Molecular Immunology 105 (2019) 213–223

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Innate T cells in the intensive care unit

Edy Yong Kim[a,b,*], William M. Oldham[a,b]

[a] Brigham and Women's Hospital, Pulmonary and Critical Care Medicine, Boston, MA, 02115, United States
[b] Harvard Medical School, Boston, MA, 02115, United States

ARTICLE INFO

Keywords:
NKT cell
MAIT cell
Gamma delta T cell
Sepsis
Critical care
Cardiac arrest

ABSTRACT

Rapid onset of acute inflammation is a hallmark of critical illnesses that bring patients to the intensive care unit (ICU). In critical illness, innate T cells rapidly reach full activation and drive a robust acute inflammatory response. As "cellular adjuvants," innate T cells worsen inflammation and mortality in several common critical illnesses including sepsis, ischemia-reperfusion injury, stroke, and exacerbations of respiratory disease. Interestingly, innate T cell subsets can also promote a protective and anti-inflammatory response in sepsis, ischemia-reperfusion injury, and asthma. Therapies that target innate T cells have been validated in several models of critical illness. Here, we review the role of natural killer T (NKT) cells, mucosal-associated invariant T (MAIT) cells and γδ T cells in clinical and experimental critical illness.

1. Introduction

Patients with critical illness are admitted to the intensive care unit (ICU) and have the highest mortality rates of hospitalized patients. Indeed, 10 to 15% of patients admitted to the ICU die during admission, with higher mortality rates for septic shock, severe acute respiratory distress syndrome (ARDS), cardiac arrest, stroke and cardiovascular events (Table 1) (Zimmerman et al., 2013). Other common reasons for admission to the ICU include organ transplantation, acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD), and sickle cell crisis. Critical illnesses typically have an acute onset and rapidly progress to life-threatening illness, often within mere hours. This acute time frame suggests a role for innate T cells in critical illness, since innate T cells can reach full activation within hours of stimulation and are master regulators of the early innate immune response (Brennan et al., 2013). Innate T cells include Natural Killer T (NKT) cells, Mucosal Associated Innate T (MAIT) cells, and γδ T cells. Innate T cells are a subset of T cells distinct from the more commonly studied adaptive (i.e., "conventional") T cells (Cohen et al., 2013). Adaptive T cells respond to specific peptide antigens and generate long-lived memory responses. By contrast, innate T cells respond to a limited repertoire of non-peptide antigens in short-term responses that do not lead to memory. Here, we will review the role of NKT cells and MAIT cells in clinical and experimental critical illness, with limited discussion of γδ T cells.

1.1. NKT cells

NKT cells recognize glycolipid antigens presented by CD1d, a homologue of MHC I (Cohen et al., 2009). NKT cells recognize microbial antigens (e.g., diacylglycerol-containing glycolipids from Streptococcal pneumonia (Kinjo et al., 2011)), endogenous antigens, and synthetic antigens (e.g., analogues of α-glucosylceramide [αGalCer] (Kawano et al., 1997)). NKT cells are divided into two subsets, invariant (type 1) NKT cells and diverse (type 2) NKT cells. All invariant NKT (iNKT) cells share the same antigen specificity, which is why iNKT cells are much easier to study than diverse NKT cells. αGalCer is the canonical lipid antigen that will strongly activate all iNKT cells. In line with this shared antigen specificity, iNKT cells all express the same invariant T cell receptor (TCR) α chain: Vα24-Jα18 in humans and Vα14-Jα18 in mice.

Although a strong lipid antigen alone will activate NKT cells, most microbes do not have an antigen for NKT cells. In most infectious and non-infectious models, NKT cells are activated by inflammatory cytokines (IL-12 or IL-18) paired with a weak endogenous antigen (Brigl et al., 2011). Typically, the endogenous antigen for iNKT cells is not identified in a particular disease model. Endogenous mammalian antigens that can activate iNKT cells include α-galactosylceramide (Kain et al., 2014), α-glucosylceramide (Brennan et al., 2014), and isoglobotrihexosylceramide (Zhou et al., 2004). After activation, NKT cells produce copious cytokines which trans-activate other immune cells (e.g., neutrophils, macrophages, B cells, T cells and others). NKT cells

* Corresponding author at: Brigham and Women's Hospital, Division of Pulmonary and Critical Care Medicine, Hale BTM 3016-I, 60 Fenwood Rd., Boston, MA, 02115, United States.
E-mail address: ekim11@bwh.harvard.edu (E.Y. Kim).

https://doi.org/10.1016/j.molimm.2018.09.026
Received 12 July 2018; Received in revised form 22 August 2018; Accepted 29 September 2018
Available online 13 December 2018

Table 1
Critical illnesses with innate T cell involvement. Diseases with greater than 10% mortality rate in the ICU are in boldface.

Sepsis
Burn injury
Acute respiratory distress syndrome (ARDS)
Cardiac arrest and resuscitation
Ischemia-reperfusion injury (kidney, liver, lung)
Stroke
Asthma exacerbation
Chronic Obstructive Pulmonary Disease (COPD) exacerbation
Sickle cell crisis

express cytotoxic molecules (e.g., perforin), but the amplification of the cytokine response by NKT cells overshadows their cytotoxic effects (Brennan et al., 2013). Like adaptive T cells, iNKT cells can be divided into functional subsets based on their cytokine production: NKT1 (IFNγ), NKT2 (IL-4), NKT10 (IL-10), NKT17 (IL-17) and NKT_{FH} (follicular helper) (Kim et al., 2015a,b,c). While cell surface markers have some inexact correlation to functional groups, assessment of cytokine production or transcription factors (e.g., t-bet in NKT1) is the best way to identify these subsets.

In mice, the NK cell marker NK1.1 is not a sufficient marker for NKT cells. In C57Bl/6 mice, there are $NK1.1^+$ T cells that do not recognize CD1d and thus are not NKT cells. Also, there are $NK1.1^-$ NKT cells. Furthermore, certain strains of mice, such as Balb/c, do not stain with anti-NK1.1 antibody. For humans, the NK cell marker CD56 is not a sufficiently specific marker for NKT cells. The gold standard is identifying iNKT cells by flow cytometry with a fluorochrome-conjugated CD1d tetramer loaded with the lipid antigen αGalCer that will bind the TCR of iNKT cells. Immunohistology with CD1d tetramers is possible but challenging (King et al., 2013). iNKT cells can also be identified by a fluorochrome-conjugated monoclonal antibody (mAb) against the invariant TCR (Montoya et al., 2007). Diverse NKT (dNKT) cells are more difficult to identify and study than invariant NKT cells. Since dNKT cells have different TCRs and antigen specificities, there is also no anti-TCR mAb or antigen-loaded CD1d tetramer that will recognize all dNKT cells. Sulfatide (sulfogalactosylceramide) is a prominent example of an endogenous lipid antigen presented by CD1d that activates a subset of dNKT cells. Sulfatide has a sulfate group at the 3′ position of the galactose headgroup. However, unlike the α-linked headgroup of αGalCer, sulfatide has a β-linked galactose headgroup. In additional, sulfatide and αGalCer differ in their ceramide lipid backbones (Zajonc et al., 2005). Experimental tools include the anti-CD1d mAb that blocks activation of all NKT cells and *cd1d* knock-out (CD1d KO) mice that lack all NKT cells (invariant and diverse). *Ja18* knock-out (Jα18 KO) mice lack the invariant TCR α chain required by invariant NKT cells, so Jα18 KO mice lack invariant NKT cells but still have diverse NKT cells.

1.2. MAIT cells

MAIT cells have an invariant TCR α chain comprised of Vα7.2 and Jα33 segments. MAIT cells share antigen specificity for riboflavin (vitamin B2) and folic acid metabolites presented by MR1, a homologue of MHC I (Kjer-Nielsen et al., 2012). MAIT cells are activated by bacteria with these synthetic pathways, such as *Enterobacter* and *Salmonella*. Just as the αGalCer antigen activates iNKT cells, the riboflavin metabolite 5-OP-RU (5-2-oxopropylideneamino-6-D-ribitylaminouracil) activates MAIT cells. Tetramers of MR1 molecules loaded with 5-OP-RU identify MAIT cells by flow cytometry. MAIT cells are often identified as $Vα7.2^+CD161^+$ T cells, although this subset can include some T cells that are not MAIT cells. The folate metabolite 6-formylpterin (6-FP) is generally an inhibitory antigen for MAIT cells, but 6-FP can activate a subset of MAIT cells (Gherardin et al., 2016). MAIT cells are generally $CD4^-CD8^+$ or $CD4^-CD8^-$, although $CD4^+CD8^-$ MAIT cells exist (Reantragoon et al., 2013). Like NKT cells, MAIT cells can be activated by the inflammatory cytokines IL-12 and IL-18 without strong TCR activation by the MR1-antigen complex. Therefore, microbes like *Mycobacterium* that do not produce the riboflavin or folate metabolite antigens can still activate MAIT cells (Chua et al., 2012). The functional subsets of NKT cells do not map directly to MAIT cells. Most importantly, the transcriptional factor RORγt is limited to NKT17 cells, but most MAIT cells express RORγt and can produce IL-17 (Rahimpour et al., 2015). However, some functional subsets do overlap. For example, adipose tissue is enriched for both NKT10 cells and MAIT cells producing IL-10 (Carolan et al., 2015).

