NK receptor; PD-1: programmed cell death protein 1; TCR: T-cell receptor; TME: tumor microenvironment; TNF-α: tumor necrosis factor-alpha; 5-OP-RU: 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil; CTLA-4: cytotoxic T-lymphocyte-associated protein 4.

cytokine-based priming strategies, including administration of IL-12, IL-18, or IL-15, to enhance MAIT-mediated antitumor immunity [76–78].

Another promising avenue involves modulating MR1-dependent antigen presentation. MAIT cells recognize riboflavin-derived metabolites presented by MR1, and synthetic agonists such as 5-A-RU derivatives can enhance MAIT activation and tumor cell lysis in preclinical models, which raises the possibility of using MR1 ligands as immunological adjuvants to selectively activate MAIT cells within tumors [9,16,79,80]. However, the nature and availability of tumor-derived MR1 ligands remain incompletely understood, representing both an opportunity and a limitation for therapeutic targeting.

Expanding on MR1-dependent MAIT cell activation, recent evidence has identified a metabolite-driven strategy to enhance MAIT cell-mediated antitumor immunity in CRC. In preclinical CRC

Box 2. Cell engineering and translational strategies for MAIT immunotherapy

Beyond cytokine priming and MR1-directed activation, several cell-based and immune engineering strategies are being developed to harness the antitumor potential of MAIT cells. Their donor-unrestricted antigen recognition, tissue tropism, and limited alloreactivity make MAIT cells particularly attractive candidates for adoptive immunotherapy. In preclinical CRC models, adoptive transfer of *ex vivo*-expanded MAIT cells significantly suppressed tumor growth, which was accompanied by increased expression of eosinophil-recruiting cytokines within the TME [40]. Consistent with these findings, activation of human peripheral leukocytes with MR1 ligands enhanced eotaxin-1 production, promoted eosinophil activation, and increased tumor cell killing, suggesting that MAIT cells may exert antitumor effects both through direct cytotoxicity and by orchestrating broader immune responses [40].

More recently, antibody-based approaches have been developed to redirect endogenous MAIT cells toward malignant cells. Bispecific T-cell engagers targeting MAIT cells have demonstrated potent tumor cell cytotoxicity, and their efficacy can be further enhanced through metabolic conditioning [69]. Exposure of MAIT cells to sodium lactate increases mitochondrial metabolism and augments the production of IFN-γ and granzymes, thereby improving engager-mediated cytotoxic activity despite the metabolically restrictive TME [69]. In parallel, genetic engineering of MAIT cells to express chimeric antigen receptors (CARs) has emerged as another promising strategy. CAR-MAIT cells display cytotoxic activity comparable to conventional CAR-T cells while producing lower levels of IFN-γ, potentially reducing treatment-associated toxicities [28]. Furthermore, MAIT cells retain their responsiveness to MR1 ligands such as 5-A-RU following CAR engineering, allowing simultaneous antigen-specific targeting and MR1-mediated activation [28]. Collectively, these advances highlight the versatility of MAIT cells as a platform for next-generation cellular immunotherapies and support their continued development for the treatment of GI malignancies [70,71].

Despite encouraging preclinical results, several translational challenges remain before MAIT cell-targeted therapies can be broadly applied in the clinic. Cytokine-based priming strategies, particularly those involving IL-12, IL-15, or IL-18, may induce systemic immune activation and dose-limiting toxicities, necessitating approaches that restrict cytokine activity to the tumor site [72]. Likewise, although synthetic MR1 ligands such as 5-OP-RU are highly potent MAIT cell agonists, their rapid chemical degradation and limited *in vivo* stability present significant pharmacokinetic challenges [73]. Future efforts will likely focus on improving the therapeutic index of these agents through targeted delivery systems, sustained-release formulations, or prodrug strategies that enhance ligand stability and selectively promote MAIT cell activation within the TME while minimizing systemic toxicity.

models, oral ethyl acetoacetate suppressed tumor growth by selectively expanding and activating cytotoxic MAIT cells in an MR1-dependent manner, while increasing MR1 expression on tumor-associated monocytes [81]. Mechanistically, acetoacetate is converted to methylglyoxal, which reacts with microbial 5-Amino-6-D-ribitylaminouracil (5-A-RU) to generate the potent MR1 ligand 5-OP-RU, thereby promoting MAIT cell activation and tumor cell killing [81]. These findings highlight the acetoacetate–MR1–MAIT axis as a promising therapeutic target for immunotherapy.

