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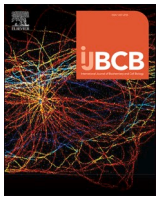

The duplexity of unconventional T cells in cancer

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ABSTRACT

Unconventional T cells and their involvement in cancer are understudied in comparison to conventional T cells, but recent findings indicate that these cells play important roles in both cancer progression and inhibition. Here, we briefly review the dichotomous role of three unconventional T cell lineages: γδ T cells, MAIT cells and NKT cells. Studies using mouse models of cancer show how this unconventional trilogy interacts with cancer epithelial cells and other immune cell populations during tumour evolution. These reports highlight various potential avenues for therapeutic intervention that may be exploited for cancer immunotherapy.

1. Introduction

T cell receptor (TCR)-expressing cells consist of two groups. One group is the well-known conventional T cells that are educated by dendritic cells and recognise processed peptides through major histocompatibility complex (MHC) molecules. The other group is the understudied, enigmatic unconventional T cells that sense a variety of molecules through their TCR, including peptides, lipids, metabolites and surface proteins. In the cancer immunology field, the trilogy of unconventional T cells – γδ T cells, mucosal-associated invariant T (MAIT) cells and natural killer T (NKT) cells – have received far less attention than conventional T cells. However, in recent years, there has been a growing appreciation of the diverse role of unconventional T cells in cancer. Although these cells express a TCR, their innate-like properties, such as independence of antigen-mediated education via MHC molecules and rapid response to their cytokine milieu, and the plasticity of γδ T cells, MAIT cells and NKT cells, provides these cells with the ability to quickly adapt to their surroundings. But at the same time, these qualities leave them susceptible to manipulation by tumour-derived factors. Here, we briefly review the pro- and anti-tumorigenic role of unconventional T cells in cancer, as well as their potential for therapeutic exploitation. We specifically focus on recent functional data from mouse models. Unconventional T cell evolution, development, tissue-specific niches and function during non-tumour immunity has been reviewed elsewhere (Mayassi, 2021; Pellicci et al., 2020).

2. Pro-tumour functions of unconventional T cells

2.1. Pro-tumour γδ T cells

Among the three types of unconventional T cells with known accessory roles in cancer progression and metastatic dissemination, γδ T cells are the best studied (Silva-Santos et al., 2019). γδ T cells are defined by their unique TCR, which consists of gamma and delta chains that bind CD3 molecules. In mice, γδ T cells mediate many pro-tumour functions through expression of IL-17A, a pleiotropic cytokine that modulates the behaviour of cancer cells, immune cells and stromal cells (Fig. 1A). There are two subsets of γδ T cells expressing different TCRs that primarily produce IL-17A: Vγ4$^+$ and Vγ6$^+$ cells. However, it is unclear whether IL-17A-producing Vγ4$^+$ and Vγ6$^+$ cells have distinct functions or whether their TCR is important for IL-17A production. It is also unclear what their TCRs recognise. In mouse models of *Apc*-mutant colon cancer, IL-17A-producing γδ T cells encourage early tumour development via direct stimulation of the IL-17 receptor on intestinal epithelial cells, which promotes their proliferation and inhibits their expression of CXCL9 and CXCL10 to prevent anti-tumour CD8$^+$ T cell recruitment (Wang, 2014; Housseau, 2016; Chen, 2019). Within the gut, these IL-17A-producing γδ T cells are activated by microbiome-induced IL-23 resulting from disruption of mucosal barrier by early tumours (Grivennikov, 2012). IL-17A-producing γδ T cells are also important in mouse models of breast, liver and ovarian cancers where they re-educate myeloid cells, such as neutrophils and macrophages, towards an