1.3. Tissue distribution

After developing in the thymus, innate T cells migrate to peripheral tissues (Table 2). Since they reside in the periphery, innate T cells are well positioned to respond early to infections and cause end-organ inflammation in critical illness. Unlike adaptive T cells, NKT cells and MAIT cells do not have a large presence in lymph nodes. MAIT cells are by far the most abundant innate T cell in humans. MAIT cells represent as much as 10% of circulating T cells and 25% of hepatic T cells. By contrast, iNKT cells are rare in humans (i.e., 0.01 to 0.5% of circulating T cells). In the opposite ratio as humans, mice have much greater numbers of NKT cells and few MAIT cells. In mice, NKT cells comprise 30% of hepatic T cells, and MAIT cells are less than 1%. These baseline cell numbers can change dramatically as innate T cells proliferate, migrate or undergo apoptosis during illness (Chiba et al., 2008). For example, although there are few MAIT cells in murine lung at baseline, MAIT cells accumulate markedly in the lung during experimental bacterial pneumonia due to *Klebsiella* (Georgel et al., 2011), *Salmonella* (Chen et al., 2017b), and *F. tularensis* (Meierovics and Cowley, 2016).

Being abundant in humans, MAIT cells are of particular interest in clinical studies; and NKT cells are a greater focus in mouse models. However, both cell types merit study in both clinical and experimental disease. For example, the relatively few iNKT cells in humans can have an outsized impact since all iNKT cells can be activated in concert by the same antigen or stimulus. To illustrate this point, we note that a very small fraction of adaptive T cells will respond to a given illness. For example, among patients with immunity to influenza, influenza-specific adaptive T cells were undetectable in half of the patients or averaged just 0.2% of T cells if detected at all (Boon et al., 2002). However, this small fraction of adaptive T cells is often sufficient to mount a robust response if a patient re-encounters this influenza strain. This analogy suggests that iNKT cells, even if only 0.2% of T cells in a patient, may still drive a significant response since all the iNKT cells could be activated in concert.

2. Sepsis

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al., 2016). Sepsis affects over two million patients in the U.S. each year (Gaieski et al., 2013). In the ICU, sepsis accounts for 30% of admissions worldwide and has a mortality rate of 25% (Vincent et al., 2014). Survival of clinical sepsis is improving due to earlier recognition and aggressive supportive treatment. However, improved clinical outcomes have been unable to keep pace with a rising incidence owing to an aging population with increased medical comorbidities (Gaieski et al., 2013; Iwashyna et al., 2012). Early activation of both pro- and anti-inflammatory processes occur following infection in patients with sepsis. While pro-inflammatory mediators serve to combat and contain microbial invaders, the over-exuberant early immune response in septic patients causes collateral tissue damage and mortality. However, sepsis also causes immunosuppression that impairs clearance of the primary infection and creates susceptibility to secondary nosocomial infections (Hotchkiss et al., 2013). Innate T cells, as critical intermediaries bridging innate and adaptive immune responses, contribute to the unbalanced immune

Table 2
Distribution of innate T cells at baseline. The number of diverse NKT cells is difficult to assess.

			Percentage of all T cells					
			Peripheral blood		Liver		Lung	
	Antigen	Antigen presenting molecule	Human	Mouse	Human	Mouse	Human	Mouse
iNKT cells	Glyco-sphingolipid	CD1d	0.01-0.5% (Kenna et al., 2003; Kita et al., 2002)	0.2-0.5% (Eberl et al., 1999)	<4% (Kenna et al., 2003; Kita et al., 2002)	30% (Eberl et al., 1999; Matsuda et al., 2000; Thomas et al., 2011)	<0.1% (Konishi et al., 2004)	5-10% (Scanlon et al., 2011; Thomas et al., 2011)
MAIT cells	Vitamin B2 derivative	MR1	1-10% (Dusseaux et al., 2011; Tang et al., 2013; van Wilgenburg et al., 2016)	0.1% (Rahimpour et al., 2015; Tilloy et al., 1999)	9%-25% (Dusseaux et al., 2011; Tang et al., 2013; van Wilgenburg et al., 2016)	<1% (Rahimpour et al., 2015)	0.2-10% (Hinks et al., 2016)	3% (Rahimpour et al., 2015)
γδ T cells	Largely unknown	Largely not known	1-8% (Groh et al., 1989; Kenna et al., 2004; Parker, 1990; Tang et al., 2013)	0.5-4% (Funda et al., 1995)	5-10% (Kenna et al., 2004; Tang et al., 2013)	10-20% (Ohteki et al., 1991)	1-5% (Pons et al., 2005; Urboniene et al., 2013)	<5% (Uezu et al., 2004; Wu et al., 2017)

response underlying the sepsis syndrome (Szabo et al., 2015). Apart from its effect on septic immunopathology, innate T cells also play key roles in clearance of primary infections, which has been reviewed extensively elsewhere (Chandra and Kronenberg, 2015; Cohen et al., 2009).

2.1. NKT cells in sepsis

During clinical sepsis, patients have increased circulating iNKT cells, both in absolute number and as a percentage of T cells. This increase in iNKT cell number may reflect mobilization or proliferation, both of which are seen in mouse models of infection. Increased percentages of iNKT cells correlated with mortality in geriatric patients in two sepsis studies (Anantha et al., 2014; Heffernan et al., 2013); however, this has not been a universal finding (Grimaldi et al., 2014). A prominent experimental model of sepsis is cecal ligation and puncture (CLP), in which the cecum is ligated and punctured with a needle. CLP causes a steady leak of intestinal contents and bacterial peritonitis. In the CLP model, hepatic iNKT cells are activated (as shown by increased surface expression of CD69 and CD25 (Hu et al., 2009)) and migrate to the peritoneum (Heffernan et al., 2013). CD1d blocking mAb (Rhee et al., 2003) and Jα18 KO mice (Hu et al., 2009) demonstrated that iNKT cells worsen survival in the CLP model of sepsis. Another study of CLP sepsis using CD1d KO mice showed that NKT cells had no effect on mortality (Etogo et al., 2008). Possible explanations include a role for diverse NKT cells, microbiome, or CLP technique. In the LPS sepsis model, our laboratory has found that some effects of NKT cells are seen in moderate sepsis but lost in very severe sepsis. Similarly, the worse severity of sepsis in the study by Etogo et al. may have masked the effect of NKT cells. Etogo et al. had 100% mortality by 24 h, compared to 20% mortality by 24 h for Hu et al.

Several mechanisms contribute to the maladaptive role of iNKT cells in sepsis. In experimental sepsis, iNKT cells drive systemic expression of inflammatory cytokines (e.g., IL-6, TNFα, and IFNγ) and chemokines (e.g., MCP-1). iNKT cells also drive increased levels of the anti-inflammatory cytokine IL-10, which may be a response to increased inflammation (Hu et al., 2009; Kim et al., 2014; Rhee et al., 2003). iNKT cells themselves produce cytokines and, more importantly, stimulate cytokine production by other innate immune cells (Hu et al., 2009). Multiple inputs regulate iNKT cells in sepsis. PD-1 is required for iNKT cell migration to the peritoneum in the CLP model (Heffernan et al., 2013). Complement C5a increases the recruitment and activity of iNKT cells in sepsis (Fusakio et al., 2011; Klos et al., 2009). Blockade of C5a reduced mortality in septic wild-type mice, but not in CD1d KO mice (Kim et al., 2014). C5a and iNKT cells may have a positive feedback loop, as iNKT cells contribute substantially to C5a production during sepsis (Kim et al., 2014). iNKT cells also worsen outcomes in LPS sepsis. In the Schwartzman reaction, Jα18 KO mice primed with a first dose of LPS are resistant to death from a second dose of LPS compared to wild-type mice (Dieli et al., 2000). In addition, activating iNKT cells with αGalCer antigen increases the susceptibility of wild type mice to LPS-mediated death (Ito et al., 2006).

These studies suggest that inhibiting or reprogramming iNKT cells may improve outcomes in acute sepsis. One strategy is treatment with exogenous antigen or cytokine to skew iNKT cell responses. OCH is an altered glycolipid antigen that skews iNKT cells toward a NKT2 cytokine profile (i.e., IL-4) (Miyamoto et al., 2001; Yu et al., 2005). Treatment with OCH prolonged survival in a mouse model of intraabdominal sepsis (Anantha et al., 2014). Treating patients with NKT cell antigens may be feasible, as cancer patients have been treated safely with αGalCer, although sepsis is certainly a different clinical context (Kunii et al., 2009; Motohashi et al., 2009). Treatment with IL-30 (a subunit of IL-27 in the IL-12 family) improved survival in LPS and CLP sepsis by skewing iNKT cells toward increased IL-10 and decreased IFNγ and TNFα production (Yan et al., 2016). Another strategy is modulating immune checkpoint receptors on innate T cells, such as the inhibitory immune checkpoint receptor Tim-3. After treatment with galectin-9 (an agonist of Tim-3), mice expand their splenic iNKT cell population. Treatment with galectin-9 decreased inflammatory cytokines and improved survival in the CLP model, but it is not certain that this effect is mediated by NKT cells (Kadowaki et al., 2013). If the protective effect of galectin-9 was mediated by iNKT cells, it would not be clear whether galectin-9 treatment expanded a beneficial iNKT cell subset or simply inhibited the function of a pathogenic subset. Confusingly, treatment

with an inhibitor of Tim-3 signaling (α-lactose) also increased the number of iNKT cells and attenuated the levels of inflammatory cytokines (Yao et al., 2017). Adoptive transfer of Tim-3-deficient NKT cells might help clarify the relationship between immune checkpoint therapy and iNKT cells. Like NKT cells, MAIT cells also upregulate surface expression of immune checkpoint molecules, like LAG-3, TIM-3 and PD-1, in sepsis models (Shaler et al., 2017). Investigation of innate T cells and immune checkpoint therapy in sepsis is very topical, since clinical trials of PD-1/PD-L1 blockade are underway in sepsis. An alternative strategy is activating an anti-inflammatory subset of innate T cells like sulfatide-reactive diverse NKT cells. In *S. aureus* sepsis, treatment with sulfatide antigen activated diverse NKT cells, decreased production of inflammatory cytokines and improved survival of mice in a CD1d-dependent manner (Kwiecinski et al., 2013).