Risks of tumor promotion and inflammation

The functional polarization of MAIT cells is increasingly recognized as a dynamic process governed by the TME rather than a fixed cellular state. Although the mechanisms remain incompletely defined in GI cancers, current evidence suggests that distinct cytokine and metabolic cues influence MAIT cell fate. Proinflammatory cytokines such as IL-12 and IL-18 promote MAIT1-like responses characterized by IFN-γ production and enhanced cytotoxicity, whereas cytokines including IL-1β, IL-23, and TGF-β, together with chronic antigen stimulation, are thought to favor MAIT17-like differentiation and IL-17 production [82,83]. In parallel, persistent exposure to microbial antigens, hypoxia, metabolic stress, and interactions with immunosuppressive cells such as TAMs and myeloid-derived suppressor cells may further reinforce dysfunctional or pro-tumor phenotypes by inducing immune checkpoint expression and limiting effector function [84].

Despite their therapeutic promise, targeting MAIT cells carries significant risks because of their heterogeneity within tumors. Distinct functional subsets, such as MAIT1-like IFN-γ-producing and MAIT17-like IL-17-producing cells, may coexist and respond differently to therapeutic interventions. The functional plasticity of MAIT cells, shaped by cytokine signals and the TME,

underlies their dual roles in either promoting or restraining tumor progression [85,86]. Importantly, IL-17-producing MAIT cells have been linked to pro-tumorigenic inflammation and disease progression, whereas IFN-γ-producing MAIT cells are generally associated with antitumor immunity, highlighting a functional dichotomy between MAIT17-like and MAIT1-like states [87]. In certain tumor contexts, such as glioblastoma, IL-17-producing MAIT cells have also been implicated in tumor-promoting immune interactions, including the recruitment or activation of pro-tumor neutrophil populations [88]. Without precise control, strategies aimed at boosting MAIT cell activity could therefore inadvertently expand regulatory or tumor-promoting subsets, underscoring the need for state-specific targeting approaches, such as selective modulation of transcriptional programs or checkpoint pathways, to bias MAIT cells toward beneficial antitumor phenotypes while limiting pathogenic or immunosuppressive outputs.

Cytokine-driven activation strategies also pose a risk of excessive inflammation. IL-12, IL-15, and IL-18 can robustly activate MAIT cells, even in a TCR-independent manner, inducing potent effector responses, including IFN-γ production and cytotoxic mediator release [24,89–92]. However, sustained or excessive cytokine stimulation may lead to uncontrolled cytokine release, tissue damage, or the reinforcement of immunosuppressive feedback loops within the TME. Notably, IL-12 and IL-18 signaling can also drive IL-17A and IL-17F production by MAIT cells following prolonged stimulation, contributing to proinflammatory programs that are independent of classical IL-23 pathways, which is particularly relevant given that IL-17-producing MAIT cells have been associated with tumor-promoting effects and pro-tumorigenic inflammation in several cancer contexts [87,93,94].

Box 3. Combinatorial strategies to enhance MAIT cell-based immunotherapy

One key opportunity lies in combining MAIT-directed approaches with immune checkpoint blockade [95–97]. Tumor-infiltrating MAIT cells frequently upregulate inhibitory receptors, including PD-1 and CTLA-4, reflecting functional exhaustion within the TME [98,99]. Because PD-1 expression may reflect chronic MR1-dependent antigen stimulation rather than terminal dysfunction, checkpoint blockade alone may be insufficient to restore durable MAIT cell activity. Combining checkpoint inhibition with strategies that reprogram the cytokine milieu or enhance MR1 ligand presentation may therefore produce more sustained antitumor responses.

Inflammatory cytokines such as IL-12, IL-15, and IL-18 can further induce checkpoint expression on MAIT cells, highlighting a dynamic coupling between activation and inhibitory feedback programs [100]. While blockade of PD-1 and CTLA-4 has been shown to restore T-cell function and enhance antitumor immunity in both preclinical and clinical settings, emerging evidence further suggests that MAIT cells can exhibit similar exhausted phenotypes and may contribute to responses to anti-PD-1 therapy, supporting their potential as targets or mediators of immune checkpoint blockade (ICB)-based strategies [101–105].