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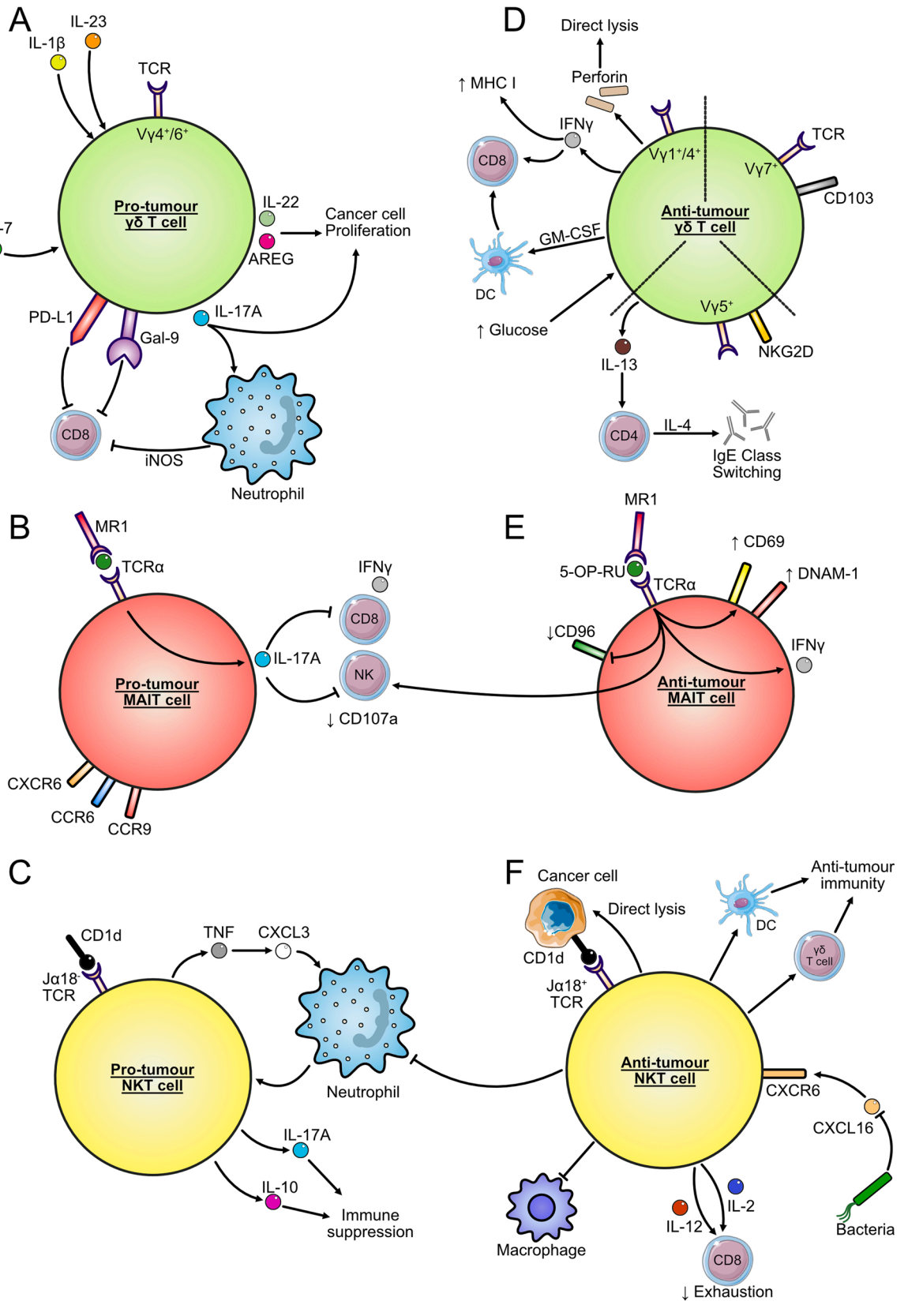