2.2. MAIT cells and γδ T cells in sepsis

Compared to NKT cells, much less is known about MAIT cells in sepsis. There is a marked reduction of MAIT cells in circulation in septic patients compared to non-infected critically ill and healthy control patients. A persistent reduction in MAIT cell number was associated with the development of secondary infections (Grimaldi et al., 2014). Interpreting the decreased number of circulating MAIT cells is difficult, as this change could reflect trafficking of MAIT cells to end-organs or apoptosis. In vitro studies of human cells and humanized mice show that MAIT cells are a dominant source of inflammatory cytokines (i.e., IFNγ and TNFα) after exposure to bacterial super-antigen (Shaler et al., 2017). This model may have relevance to toxic shock or a subset of sepsis.

In clinical sepsis, γδ T cells are activated with increased surface expression of CD69 and HLA-DR (Matsushima et al., 2004). Like MAIT cells, γδ T cells are decreased in number in the peripheral circulation by as much as 80% (Andreu-Ballester et al., 2013; Heffernan et al., 2013; Venet et al., 2006). Like MAIT cells, it is unclear whether this decrease in circulation reflects migration to end-organs, cell death or difficulty in detection. Lower γδ T cell numbers correlated with more severe clinical sepsis and worse mortality (Andreu-Ballester et al., 2014; Andreu-Ballester et al., 2013). This reduction in γδ T cells was also seen in non-infected critically ill patients, and any causal relationship between γδ T cells and clinical sepsis remains to be determined (Grimaldi et al., 2014; Matsushima et al., 2004). In the CLP model of experimental sepsis, γδ T cell were activated and their numbers increased in spleen, gut epithelium and lung (Chung et al., 2006; Costa et al., 2015). In the CLP model of sepsis, γδ T cell-deficient mice had decreased inflammatory cytokines and improved survival (Chung et al., 2006; Costa et al., 2015). A key question is what subsets of γδ T cells are important in sepsis. γδ T cell subsets with different gamma chain subunits in their TCR often have distinct functions. One study suggested that the $V\gamma4^+$ subset of γδ T cells drives inflammation and mortality in sepsis (Costa et al., 2015).

2.3. Post-sepsis and post-burn injury immunosuppression

Previously healthy patients can become profoundly immunocompromised after sepsis or trauma (Church et al., 2006; Hotchkiss et al., 2013). After recovering from the early, inflammatory phase of sepsis, patients become susceptible to secondary infections, including opportunistic infections that would not infect a healthy host, such as candidemia or ventilator-associated pneumonia due to *Stenotrophomonas*. Mechanisms of post-sepsis immunosuppression include anti-inflammatory cytokines (e.g., IL-4 or IL-10) and immunosuppressive cells like regulatory T cells and myeloid derived suppressor cells (MDSCs) (Delano et al., 2007; Hotchkiss et al., 2013; Uhel et al., 2017; Venet et al., 2006; Wisnoski et al., 2007). The role of innate T cells in post-sepsis immunosuppression is poorly understood and is a focus of our laboratory. We have established that iNKT cells drive post-sepsis immunosuppression and susceptibility to secondary candidemia via novel mechanisms (Kim et al., 2017).

Trauma due to burn injury is often complicated by hospital-acquired secondary infection. Severe burn injury requires intensive care for wound management, hemodynamic abnormalities, fluid imbalance, respiratory failure, and multi-system organ failure. Burn injury triggers an early systemic inflammatory response and post-burn immunosuppression (Church et al., 2006). In the dorsal scalding model of burn injury, murine iNKT cells producing IL-4 drove post-burn immunosuppression (Faunce et al., 2003; Palmer et al., 2006). Adoptive transfer of iNKT cells from post-burn mice into healthy recipient mice showed that post-burn iNKT cells suppressed adaptive T cell function (as measured by delayed hypersensitivity and cytokine production) (Palmer et al., 2006). As a possible therapeutic strategy, treatment with αGalCer after burn injury drove iNKT cells towards IFNγ (and away from IL-4) and prevented post-burn immunosuppression (Tulley et al., 2008). Although iNKT cells drive immunosuppression after sepsis and burn injury, iNKT also can alleviate immunosuppression in other contexts. After influenza infection, iNKT cells improve immunocompetence by “suppressing the suppressor.” In experimental influenza infection, iNKT cells reduce the immunosuppressive activity of MDSCs (De Santo et al., 2008). The role of MAIT cells in post-sepsis or burn immunosuppression is undefined and a potential area of study.

3. Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a common diagnosis in the ICU and has 40% mortality (Bellani et al., 2016). ARDS is acute and diffuse lung injury that causes poor oxygen and carbon dioxide exchange. A wide variety of insults can trigger ARDS, such as lung injury due to pneumonia or aspiration pneumonitis; systemic illness such as sepsis, burn injury or trauma; and abdominal processes such as acute pancreatitis or abdominal surgery. Several mouse models of ARDS exist. In a direct injury model, mice are treated with intra-tracheal or aerosolized LPS. Intravenous LPS sepsis can also lead to ARDS. In both models, iNKT cells are not necessary for lung injury. However, iNKT cells do have the capacity to worsen ARDS, as treatment with αGalCer exacerbated ARDS. In the LPS models, activation of iNKT cells with αGalCer increased levels of IFNγ and TNFα, increased cellular infiltrates and worsened respiratory failure (Aoyagi et al., 2011; Ito et al., 2006). In the inhaled LPS model, iNKT cells trans-activated NK cells and Ly6c+ macrophages to produce IFNγ. This NKT cell-IFNγ axis also suppressed recruitment of protective regulatory T cells producing IL-10 (Toyama et al., 2018).

In the mouse model of αGalCer followed by intravenous LPS sepsis, there was little hepatic injury despite the large native population of iNKT cells in the liver. One study argues that the liver is protected because hepatic iNKT cells produce the anti-inflammatory cytokines IL-4 and IL-10 in addition to IFNγ, whereas pulmonary iNKT cells only produce IFNγ (Dagvadorj et al., 2010). Overall, given that iNKT cells have no effect in experimental ARDS unless pre-treated with αGalCer, the significance of iNKT cells in acute lung injury is unclear. One future direction is testing the ventilator-induced lung injury model, which simulates an important aspect of clinical ARDS and may have a different immunopathology than LPS.

4. Ischemia-reperfusion injury

Ischemia-reperfusion injury (IRI) underlies several critical illnesses. Cardiac arrest followed by cardiopulmonary resuscitation (CPR) can be considered “global IRI.” Our laboratory is the first group to investigate the role of innate T cells in cardiac arrest. We have discovered that sulfatide-specific dNKT cells are protective after cardiac arrest and resuscitation (Kim et al., 2015a). Examples of organ-specific IRI include stroke or myocardial infarction (i.e., “heart attack”) if the clot in the cerebral or coronary artery is cleared by treatment. Organ transplantation is another scenario for IRI. Here, the donated organ is ischemic

for hours prior to implantation in the recipient patient. After direct damage from ischemia, reperfusion brings inflammation that causes additional injury. IRI models also may give insight into hypotensive injury due to sepsis or hemorrhagic shock. In sepsis or shock, organs experience relative ischemia followed by reperfusion as normal blood pressures are restored.

4.1. Renal, hepatic and lung ischemia-reperfusion injury

To model organ-specific IRI, the feeding artery to an organ (e.g., renal artery) is clamped for short periods of time (e.g., 30 min). Then the clamp is opened, and the organ is reperfused. iNKT cells worsen injury in renal (Li et al., 2007a, 2007b; Zhang et al., 2016), hepatic (Kazuhiko et al., 2005; Kuboki et al., 2009; Lappas et al., 2006), and lung (Sharma et al., 2013, 2011) IRI. iNKT cells appear in the kidney as early as 30 min after IRI (Li et al., 2007a, 2007b)). In hepatic IRI, iNKT cell numbers peak in the liver at 12 h after reperfusion (Kazuhiko et al., 2005). iNKT cells drove injury via IFNγ in both renal and hepatic IRI (Lappas et al., 2006; Li et al., 2007a, 2007b). Interestingly, iNKT cells drove neutrophils to produce significant amounts of IFNγ in renal IRI (Li et al., 2007a, 2007b). While renal and hepatic IRI was driven by IFNγ, iNKT cell-dependent lung IRI was caused by IL-17 A and neutrophils (Sharma et al., 2011). Several pathways regulate iNKT cells in IRI. The receptor for advanced glycation end products (RAGE) increases production of IL-17 A by iNKT cells and worsens injury (Sharma et al., 2013). On the protective side, hypoxia-inducible factor (HIF)-2α increases expression of protective adenosine A_{2A} receptor on NKT cells (Lappas et al., 2006; Zhang et al., 2016).

Earlier studies did not investigate the role of diverse NKT cells. On closer inspection, dNKT cells can protect against IRI and oppose the injury caused by iNKT cells. Sulfatide-reactive dNKT cells protect against IRI in brain, liver and kidney. Intriguingly, sulfatide lipid is highly enriched in brain myelin and is also found in kidney and, to a lesser extent, liver (Mirzaian et al., 2015). Sulfatide-reactive dNKT cells reduced brain injury in our laboratory's study of experimental cardiac arrest and resuscitation (Kim et al., 2015a). Similarly, activating dNKT cells with sulfatide before IRI protected against kidney and hepatic injury (Arrenberg et al., 2011; Yang et al., 2011). In renal IRI, dNKT cells protected by increasing levels of IL-10, which upregulated HIF-1α. In hepatic IRI, dNKT cells reduced levels of IFNγ and inflammation. The role of sulfatide-specific dNKT cells is undefined in clinical IRI. The study of sulfatide-specific innate T cells is more complicated in clinical disease. Unlike in the mouse, sulfatide is reported to activate human invariant NKT cells (Stax et al., 2017). Furthermore, a subset of γδ T cells recognize sulfatide lipid presented by CD1d. One study suggested that the majority of sulfatide-CD1d specific T cells in human circulation are γδ T cells, although this finding needs further examination (Bai et al., 2012). γδ T cells could have a role in clinical IRI. In experimental IRI, γδ T cells worsened injury in a mouse model of renal IRI (Hochegger et al., 2007) but had no effect on hepatic IRI (Kuboki et al., 2009). The role of MAIT cells in IRI remains undefined.