Another promising strategy is the combination of MAIT cell activation with innate immune modulation. MAIT cells rapidly produce effector cytokines such as IFN-γ, TNF, and IL-17 following activation, which can promote macrophage activation, enhance dendritic cell maturation, and support NK-cell-mediated cytotoxic responses, thereby positioning MAIT cells as key amplifiers of coordinated innate-adaptive immunity [106]. In this context, MAIT cells may function as bridges, and therapeutic strategies that co-target these interacting cell populations could produce synergistic effects by amplifying immune activation while overcoming suppressive circuits.

Additionally, combining MAIT cell-targeted therapies with microbiota modulation offers a unique avenue to reshape the TME. MAIT cells are intrinsically linked to microbial-derived metabolites presented by MR1 and are imprinted by the microbiota early in life, with lasting effects on their development and functional programming [107,108]. This tight coupling to microbial signals positions MAIT cells as key sensors of host–microbiome interactions, which are increasingly recognized as determinants of immunotherapy responsiveness.

Finally, engineered MAIT cell therapies may be combined with conventional modalities such as chemotherapy or radiotherapy. These treatments remodel the TME by increasing antigen availability, altering cytokine landscapes, and modulating immune infiltration, thereby enhancing the effectiveness of immunotherapy. Rational sequencing and combination of these modalities may, therefore, maximize therapeutic benefit by creating a permissive environment for MAIT cell activation while minimizing tumor-promoting programs.

Concluding remarks and future perspectives

MAIT cells represent a promising yet complex component of GI cancer immunity, characterized by functional plasticity and strong dependence on tissue context. Future research should focus on developing strategies to selectively enhance antitumor MAIT cell responses while limiting pro-tumorigenic or inflammatory programs (see Outstanding questions). This includes optimizing cytokine priming, refining MR1-targeted approaches, and leveraging immune checkpoint blockade to reverse exhaustion. Additionally, combining MAIT cell-based therapies with microbiome modulation and conventional treatments may provide synergistic benefits by reshaping the TME (Box 3).

A key challenge lies in interpatient variability and tumor-type heterogeneity, which influence MAIT cell abundance, phenotype, and function (Table 1). An important consideration for the clinical translation of MAIT cell-targeted therapies is the limitations of current preclinical models. Unlike humans, laboratory mice maintained under specific-pathogen-free (SPF) conditions possess substantially lower frequencies of MAIT cells and exhibit differences in their development, tissue distribution, and functional maturation, largely owing to distinct microbial exposures [10,13,109–111]. These species-specific differences may influence the interpretation and translatability of findings derived from murine cancer models. Future studies incorporating humanized mouse models, microbiota-humanized systems, and *ex vivo* human tissue platforms will be instrumental in more accurately recapitulating human MAIT cell biology and accelerating the development of clinically relevant MAIT cell-based immunotherapies.

Outstanding questions

What are the key molecular and environmental cues that determine whether MAIT cells exert antitumor versus pro-tumorigenic functions across different GI cancers?

How do tumor-specific microenvironments (e.g., liver vs. intestine) differentially regulate MAIT cell activation, exhaustion, and functional plasticity?

What are the endogenous tumor-derived or microbial-derived MR1 ligands present in GI cancers, and how do they shape MAIT cell responses?

How does the microbiome composition influence MAIT cell function and responsiveness to immunotherapies in GI malignancies?

Can MAIT cell subsets (e.g., MAIT1 vs. MAIT17) be selectively targeted or reprogrammed to enhance antitumor immunity while minimizing pro-tumor inflammation?

What are the mechanisms underlying MAIT cell exhaustion, and how effectively can immune checkpoint blockade restore their function in patients?

How can MAIT cells be optimally integrated into combinatorial therapies, including checkpoint inhibitors, microbiome modulation, and conventional treatments?

Are MAIT cells reliable and robust biomarkers for predicting disease progression, therapeutic response, or patient stratification in GI cancers?

What are the safety risks associated with MAIT cell-based therapies, particularly regarding cytokine-driven inflammation or unintended immune activation?

How can engineered or adoptively transferred MAIT cells be designed to improve persistence, specificity, and efficacy in the tumor microenvironment?

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Declaration of interests

L.Y. is a scientific advisor to AlzChem and Amberstone Biosciences. None of the declared companies contributed to this study. The other authors declare no competing interests.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT to assist with improving the clarity, organization, and scientific language of the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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