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Fig. 1. Mechanisms of unconventional T cell contribution to cancer progression. (A) Pro-tumour γδ T cells are activated through TCR-independent mechanisms (IL-1β, IL-23 and IL-7) and are characterised by IL-17A production. Following activation, they can induce cancer cell proliferation (via secretion of IL-22/AREG), recruit immunosuppressive neutrophils, and drive immune suppression through checkpoint molecule expression (PD-L1 and Galectin-9 [Gal-9]). (B) Pro-tumour MAIT cells are identified through expression of distinct surface markers (CXCR6, CCR6/9), and interactions between MR1 and TCRα directly drives IL-17A production which impairs anti-tumour immunity. (C) Pro-tumour NKT cells respond to CD1d recognition by their TCR, they produce immune regulating cytokines (IL-17A/IL-10) and can recruit immunosuppressive neutrophils (TNF and CXCL3) that facilitate tumorigenesis. (D) Anti-tumour γδ T cells can be divided into three subgroups, depending on their distinct TCR usage. Vγ1 or Vγ4-expressing γδ T cells mediate direct tumour cell lysis via IFNγ and perforin secretion. Potent IFNγ production also upregulates MHC class I molecules on cancer cells and augments the anti-tumour function of cytotoxic $CD8^+$ T cells. Indirect anti-tumour immunity is additionally modulated by recruitment of dendritic cells through GM-CSF production leading to increased (neo)antigen cross-presentation to $CD8^+$ T cells. High Glucose levels increase IFNγ production, general fitness and improve tumour cell killing. Besides sensing tumour cells via NKG2D, epidermal $V\gamma5^+$ cells are capable of inducing a type 2 immune response via secretion of IL-13 in a $CD4^+$ T cell/IL-4 dependent manner, ultimately leading to IgE class switching in B cells. $V\gamma7^+$ gut-resident γδ T cells are capable of sensing nascent tumour cells via CD103-EpCAM interaction. (E) Activation of anti-tumour MAIT cells is mediated by TCRα interaction with 5-(2-oxopropylideneamino)−6-D-ribitylaminouracil (5-OP-RU)-loaded MR1 molecules. Upon activation, anti-tumour MAIT cells upregulate the activation markers CD69 and DNAM-1 as well as IFNγ production. Simultaneously, the inhibitory molecule CD96 is downregulated. MAIT cells can mediate anti-tumour immunity by activating NK cells. (F) Type I $Ja18^+$ NKT cells mediate direct lysis of $CD1d^+$ cancer cells. NKT cells regulate anti-tumour immunity by enhancing $V\gamma1^+/V\gamma4^+$ γδ T cells and dendritic cells as well as dampening immunosuppressive neutrophils and macrophages. NKT cells additionally boost anti-tumour immunity by preventing $CD8^+$ T cell exhaustion mediated by IL-2 and IL-12 secretion. In the liver, microbiota suppress expression of CXCL16, preventing $CXCR6^+$ NKT cells from entering tumours.

immunosuppressive and pro-angiogenic phenotype (Rei, 2014; Benevides, 2015; Ma, 2014; Coffelt, 2015; Wellenstein, 2019). In a KRAS mutant, p53-deficient lung cancer model, γδ T cells encourage neutrophil infiltration into lungs to further disease progression (Jin, 2019). Not only do γδ T cells control myeloid cell behaviour, but IL-17A-producing γδ T cells can also respond to signals from neutrophils and macrophages, and these myeloid cells can either promote or inhibit γδ T cell function (Coffelt, 2015; Wellenstein, 2019; Mensurado, 2018). To foster breast cancer metastasis formation, p53-deficient cancer cells release WNT ligands to stimulate IL-1β from tumour-associated macrophages, and IL-1β activates γδ T cells to produce IL-17A (Coffelt, 2015; Wellenstein, 2019). Similarly, IL-1β and IL-23 from myeloid cells can be up-regulated by the lung microbiome to stimulate IL-17A from γδ T cells (Jin, 2019). These data reinforce how crosstalk between γδ T cells, neutrophils and macrophages is important to drive cancer progression. Recent data indicate that ageing favours the expansion of both $V\gamma4^+$ and $V\gamma6^+$ cells, leading to accelerated tumour growth in transplantable lung cancer models. This expansion occurs in the lymph nodes of old mice by increased expression of IL-7 (but not IL-1β or IL-23), which induces proliferation of IL-17A-producing γδ T cells without affecting their phenotype (Chen, 2019). In addition to IL-17A, γδ T cells can also produce amphiregulin (AREG), a ligand for the epidermal growth factor receptor (EGFR), and IL-22; both of these molecules can stimulate proliferation of cancer cells (Jin, 2019). Pro-tumorigenic γδ T cells in models of pancreatic cancer and fibrosarcoma may express PD-L1, Galectin-1 or Galectin-9 to suppress cytotoxic T cells (Rutkowski, 2015; Daley, 2016). Therefore, the functions of γδ T cell subsets exert their pro-tumorigenic function through a variety of mechanisms.