4.2. Stroke

Strokes are either ischemic due to occlusion of a blood vessel or hemorrhagic from blood vessel rupture. An ischemic stroke can undergo hemorrhagic conversion as the injury evolves. An ischemic stroke can also involve reperfusion injury if the thrombus is lysed with tissue plasminogen activator (tPA) or cleared with direct endovascular intervention, which is usually done within the first 4 to 6 h after symptom onset. The most common mouse model of ischemic stroke is occlusion of the middle-cerebral artery (MCA). In this mouse model of stroke, *rag1-/-*, *ifng-/-* and *prf-/-* (perforin-deficient) mice all had reduced brain infarct size (Liesz et al., 2011; Yilmaz et al., 2006). The involvement of lymphocytes, IFNγ, and perforin suggested a role for innate T cells. IL-17A-producing γδ T cells worsened stroke injury in one study (Shichita et al., 2009), although another study showed no role for γδ T cells (Kleinschnitz et al., 2011). The reasons for this discrepancy are unclear. CD1d KO mice showed that NKT are not involved in stroke (Wong et al., 2011).

After surviving the early phase of stroke, patients become more susceptible to infection. Several clinical trials have tested antibiotic treatment after stroke to prevent secondary infections, with mixed results (Shi et al., 2018). NKT cells did not affect brain injury after stroke, but NKT cells are important in protecting against opportunistic infections after stroke. NKT cell-deficient mice did have much higher rates of spontaneous infection after stroke compared to wild-type mice (Sharma et al., 2011). Shi et al. identified that stroke activated the sympathetic nervous system in the liver, and this noradrenergic signaling caused hepatic iNKT cells to become stationary or "pirouet" in place and presumably become less effective at surveying for infection, as shown by intra-vital microscopy (Wong et al., 2011). Both blockade of β-adrenergic signaling with propranolol or activation of iNKT cells with αGalCer antigen protected against post-stroke infection. These interventions shifted iNKT cells toward production of IFNγ and away from IL-10. The role of MAIT cells in stroke is unknown. More broadly, the role of all innate T cells in clinical stroke needs to be explored.

5. Acute exacerbation of chronic disease

5.1. Asthma or COPD exacerbation

Acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD) lead to respiratory failure due to bronchospasm and increased airway secretions. Patients can require either non-invasive positive pressure ventilation by mask (NIPPV) or endotracheal intubation and mechanical ventilation. Aside from glucocorticoid steroids, we lack effective immunomodulatory therapies for acute exacerbations. Thus, understanding the immunology of acute exacerbation is a priority. As proof of principle for iNKT cell involvement, intra-nasal challenge with the NKT cell antigen αGalCer was sufficient to induce airway hyper-reactivity and eosinophilia, two hallmarks of allergic asthma (Meyer et al., 2006). Viral infection (e.g., by respiratory syncytial virus [RSV]) is a common cause of asthma or COPD exacerbations. In our prior work, respiratory infection of mice by Sendai virus (a relative of RSV) modelled the development of asthma and COPD and their acute exacerbations. iNKT cells induced chronic production of IL-13 by macrophages, which lead to life-long goblet cell metaplasia and airway hyper-reactivity, two hallmarks of asthma and COPD (Kim et al., 2008). Remarkably, this NKT cell-driven axis first appears one month after the clearance of the Sendai viral infection. This model represents a rare example of chronic activation of NKT cells in the absence of repeated exogenous stimuli. In the ovalbumin (OVA) model of allergic asthma, mice are sensitized by intra-peritoneal injection with adjuvant (e.g., alum) and challenged by repeated intra-nasal or aerosol challenge. In the OVA model, NKT cells drove Th2-like inflammation (i.e., IL-4 and IL-13) and airway hyper-reactivity (Akbari et al., 2003). As in several other disease models, treatment with sulfatide lipid antigen is a potential treatment. Sulfatide antigen treatment activated diverse NKT cells, reduced inflammation and improved disease in the OVA model (Zhang et al., 2018).

We demonstrated increased iNKT cells and IL-13-producing macrophages in clinical asthma and COPD (Kim et al., 2008). In clinical asthma, there is keen interest in MAIT cells. One study examined MAIT cells ($TCRV\alpha7.2^+CD161^+$) and iNKT cells ($TCRV\alpha24^+$) in circulation in one year old infants in the prospective Urban Environment and Childhood Asthma (URECA) cohort of infants at high risk to develop asthma (n = 110). Increased MAIT cell percentages at one year of age correlated with increased Th1 phenotype in infancy and decreased risk of developing asthma later in childhood (Chandra et al., 2018). No correlation was seen with iNKT cells. A second, smaller study suggested that MAIT cells may have a deleterious role later in life. In older

asthmatic children (mean age 11 years, n = 11), an increased percentage of IL-17$^+$ MAIT cells (TCRVα7.2$^+$CD161$^+$) correlated with increased exacerbations (Lezmi et al., 2018). IL-17$^+$ γδ T cells and iNKT cells did not correlate with exacerbation. Further study is required to confirm the hypothesis that MAIT cells are protective in infancy but injurious in older children. If confirmed, one possible explanation is that, as a child develops disease, the immunological milieu activates MAIT cells to produce IL-17, which worsens inflammation and drives a detrimental feedback loop. An intriguing question is the role of innate T cells in the different subtypes of clinical asthma: IL-17/neutrophilic asthma, IFNγ-predominant severe asthma, or classic Th2-predominant/allergic asthma.

5.2. Sickle cell crisis

Patients with sickle cell disease have a mutated β-hemoglobin gene. These patients have intermittent vaso-occlusive episodes causing pain and chronic damage to multiple organ systems. Sickle cell patients are admitted to the ICU for acute pain crisis, acute chest syndrome (pulmonary injury and hypoxemia), or stroke (Kato et al., 2018). Acute care is supportive, with exchange blood transfusions and glucocorticoid steroids limited to the most severe situations. Patients with sickle cell disease have increased numbers of circulating iNKT cells (> 4% of T cells, versus < 1% in healthy controls). iNKT cells from sickle cell patients are more activated and produce more IFNγ (Wallace et al., 2009), which suggests a pathogenic role for iNKT cells. A model of sickle cell disease is the NY1DD mouse, which has human α- and β5-globin transgenes and deletion of the mouse β-globin gene (Fabry et al., 1992). This mouse model demonstrated that activated iNKT cells are recruited to the lung and cause lung injury via IFNγ. In sickle cell disease, a phase I clinical trial tested depletion of iNKT cells with the monoclonal antibody NKTT120 that targets the invariant NKT cell TCR (Field et al., 2017). After a single dose of NKTT120, iNKT cells were not detected in patients for as long as 5 months. A caveat is, since anti-TCR antibodies were used to detect iNKT cells, it is possible that the iNKT cells were present but no longer detected due to internalization of their TCR, although this possibility is less likely weeks and months later. Treatments used in other critical illnesses, such as altered antigens to skew behavior or antigens activating protective subsets, may also apply to sickle cell disease.

6. Chronic disease

In addition to driving acute illness, innate T cells are implicated in the chronic diseases that are risk factors for critical illness. A common diagnosis in the ICU is diabetic ketoacidosis (DKA)—a crisis for diabetic patients with severe metabolic acidosis, hyperglycemia and electrolyte derangement requiring intravenous insulin infusion and fluids. Innate T cells may be involved in the development of the underlying metabolic syndrome and diabetes mellitus. iNKT cells are protective in experimental diabetes (Beaudoin et al., 2002; Biden et al., 2014) and obesity (Lynch et al., 2012). MAIT cells are reduced in circulation at the onset of clinical type 1 diabetes (Rouxel et al., 2017), type II diabetes, and severe obesity (Magalhaes et al., 2015). Future studies may delineate whether MAIT cells are predominantly pathogenic (e.g., leaving circulation to infiltrate and damage the pancreas) or protective (and thus reduced in number at the onset of disease). Hepatic failure due to cirrhosis (i.e., hepatic fibrosis) is a major risk factor for critical illness. Cirrhotic patients are susceptible to sepsis (including opportunistic infections like candidemia) and catastrophic gastrointestinal hemorrhage. In mouse models of hepatic disease, iNKT cells are pathogenic, and γδ T cells are protective (Hammerich et al., 2014). However, given the many etiologies of cirrhosis (e.g., alcohol abuse, steatohepatitis, and hepatitis C infection), the role of innate T cells is likely complicated. Innate T cells may modulate the underlying cardiovascular disease that leads to myocardial infarction, heart failure and stroke. In several studies, iNKT cell-deficient mice are protected against atherosclerosis (Nakai et al., 2004; Rogers et al., 2008; VanderLaan et al., 2007). Finally, oncology patients are susceptible to sepsis due to immunosuppression from malignancy or chemotherapy. Innate T cells can be protective and aid tumor surveillance (Godfrey et al., 2018), or innate T cells can drive tumor-associated immunosuppression (Izhak et al., 2013; Renukaradhya et al., 2008). Oncology patients are developing novel critical illnesses due to complications of immunotherapies like immune checkpoint therapy or chimeric antigen receptor T (CAR-T) cells. Future studies could investigate whether secondary activation of innate T cells occurs during adverse reactions to these new therapies.

7. Discussion

Clinical and experimental studies have implicated innate T cells in most of the critical illnesses that bring patients to the ICU (Table 1). In line with their role as “cellular adjuvants,” innate T cells worsen critical illness by coordinating harmful inflammatory responses. In experimental models, iNKT cells drive IFNγ production that worsen outcomes in sepsis, post-sepsis immunosuppression, kidney and liver ischemia-reperfusion injury, sickle cell crisis and possibly ARDS. NKT cell-mediated IL-17 worsens lung ischemia-reperfusion injury. IL-13 drives asthma and COPD exacerbations (Fig. 1A). γδ T cells worsen sepsis and stroke via IFNγ or IL-17 A, respectively (Fig. 1B). Innate T cells also have pathogenic anti-inflammatory effects, as in post-burn immunosuppression caused by NKT cell-driven IL-4 production (Fig. 1A). Thus, innate T cells are attractive targets for therapeutic intervention. Several approaches can modify the behavior of pathogenic innate T cells. Exogenous treatment with altered lipid antigens (e.g. OCH), cytokines (e.g., IL-30) or immune checkpoint modulators (e.g., Tim-3 ligands) skew iNKT cell towards anti-inflammatory cytokines and improve outcomes in sepsis (Fig. 2A). In the opposite scenario, treatment with αGalCer activates iNKT cells to produce IFNγ and ameliorate post-burn and post-stroke immunosuppression (Fig. 2B). Alternatively, one can activate a protective innate T cell subset. Treatment with sulfatide lipid antigen activates dNKT cells and improves outcomes in sepsis, ischemia-reperfusion injury and asthma exacerbation (Fig. 2C).

There are several challenges unique to studying critical care medicine. A major technical challenge for experimental models is the complexity of critical care in the ICU. For example, septic patients are often intubated for mechanical ventilation, on continuous intravenous infusions of vasopressors to raise their blood pressure and on hemodialysis. Very few laboratories can replicate that level of supportive care. Thus, ICU patients experience a severity of systemic illness that is usually not modelled in the laboratory. For example, we faced the challenge of modeling the “two hits” of post-sepsis immunosuppression: primary sepsis followed by secondary, opportunistic infection. Without the benefit of continuous mechanical ventilator or vasopressors, we needed severe sepsis with 100% survival that allowed the subsequent challenge with a secondary infection. In this case, we opted for the model of LPS sepsis rather than cecal ligation and puncture (CLP). Since LPS sepsis is more transient than the CLP model, LPS sepsis titrated to 100% survival had a worse “peak illness” than the CLP model titrated to 100% survival. As a trade off, we lost the sustained illness of the CLP model. While not practical, a miniature murine ICU would be an ideal way to model the later complications of sepsis like immunosuppression or ARDS. A second technical challenge is that most clinical studies are limited to the peripheral circulation. However, innate T cells primarily reside in end-organs, so the peripheral circulation gives a very limited picture of human innate T cell function. Obtaining tissue from critically ill patients is a challenge. Routine research protocols, like bronchoscopic biopsies, are less feasible in critically ill patients. Possible options for tissue analysis include explanted organs after organ transplantation, post-mortem examinations, or novel imaging like immuno-positron emission tomography (immuno-PET). Immuno-PET uses radiolabeled antibodies or small-molecule PET probes to track immune cells

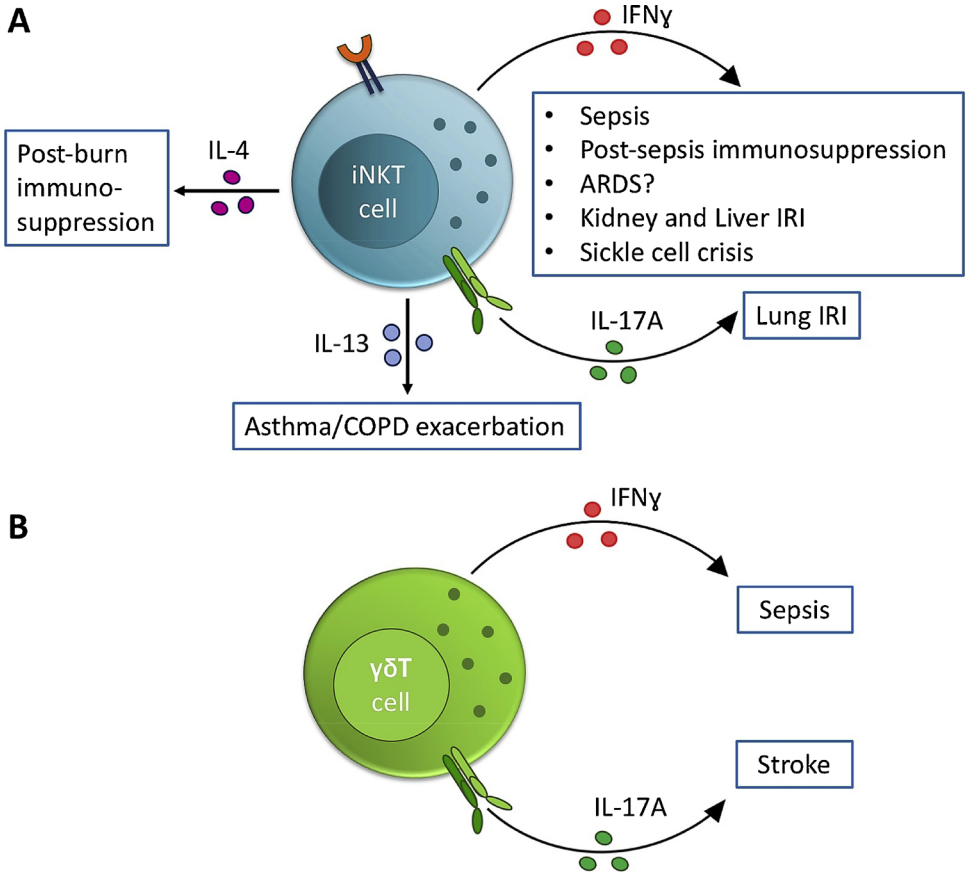

Fig. 1. Innate T cells drive critical illness. **(A)** Invariant NKT (iNKT) cells drive the production of inflammatory and immunosuppressive cytokines that worsen outcomes in experimental critical illnesses. IRI = ischemia-reperfusion injury. ARDS = acute respiratory distress syndrome. **(B)** γδ T cells drive the production of inflammatory cytokines that worsen outcomes in experimental sepsis and stroke.

in vivo (Tavare et al., 2014).

There are a several exciting opportunities unique to studying innate T cells in critical care medicine. Most studies to date have focused on the early phase after innate T cell activation. Less is known about the resolution of innate T cell responses in critical illness. After activation, innate T cells often undergo a refractory period when the innate T cell is unresponsive to further stimulation (Chiba et al., 2008). The implications of this phenomenon in critical illness (e.g., post-illness immunosuppression) is unknown. The role of innate T cells has not been well explored in many critical illnesses. For example, trauma patients have decreased MAIT and iNKT cells in circulation (Kim et al., 2015a, 2015b). However, relatively little experimental work on innate T cells has been done in trauma (Chen et al., 2017a). Another opportunity is the growing appreciation for neuro-inflammation in critical illnesses other than stroke, such as in sepsis (Singer et al., 2018). The role, if any, for innate T cells is unexplored. Despite intense efforts, supportive care remains a mainstay of treatment in the ICU. Attempts at immunological interventions have failed, such as the clinical trial of the IL-1 receptor antagonist in sepsis (Fisher et al., 1994; Opal et al., 1997). We hope that further exploration of innate T cells in critical illness could generate new approaches for therapeutic interventions in the ICU.

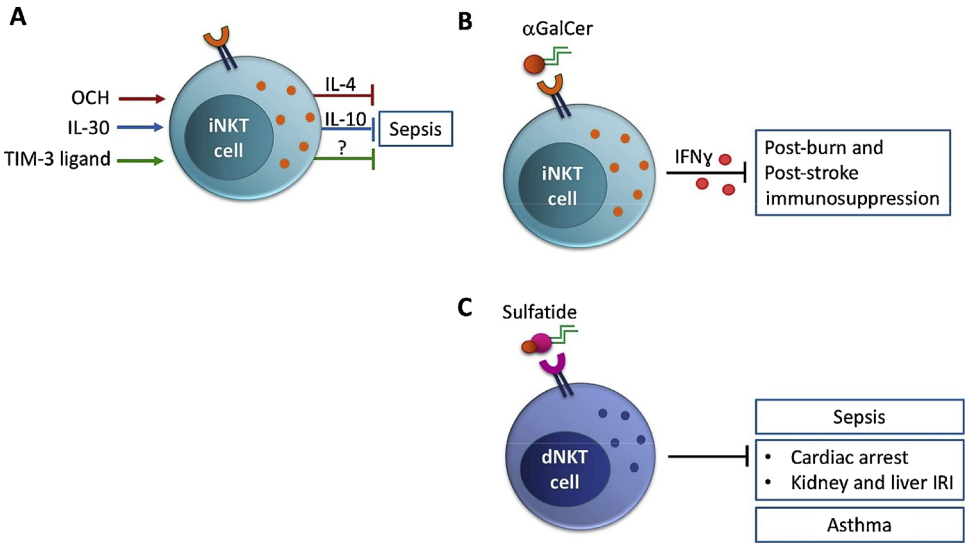

Fig. 2. Innate T cells are therapeutic targets in critical illness. **(A)** Treatment with altered lipid antigens (OCH), exogenous cytokines (IL-30) or ligands for immune checkpoint receptors (Tim-3) skew iNKT cells towards an anti-inflammatory phenotype and improve outcomes in experimental sepsis. **(B)** αGalCer antigen activates iNKT cells, which coordinate production of IFNγ and ameliorate post-burn and post-stroke immunosuppression. **(C)** Sulfatide antigen activates diverse NKT cells, which improve outcomes in experimental sepsis, ischemia-reperfusion injury (IRI) and asthma exacerbation.