2.2. Pro-tumour MAIT cells

MAIT cells use their TCR to bind the non-polymorphic MHC class-I related (MR1) receptor on other cells. This interaction dictates the development and function of MAIT cells through binding of microbial metabolites, such as the vitamin B metabolite 5-OP-RU which is expressed on various immune cells. As such, MR1-deficient mice, which lack MAIT cells, can be used to test the importance of these cells in cancer progression. In fact, injection of melanoma cells into the tail vein of $Mr1^{-/-}$ mice or induction of fibrosarcoma by carcinogen injection into $Mr1^{-/-}$ mice exhibit reduced tumour growth when compared to wild-type mice, indicating that MAIT cells promote cancer progression in these models (Yan, 2020). MAIT cells can suppress the activity of NK cells and $CD8^+$ T cells, as shown by a reduction in IFNγ production and the degranulation marker, CD107a (Fig. 1B). Similar results have been reported using intravenous inoculation of B16 melanoma cells into $B6\text{-}MAIT^{CAST}$ mice, which exhibit greater frequencies of MAIT cells than wild-type C57BL/6 mice due to increased rearrangements of the TCRα (Vα19 Jα33) locus (Cui, 2015). In these experiments with $B6\text{-}MAIT^{CAST}$ mice, MAIT cells support tumour growth through dampening NK cell maturation (Petley, 2021). Like γδ T cells, MAIT cells are triggered to express IL-17A (as well as TNF) in these models. There is evidence that MAIT cell-derived IL-17A impacts IFNγ and CD107a expression in NK cells, since adoptive transfer of MAIT cells from $Il17a^{-/-}$ mice into $Mr1^{-/-}$ mice fails to suppress NK cells (Yan, 2020). Together, these data suggest some common functionality between unconventional T cells. However, the activation of IL-17A-producing MAIT cells and γδ T cells may be different, because IL-17A expression in MAIT cells is dependent on MR1-induced TCR stimulation whereas IL-17A expression in γδ T cells is dependent on the cytokines, IL-1β and IL-23.

2.3. Pro-tumour NKT cells

Like MAIT cells, the TCR expressed by NKT cells consists of alpha/beta heterodimers, and their TCR binds lipids presented by CD1d rather than metabolites. NKT cells can also produce IL-17A, but whether these cells use IL-17A to promote cancer progression is unknown. NKT cells consist of at least two subsets that are defined by expression or lack of expression of the Vα14 Jα18 invariant TCR chain (Type I and Type II NKT cells, respectively). NKT cells are stimulated by lipids presented by the CD1d molecule, and $Cd1d^{-/-}$ mice (which lack all NKT cell subsets) or $J\alpha18^{-/-}$ mice (which lack $J\alpha18^+$ NKT cells) have been used to test the functionality of NKT cells in cancer. The use of transplantable cancer cell lines in these knockout mice has shown that $J\alpha18^-$ NKT cells, not $J\alpha18^+$ NKT cells, contribute to tumour growth and immunosuppression (Terabe, 2005, 2000; Ambrosino, 2007). The mechanism of occurs through encouragement of neutrophils (Terabe, 2003), in a similar fashion to IL-17A-producing γδ T cell control over immunosuppressive neutrophils (Benevides, 2015; Ma, 2014; Coffelt, 2015; Wellenstein, 2019; Jin, 2019). Both $J\alpha18^+$ and $J\alpha18^-$ NKT cells advance the development of intestinal polyps in the spontaneous Apc^{MIN} colon cancer model, and these NKT cells express IL-17A and IL-10 (Wang, 2018). Therefore, there may be some overlap between NKT cell function and other unconventional T cells in furthering cancer progression (Fig. 1C).