8. Funding

EYK is supported by the American Heart Association15FTF25080205 and NHLBIR01HL123546. WMO is supported by the NHLBIK08HL128802.

References

Akbari, O., Stock, P., Meyer, E., Kronenberg, M., Sidobre, S., Nakayama, T., Taniguchi, M., Grusby, M.J., DeKruyff, R.H., Umetsu, D.T., 2003. Essential role of NKT cells producing IL-4 and IL-13 in the development of allergen-induced airway hyperreactivity. Nat. Med. 9, 582–588. https://doi.org/10.1038/nm851.

Anantha, R.V., Mazzuca, D.M., Xu, S.X., Porcelli, S.A., Fraser, D.D., Martin, C.M., Welch, I., Mele, T., Haeryfar, S.M.M., Mccormick, J.K., 2014. T helper type 2-polarized invariant natural killer T cells reduce disease severity in acute intra-abdominal sepsis. Clin. Exp. Immunol. 178, 292–309. https://doi.org/10.1111/cei.12404.

Andreu-Ballester, J.C., Tormo-Calandín, C., Garcia-Ballesteros, C., Pérez-Griera, J., Amigó, V., Almela-Quilis, A., Ruiz del Castillo, J., Peñarroja-Otero, C., Ballester, F., 2013. Association of γδ T cells with disease severity and mortality in septic patients. Clin. Vaccine Immunol. 20, 738–746. https://doi.org/10.1128/CVI.00752-12.

Andreu-Ballester, J.C., Cuellar, C., Garcia-Ballesteros, C., Pérez-Griera, J., Amigó, V., Peiró-Gómez, A., Peñarroja-Otero, C., Ballester, F., Mayans, J., Tormo-Calandín, C., 2014. Deficit of interleukin 7 in septic patients. Int. Immunopharmacol. 23, 73–76. https://doi.org/10.1016/j.intimp.2014.08.015.

Aoyagi, T., Yamamoto, N., Hatta, M., Tanno, D., Miyazato, A., Ishii, K., Suzuki, K., Nakayama, T., Taniguchi, M., Kunishima, H., Hirakata, Y., Kaku, M., Kawakami, K., 2011. Activation of pulmonary invariant NKT cells leads to exacerbation of acute lung injury caused by LPS through local production of IFN-gamma and TNF-alpha by Gr-1+ monocytes. Int. Immunol. 23, 97–108. https://doi.org/10.1093/intimm/dxq460.

Arrenberg, P., Maricic, I., Kumar, V., 2011. Sulfatide-mediated activation of type II natural killer T cells prevents hepatic ischemic reperfusion injury in mice. Gastroenterology 140, 646–655. https://doi.org/10.1053/j.gastro.2010.10.003.

Bai, L., Picard, D., Anderson, B., Chaudhary, V., Luoma, A., Jabri, B., Adams, E.J., Savage, P.B., Bendelac, A., 2012. The majority of CD1d-sulfatide-specific T cells in human blood use a semiinvariant Vdelta1 TCR. Eur. J. Immunol. 42, 2505–2510. https://doi.org/10.1002/eji.201242531.

Beaudoin, L., Laloux, V.E., Novak, J., Lucas, B., Lehuen, A., 2002. NKT cells inhibit the onset of diabetes by impairing the development of pathogenic T cells specific for pancreatic β cells. Immunity 17, 725–736. https://doi.org/10.1016/S1074-7613(02)00473-9.

Bellani, G., Laffey, J.G., Pham, T., Fan, E., Brochard, L., Esteban, A., Gattinoni, L., van Haren, F., Larsson, A., McAuley, D.F., Ranieri, M., Rubenfeld, G., Thompson, B.T., Wrigge, H., Slutsky, A.S., Pesenti, A., Investigators, L.S., Group, E.T., 2016. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 315, 788–800. https://doi.org/10.1001/jama.2016.0291.

Biden, T.J., Boslem, E., Chu, K.Y., Sue, N., 2014. Lipotoxic endoplasmic reticulum stress, β cell failure, and type 2 diabetes mellitus. Trends Endocrinol. Metab. 25, 389–398. https://doi.org/10.1016/j.tem.2014.02.003.

Boon, A.C.M., Fringuelli, E., Graus, Y.M.F., Fouchier, R.A.M., Sintnicolaas, K., Iorio, A.M., Rimmelzwaan, G.F., Osterhaus, A.D.M.E., 2002. Influenza A virus specific T cell immunity in humans during aging. Virology 299, 100–108. https://doi.org/10.1006/viro.2002.1491.

Brennan, P.J., Brigl, M., Brenner, M.B., 2013. Invariant natural killer T cells: an innate activation scheme linked to diverse effector functions. Nat. Rev. Immunol. 13, 101–117. https://doi.org/10.1038/nri3369.

Brennan, P.J., Tatituri, R.V.V., Heiss, C., Watts, G.F.M., Hsu, F.-F., Veerapen, N., Cox, L.R., Azadi, P., Besra, G.S., Brenner, M.B., 2014. Activation of iNKT cells by a distinct constituent of the endogenous glucosylceramide fraction. Proc. Natl. Acad. Sci. 111, 13433–13438. https://doi.org/10.1073/pnas.1415357111.

Brigl, M., Tatituri, R.V.V., Watts, G.F.M., Bhowruth, V., Leadbetter, E.A., Barton, N., Cohen, N.R., Hsu, F.-F., Besra, G.S., Brenner, M.B., 2011. Innate and cytokine-driven signals, rather than microbial antigens, dominate in natural killer T cell activation during microbial infection. J. Exp. Med. 208, 1163–1177. https://doi.org/10.1084/jem.20102555.

Carolan, E., Tobin, L.M., Mangan, B.A., Corrigan, M., Gaoatswe, G., Byrne, G., Geoghegan, J., Cody, D., O'Connell, J., Winter, D.C., Doherty, D.G., Lynch, L., O'Shea, D., Hogan, A.E., 2015. Altered distribution and increased IL-17 production by mucosal-associated invariant t cells in adult and childhood obesity. J. Immunol. 194, 5775–5780. https://doi.org/10.4049/jimmunol.1402945.

Chandra, S., Kronenberg, M., 2015. Activation and function of iNKT and MAIT cells. Advances in Immunology, 1st ed. Elsevier Inc.https://doi.org/10.1016/bs.ai.2015.03.003.

Chandra, S., Wingender, G., Greenbaum, J.A., Khurana, A., Gholami, A.M., Ganesan, A.-P., Rosenbach, M., Jaffee, K., Gern, J.E., Wood, R., O'Connor, G., Sandel, M., Kattan, M., Bacharier, L., Togias, A., Horner, A.A., Kronenberg, M., 2018. Development of asthma in inner-city children: possible roles of MAIT cells and variation in the home environment. J. Immunol. 200, 1995–2003. https://doi.org/10.4049/jimmunol.1701525.

Chen, S., Hoffman, R.A., Scott, M., Manson, J., Loughran, P., Ramadan, M., Demetris, A.J., Billiar, T.R., 2017a. NK1.1 $^{+}$ cells promote sustained tissue injury and inflammation after trauma with hemorrhagic shock. J. Leukoc. Biol. 102, 127–134. https://doi.org/10.1189/jlb.3A0716-333R.

Chen, Z., Wang, H., D'Souza, C., Sun, S., Kostenko, L., Eckle, S.B.G., Meehan, B.S., Jackson, D.C., Strugnell, R.A., Cao, H., Wang, N., Fairlie, D.P., Liu, L., Godfrey, D.I., Rossjohn, J., McCluskey, J., Corbett, A.J., 2017b. Mucosal-associated invariant T-cell activation and accumulation after in vivo infection depends on microbial riboflavin synthesis and co-stimulatory signals. Mucosal Immunol. 10, 58–68. https://doi.org/10.1038/mi.2016.39.

Chiba, A., Dascher, C.C., Besra, G.S., Brenner, M.B., 2008. Rapid NKT cell responses are self-terminating during the course of microbial infection. J. Immunol. 181, 2292–2302.

Chua, W.J., Truscott, S.M., Eickhoff, C.S., Blazevic, A., Hoft, D.F., Hansen, T.H., 2012. Polyclonal mucosa-associated invariant T cells have unique innate functions in bacterial infection. Infect. Immun. 80, 3256–3267. https://doi.org/10.1128/IAI.00279-12.

Chung, C.-S., Watkins, L., Funches, A., Lomas-Neira, J., Cioffi, W.G., Ayala, A., 2006. Deficiency of gammadelta T lymphocytes contributes to mortality and immunosuppression in sepsis. Am. J. Physiol. Regul. Integr. Comp. Physiol. 291, R1338–R1343. https://doi.org/10.1152/ajpregu.00283.2006.

Church, D., Elsayed, S., Reid, O., Winston, B., Lindsay, R., 2006. Burn wound infections. Clin. Microbiol. Rev. 19, 403–434. https://doi.org/10.1128/CMR.19.2.403-434.2006.

Cohen, N.R., Garg, S., Brenner, M.B., 2009. Antigen Presentation by CD1 Lipids, T Cells, and NKT Cells in Microbial Immunity. Adv. Immunol. 102, 1–94. https://doi.org/10.1016/S0065-2776(09)01201-2.