3. Anti-tumour functions of unconventional T cells

3.1. Anti-tumour γδ T cells

γδ T cells were discovered in the 1980 s and have been associated with anti-tumour function ever since. In mice, skin-resident γδ T cells expressing the Vγ5 TCR protect against cutaneous tumour development by orchestrating a Type-2 immune response via secretion of IL-13 and B cell immunoglobulin class switching to IgE (Girardi, 2001, 2003; Strid, 2008; Dalessandri, 2016; Crawford, 2018). While epidermal $V\gamma5^+$ cells recognise nascent cancer cells via the NKG2D receptor (Girardi, 2001; Strid, 2008), gut-resident γδ T cells expressing the Vγ7 TCR recognise

nascent cancer cells through CD103-EpCAM interactions and inhibit their development (Morikawa, 2021). With regards to their TCR, gut resident Vγ7$^+$ cells interact with epithelial-derived BTNL1 and BTNL6, whereas Vγ5$^+$ cells in the skin are shaped by their ligation with SKINT1 (Boyden, 2008; Di Marco Barros, 2016). However, the effects of these interactions in the context of cancer remain unknown. Anti-tumour γδ T cells with the ability to traffic to lymph nodes mainly express Vγ1 and Vγ4 TCRs, and these cells counteract cancer progression in transplantable and spontaneous mouse models of cancer (Lanca, 2013; Liu, 2008; Street, 2004). TCR ligands for these subtypes have yet to be identified. Adoptive transfer of Vγ1$^+$/Vγ4$^+$ cells can also delay tumour growth and metastasis through secretion of IFNγ and perforin (Liu, 2008; He, 2010; Beck, 2010). Besides their capability to elicit direct tumour cell lysis, IFNγ-producing γδ T cells can augment anti-tumour CD8$^+$ T cell function and increase cancer cell visibility by upregulating expression of MHC-I molecules (Gao, 2003; Riond, 2009). More recently, γδ T cells were shown to modulate dendritic cell recruitment to gastric tumours via GM-CSF expression, effectively mounting an anti-tumour CD8$^+$ T cell response (Medina, 2019). Another recent study investigated the distinct metabolic landscape of γδ T cell subsets and revealed that glucose supplementation is beneficial specifically for IFNγ-producing anti-tumour γδ T cells. Proof-of-principle experiments show that IFNγ-producing γδ T cells expanded in high glucose medium are more efficient in controlling E0771 mammary tumours than IFNγ-producing γδ T cells expanded with normal glucose levels (Lopes, 2021). These studies indicate that both tissue-resident and circulating γδ T cells may be exploited for cancer immunotherapy (Fig. 1D).

3.2. Anti-tumour MAIT cells

The anti-tumour activity of MAIT cells has been illustrated in two recent studies. These studies show that activation of MAIT cells via TCRα-MR1 interactions using the 5-(2-oxopropylideneamino)− 6-D-ribitylaminouracil (5-OP-RU) antigen reduces tumour growth of B16 melanoma and a variety of other transplantable cell lines in syngeneic mice (Petley, 2021; Ruf, 2021). Activation of MAIT cells by 5-OP-RU – delivered directly into mice or presented to cancer cells before injection into mice – seems to provoke anti-tumour responses from MAIT cells (Fig. 1E). These effects are observed in wild-type C57BL/6 mice as well as MAIT cell-rich B6-MAIT^{CAST} mice. However, antigen delivery directly to cancer cells does not result in reduced tumour growth for every cell line, since MAIT cells are unable to reduce tumour growth of 5-OP-RU--pulsed E0771 mammary cancer cells in B6-MAIT^{CAST} mice. This may be explained by the low expression of MR1 on E0771 cells. In the transplantation models where MAIT cells play an anti-tumour role, the tumour reduction phenotype can be reversed using *Mr1*$^{-/-}$ mice. These data suggest that host-derived, not cancer cell-derived, MR1, is the crucial mediator driving the anti-tumour functions of MAIT cells. Indeed, CRISPR/CAS9-mediated knockout of *Mr1* in B16 melanoma cells has no effect on the ability of MAIT cells to counteract tumour growth in wild-type mice. So how do MR1-associated antigens affect MAIT cells, and how do these cells counteract cancer progression? 5-OP-RU changes the phenotype of MAIT cells by increasing expression of IFNγ, CD69 and the NK cell activation receptor, DNAM-1, while decreasing expression of the inhibitory ligand, CD96. 5-OP-RU-treated mice also exhibit enhanced activation and activity of cytotoxic NK cells, whose depletion abrogates the reduction in tumour growth. Therefore, MAIT cells encourage NK cell-mediated anti-tumour immunity, underscoring their ability to influence other effector populations to inhibit cancer progression (Petley, 2021; Ruf, 2021). There are also discrepancies in the literature that need resolving. For example, in the same B16 melanoma model, MAIT cells can exhibit both pro- and ant-tumour functions (Yan, 2020; Petley, 2021; Ruf, 2021). These contradictory observations may be explained by the use of 5-OP-RU-mediated TCR stimulation to skew cells towards an anti-tumour phenotype; although, further work is needed for clarification.

3.3. Anti-tumour NKT cells

Several studies from 10 to 20 years ago have shown that endogenous Type I, Jα18$^+$ NKT cells counteract tumour growth and elicit anti-tumour immunity in transplantable cancer models of melanoma, lung cancer, sarcoma, prostate cancer and lymphoma [reviewed in (Fujii and Shimizu, 2019; Godfrey, 2018). In addition, adoptive transfer of NKT cells into B16 melanoma-bearing mice indicates that these cells have potent anti-tumour properties with the ability to control tumour growth (Li, 2019). NKT cells directly kill CD1d$^+$ cancer cells, but they can also enhance anti-tumour γδ T cells and dendritic cells as well as inhibit immunosuppressive neutrophils to prevent cancer progression (Fujii and Shimizu, 2019; Godfrey, 2018). More recent studies have shown that NKT cells protect against tumorigenesis in a spontaneous mouse model of KRAS-driven pancreatic cancer by dampening the pro-tumorigenic functions of macrophages (Janakiram, 2017). NKT cells can even restore the effector functions of exhausted CD8 + T cells after these cells become resistant to anti-PD-1 therapy, by providing cytokines, such as IL-2 and IL-12 (Bae, 2018). Very little information on the mechanisms that regulate NKT cells is known; although, insights have been uncovered in mouse models of primary hepatocellular carcinoma and liver metastasis (Fig. 1F). Antibiotic treatment of these tumour models increases CXCR6-expressing NKT cell numbers and reduces liver tumour growth in a NKT cell-dependent manner (Ma, 2018). Here, the microbiome controls expression of the CXCL16 chemokine, the ligand for CXCR6, in liver sinusoidal endothelial cells via modification of bile acid metabolism. Bile acids recirculate back to the liver from the gut to dampen CXCL16 expression, which prevents expansion of anti-tumour NKT cells. These data suggest that antibiotics may be beneficial for cancer patients with liver tumours.

4. Discussion

Although unconventional T cells have received less attention than conventional T cells for their participation in cancer progression, it is clear from the studies discussed above that these rare cells are crucial players. Going forward, it will be essential to establish the context in which pro- or anti-tumorigenic γδ T cells, MAIT cells and NKT cells are favoured; to determine the cancer types where these cells play a role; and to understand how these cells are regulated in different scenarios, including how genetic mutations and metabolic changes in cancer cells affects presentation of unconventional TCR ligands. The name given to γδ T cells, MAIT cells and NKT cells are de facto umbrella terms to describe a group of cells with similar characteristics, but each population encompasses both pro- and anti-tumorigenic subsets. Thus, it will be important for the research community to move beyond knockout mice that deplete entire populations and to generate specific models for manipulation of specific cell subsets. Data from single-cell RNA sequencing experiments should help further distinguish pro- and anti-tumorigenic subsets and identify similarities (and differences) to their human counterparts. Unconventional T cells in laboratory mice can exhibit differences to the same cell populations in humans, including their relative frequency, amino acid composition of their TCRs as well as their gene expression profile. Additionally, differences in microbiome between laboratory mice and humans will have impact on the development and behaviour of unconventional T cells during cancer progression. These differences must be considered when transferring information on γδ T cells, MAIT cells and NKT cells from mouse models to human cancer. Nevertheless, what is evident from the literature reviewed herein is the importance of crosstalk between unconventional T cells and other immune cell populations. More efforts on uncovering the molecular links between immune cells could open up new immunotherapeutic opportunities for cancer patients. Similarly, boosting the inherent anti-tumour properties of unconventional T cells with new strategies, such as metabolic alterations (Lopes, 2021), will be useful for cell-based therapies, especially in low (neo)antigen-expressing tumours

where conventional T cells are ineffective.

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Declarations of interest

None.

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