Cohen, N.R., Brennan, P.J., Shay, T., Watts, G.F., Brigl, M., Kang, J., Brenner, M.B., Monach, P., Shinton, S.A., Hardy, R.R., Jianu, R., Koller, D., Collins, J., Gazit, R., Garrison, B.S., Rossi, D.J., Narayan, K., Sylvia, K., Fletcher, A., Elpek, K., Bellemare-Pelletier, A., Malhotra, D., Turley, S., Best, A.J., Knell, J., Goldrath, A., Jojic, V., Koller, D., Regev, A., Cohan, N., Brennen, P., Brennar, M., Kreslavsky, T., Bezman, N.A., Sun, J.C., Kim, C.C., Lanier, L.L., Miller, J., Brown, B., Merad, M., Gautier, E.L., Jakubzick, C., Randolph, G.J., Kim, F., Rao, T.N., Wagers, A., Heng, T., Painter, M., Ericson, J., Davis, S., Ergun, A., Mingueneau, M., Mathis, D., Benoist, C., 2013. Shared and distinct transcriptional programs underlie the hybrid nature of iNKT cells. Nat. Immunol. 14, 90–99. https://doi.org/10.1038/ni.2490.

Costa, M.F., de, S., de Negreiros, C.B.T., Bornstein, V.U., Valente, R.H., Mengel, J., Henriques, M., das, G., Benjamim, C.F., Penido, C., 2015. Murine IL-17+ Vγ4 T lymphocytes accumulate in the lungs and play a protective role during severe sepsis. BMC Immunol. 16, 36. https://doi.org/10.1186/s12865-015-0098-8.

Dagvadorj, J., Tumurkhuu, G., Naiki, Y., Noman, A.S., Iftakhar, E.K.I., Badamtseren, B., Komatsu, T., Koide, N., Yoshida, T., Yokochi, T., 2010. Endotoxin-induced lung injury in alpha-galactosylceramide-sensitized mice is caused by failure of interleukin-4 production in lung natural killer T cells. Clin. Exp. Immunol. 162, 169–177. https://doi.org/10.1111/j.1365-2249.2010.04225.x.

De Santo, C., Salio, M., Masri, S.H., Lee, L.Y.H., Dong, T., Speak, A.O., Porubsky, S., Booth, S., Veerapen, N., Besra, G.S., 2008. Invariant NKT cells reduce the immunosuppressive activity of influenza A virus–induced myeloid-derived suppressor cells in mice and humans. J. Clin. Invest. 118, 4036. https://doi.org/10.1172/JCI36264.tumor.

Delano, M.J., Scumpia, P.O., Weinstein, J.S., Coco, D., Nagaraj, S., Kelly-Scumpia, K.M., O'Malley, K.A., Wynn, J.L., Antonenko, S., Al-Quran, S.Z., Swan, R., Chung, C.-S., Atkinson, M.A., Ramphal, R., Gabrilovich, D.I., Reeves, W.H., Ayala, A., Phillips, J., LaFace, D., Heyworth, P.G., Clare-Salzler, M., Moldawer, L.L., 2007. MyD88-dependent expansion of an immature GR-1 $^{+}$ CD11b $^{+}$ population induces T cell suppression and Th2 polarization in sepsis. J. Exp. Med. 204, 1463–1474. https://doi.org/10.1084/jem.20062602.

Dieli, F., Sireci, G., Russo, D., Taniguchi, M., Ivanyi, J., Fernandez, C., Troye-Blomberg, M., De Leo, G., Salerno, A., 2000. Resistance of natural killer T cell-deficient mice to systemic Shwartzman reaction. J. Exp. Med. 192, 1645–1652. https://doi.org/10.1084/jem.192.11.1645.

Etogo, A.O., Nunez, J., Lin, C.Y., Toliver-Kinsky, T.E., Sherwood, E.R., 2008. NK but not CD1-restricted NKT cells facilitate systemic inflammation during polymicrobial intra-abdominal sepsis. J. Immunol. 180, 6334–6345.

Fabry, M.E., Nagel, R.L., Pachnis, A., Suzuka, S.M., Costantini, F., 1992. High expression of human beta S- and alpha-globins in transgenic mice: hemoglobin composition and hematological consequences. Proc Natl Acad Sci U S A 89, 12150–12154.

Faunce, D.E., Gamelli, R.L., Choudhry, M.A., Kovacs, E.J., 2003. A role for CD1d-restricted NKT cells in injury-associated T cell suppression. J. Leukoc. Biol. 73, 747–755. https://doi.org/10.1189/jlb.1102540.Journal.

Field, J.J., Majerus, E., Ataga, K.I., Vichinsky, E.P., Schaub, R., Mashal, R., Nathan, D.G., 2017. NNKTT120, an anti-iNKT cell monoclonal antibody, produces rapid and sustained iNKT cell depletion in adults with sickle cell disease. PLoS One 12, e0171067. https://doi.org/10.1371/journal.pone.0171067.

Fisher, C.J., Dhainaut, J.F., Opal, S.M., Pribble, J.P., Balk, R.A., Slotman, G.J., Iberti, T.J., Rackow, E.C., Shapiro, M.J., Greenman, R.L., 1994. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. JAMA 271, 1836–1843.

Fusakio, M.E., Mohammed, J.P., Laumonnier, Y., Hoebe, K., Köhl, J., Mattner, J., 2011. C5a regulates NKT and NK cell functions in sepsis. J. Immunol. 187, 5805–5812. https://doi.org/10.4049/jimmunol.1100338.

Gaieski, D.F., Edwards, J.M., Kallan, M.J., Carr, B.G., 2013. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit. Care Med. 41, 1167–1174. https://doi.org/10.1097/CCM.0b013e31827c09f8.

Georgel, P., Radosavljevic, M., Macquin, C., Bahram, S., 2011. The non-conventional MHC class I MR1 molecule controls infection by Klebsiella pneumoniae in mice. Mol. Immunol. 48, 769–775. https://doi.org/10.1016/j.molimm.2010.12.002.

Gherardin, N.A., Keller, A.N., Woolley, R.E., Le Nours, J., Ritchie, D.S., Neeson, P.J., Birkinshaw, R.W., Eckle, S.B.G., Waddington, J.N., Liu, L., Fairlie, D.P., Uldrich, A.P., Pellicci, D.G., McCluskey, J., Godfrey, D.I., Rossjohn, J., 2016. Diversity of T Cells Restricted by the MHC Class I-Related Molecule MR1 Facilitates Differential Antigen Recognition. Immunity 44, 32–45. https://doi.org/10.1016/j.immuni.2015.12.005.

Godfrey, D.I., Le Nours, J., Andrews, D.M., Uldrich, A.P., Rossjohn, J., 2018. Unconventional T Cell Targets for Cancer Immunotherapy. Immunity 48, 453–473. https://doi.org/10.1016/j.immuni.2018.03.009.

Grimaldi, D., Le Bourhis, L., Sauneuf, B., Dechartres, A., Rousseau, C., Ouaaz, F., Milder, M., Louis, D., Chiche, J.D., Mira, J.P., Lantz, O., Pène, F., 2014. Specific MAIT cell behaviour among innate-like T lymphocytes in critically ill patients with severe infections. Intensive Care Med. 40, 192–201. https://doi.org/10.1007/s00134-013-3163-x.

Hammerich, L., Bangen, J.M., Govaere, O., Zimmermann, H.W., Gassler, N., Huss, S., Liedtke, C., Prinz, I., Lira, S.A., Luedde, T., Roskams, T., Trautwein, C., Heymann, F., Tacke, F., 2014. Chemokine receptor CCR6-dependent accumulation of gammadelta T cells in injured liver restricts hepatic inflammation and fibrosis. Hepatology 59, 630–642. https://doi.org/10.1002/hep.26697.

Heffernan, D.S., Monaghan, S.F., Thakkar, R.K., Tran, M.L., Chung, C.S., Gregory, S.H., Cioffi, W.G., Ayala, A., 2013. Inflammatory mechanisms in sepsis: elevated invariant natural killer T-cell numbers in mouse and their modulatory effect on macrophage function. Shock 40, 122–128. https://doi.org/10.1097/SHK.0b013e31829ca519.

Hochegger, K., Schatz, T., Eller, P., Tagwerker, A., Heininger, D., Mayer, G., Rosenkranz, A.R., 2007. Role of alpha/beta and gamma/delta T cells in renal ischemia-reperfusion injury. Am J Physiol Ren. Physiol 293, F741–7. https://doi.org/10.1152/ajprenal.00486.2006.

Hotchkiss, R.S., Monneret, G., Payen, D., 2013. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat. Rev. Immunol. 13, 862–874. https://doi.org/10.1038/nri3552.

Hu, C.K., Venet, F., Heffernan, D.S., Wang, Y.L., Horner, B., Huang, X., Chung, C.S., Gregory, S.H., Ayala, A., 2009. The role of hepatic invariant NKT cells in systemic/local inflammation and mortality during polymicrobial septic shock. J. Immunol. 182, 2467–2475. https://doi.org/10.4049/jimmunol.0801463.

Ito, H., Koide, N., Hassan, F., Islam, S., Tumurkhuu, G., Mori, I., Yoshida, T., Kakumu, S., Moriwaki, H., Yokochi, T., 2006. Lethal endotoxic shock using alpha-galactosylceramide sensitization as a new experimental model of septic shock. Lab. Invest. 86, 254–261. https://doi.org/10.1038/labinvest.3700388.

Iwashyna, T.J., Cooke, C.R., Wunsch, H., Kahn, J.M., 2012. Population burden of long-term survivorship after severe sepsis in older Americans. J. Am. Geriatr. Soc. 60, 1070–1077. https://doi.org/10.1111/j.1532-5415.2012.03989.x.

Izhak, L., Ambrosino, E., Kato, S., Parish, S.T., O'Konek, J.J., Weber, H., Xia, Z., Venzon, D., Berzofsky, J.A., Terabe, M., 2013. Delicate balance among three types of t cells in concurrent regulation of tumor immunity. Cancer Res. 73, 1514–1523. https://doi.org/10.1158/0008-5472.CAN-12-2567.

Kadowaki, T., Morishita, A., Niki, T., Hara, J., Sato, M., Tani, J., Miyoshi, H., Yoneyama, H., Masaki, T., Hattori, T., Matsukawa, A., Hirashima, M., 2013. Galectin-9 prolongs the survival of septic mice by expanding tim-3-expressing natural killer T cells and PDCA-1 + CD11c + macrophages. Crit. Care 17, 1–11. https://doi.org/10.1186/cc13147.

Kain, L., Webb, B., Anderson, B.L., Deng, S., Holt, M., Constanzo, A., Zhao, M., Self, K., Teyton, A., Everett, C., Kronenberg, M., Zajonc, D.M., Bendelac, A., Savage, P.B., Teyton, L., 2014. The Identification of the Endogenous Ligands of Natural Killer T Cells Reveals the Presence of Mammalian α-Linked Glycosylceramides. Immunity 41, 543–554. https://doi.org/10.1016/j.immuni.2014.08.017.

Kato, G.J., Piel, F.B., Reid, C.D., Gaston, M.H., Ohene-Frempong, K., Krishnamurti, L., Smith, W.R., Panepinto, J.A., Weatherall, D.J., Costa, F.F., Vichinsky, E.P., 2018. Sickle cell disease. Nat Rev Dis Prim. 4, 18010. https://doi.org/10.1038/nrdp.2018.10.

Kawano, T., Cui, J., Koezuka, Y., Toura, I., Kaneko, Y., Motoki, K., Ueno, H., Nakagawa, R., Sato, H., Kondo, E., Koseki, H., Taniguchi, M., 1997. CD1d-restricted and TCR-mediated activation of V(α)14 NKT cells by glycosylceramides. Science 278, 1626–1629. https://doi.org/10.1126/science.278.5343.1626. (80-.).

Kazuhiko, S., Hiroki, K., Toru, N., Takashi, K., Tetsuya, N., Hitoshi, K., Katsuyoshi, H., Toru, A., 2005. Association of NKT cells and granulocytes with liver injury after reperfusion of the portal vein. Cell. Immunol. 234, 31–38. https://doi.org/10.1016/j.cellimm.2005.04.022.

Kim, E.Y., Battaile, J.T., Patel, A.C., You, Y., Agapov, E., Grayson, M.H., Benoit, L.A., Byers, D.E., Alevy, Y., Tucker, J., Swanson, S., Tidwell, R., Tyner, J.W., Morton, J.D., Castro, M., Polineni, D., Patterson, G.A., Schwendener, R.A., Allard, J.D., Peltz, G., Holtzman, M.J., 2008. Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease. Nat. Med. 14, 633–640. https://doi.org/10.1038/nm1770.

Kim, J.H., Oh, S.J., Ahn, S., Chung, D.H., 2014. IFN-gamma-producing NKT cells exacerbate sepsis by enhancing C5a generation via IL-10-mediated inhibition of CD55 expression on neutrophils. Eur. J. Immunol. 44, 2025–2035. https://doi.org/10.1002/eji.201343937.

Kim, E.Y., Ikeda, K., Hayashida, K., Brenner, M.B., Ichinose, F., 2015a. Innate T cells improve brain injury and mortality after cardiac arrest and resuscitation. Circulation 132, A17343.

Kim, E.Y., Lynch, L., Brennan, P.J., Cohen, N.R., Brenner, M.B., 2015b. The transcriptional programs of iNKT cells. Semin. Immunol. 27, 26–32. https://doi.org/10.1016/j.smim.2015.02.005.

Kim, J.-C., Jin, H.-M., Cho, Y.-N., Kwon, Y.-S., Kee, S.-J., Park, Y.-W., 2015c. Deficiencies of circulating mucosal-associated invariant t cells and natural killer t cells in patients with acute cholecystitis. J. Korean Med. Sci. 30, 606. https://doi.org/10.3346/jkms.2015.30.5.606.

Kim, E.Y., Ner-gaon, H., Choi, J.Y., Guo, J.Y., Benoist, C., Shay, T., Brenner, M.B., 2017. Natural Killer T cells are master regulators of post-sepsis immunosuppresion. CD1-MR1 Conference.

King, I.L., Amiel, E., Tighe, M., Mohrs, K., Veerapen, N., Besra, G., Mohrs, M., Leadbetter, E.A., 2013. The mechanism of splenic invariant NKT cell activation dictates localization in vivo. J. Immunol. 191, 572–582. https://doi.org/10.4049/jimmunol.1300299.

Kinjo, Y., Illarionov, P., Vela, J.L., Pei, B., Girardi, E., Li, X., Li, Y., Imamura, M., Kaneko, Y., Okawara, A., Miyazaki, Y., Gomez-Velasco, A., Rogers, P., Dahesh, S., Uchiyama, S., Khurana, A., Kawahara, K., Yesilkaya, H., Andrew, P.W., Wong, C.H., Kawakami, K., Nizet, V., Besra, G.S., Tsuji, M., Zajonc, D.M., Kronenberg, M., 2011. Invariant natural killer T cells recognize glycolipids from pathogenic Gram-positive bacteria. Nat. Immunol. 12, 966–974. https://doi.org/10.1038/ni.2096.

Kjer-Nielsen, L., Patel, O., Corbett, A.J., Le Nours, J., Meehan, B., Liu, L., Bhati, M., Chen, Z., Kostenko, L., Reantragoon, R., Williamson, N.A., Purcell, A.W., Dudek, N.L., McConville, M.J., O'Hair, R.A.J., Khairallah, G.N., Godfrey, D.I., Fairlie, D.P., Rossjohn, J., McCluskey, J., 2012. MR1 presents microbial vitamin B metabolites to MAIT cells. Nature 491, 717–723. https://doi.org/10.1038/nature11605.

Kleinschnitz, C., Schwab, N., Kraft, P., Hagedorn, I., Dreykluft, A., Austinat, M., Nieswandt, B., Wiendl, H., Stoll, G., Dc, W., Schwarz, T., 2011. Early detrimental T-cell effects in experimental cerebral ischemia are neither related to adaptive immunity nor thrombus formation. Blood 115, 3835–3842. https://doi.org/10.1182/blood-2009-10-249078.

Klos, A., Tenner, A.J., Johswich, K.O., Ager, R.R., Reis, E.S., Kohl, J., 2009. The role of the anaphylatoxins in health and disease. Mol. Immunol. 46, 2753–2766. https://doi.org/10.1016/j.molimm.2009.04.027.

Kuboki, S., Sakai, N., Tschöp, J., Edwards, M.J., Lentsch, A.B., Caldwell, C.C., 2009. Distinct contributions of CD4 + T cell subsets in hepatic ischemia/reperfusion injury. Am. J. Physiol. Gastrointest. Liver Physiol. 296, 9. https://doi.org/10.1152/ajpgi.90464.2008.

Kunii, N., Horiguchi, S., Motohashi, S., Yamamoto, H., Ueno, N., Yamamoto, S., Sakurai, D., Taniguchi, M., Nakayama, T., Okamoto, Y., 2009. Combination therapy of in vitro-expanded natural killer T cells and α-galactosylceramide-pulsed antigen-presenting cells in patients with recurrent head and neck carcinoma. Cancer Sci. 100, 1092–1098. https://doi.org/10.1111/j.1349-7006.2009.01135.x.

Lappas, C.M., Day, Y.J., Marshall, M.A., Engelhard, V.H., Linden, J., 2006. Adenosine A2A receptor activation reduces hepatic ischemia reperfusion injury by inhibiting CD1d-dependent NKT cell activation. J. Exp. Med. 203, 2639–2648. https://doi.org/10.1084/jem.20061097.

Lezmi, G., Abou, R., Dietrich, C., Chatenoud, L., De Blic, J., Leite-de-moraes, M., 2018. Circulating IL-17-producing mucosal-associated invariant T cells (MAIT) are associated with symptoms in children with asthma. Clin. Immunol. 188, 7–11. https://doi.org/10.1016/j.clim.2017.11.009.

Li, L., Huang, L., Sung, S.-s.J., Lobo, P.I., Brown, M.G., Gregg, R.K., Engelhard, V.H., Okusa, M.D., 2007a. NKT cell activation mediates neutrophil IFN- production and renal ischemia-reperfusion injury. J. Immunol. 178, 5899–5911. https://doi.org/10.4049/jimmunol.178.9.5899.

Li, L., Huang, L., Sung, S.S., Lobo, P.I., Brown, M.G., Gregg, R.K., Engelhard, V.H., Okusa, M.D., 2007b. NKT cell activation mediates neutrophil IFN-gamma production and renal ischemia-reperfusion injury. J. Immunol. 178, 5899–5911.

Liesz, A., Zhou, W., Mracskó, É., Karcher, S., Bauer, H., Schwarting, S., Sun, L., Bruder, D., Stegemann, S., Cerwenka, A., Sommer, C., Dalpke, A.H., Veltkamp, R., 2011. Inhibition of lymphocyte trafficking shields the brain against deleterious neuroinflammation after stroke. Brain 134, 704–720. https://doi.org/10.1093/brain/awr008.

Lynch, L., Nowak, M., Varghese, B., Clark, J., Hogan, A.E., Toxavidis, V., Balk, S.P., O'Shea, D., O'Farrelly, C., Exley, M.A., 2012. Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine production. Immunity 37, 574–587. https://doi.org/10.1016/j.immuni.2012.06.016.

Magalhaes, I., Pingris, K., Poitou, C., Bessoles, S., Venteclef, N., Kiaf, B., Beaudoin, L., Da Silva, J., Allatif, O., Rossjohn, J., Kjer-nielsen, L., Mccluskey, J., Ledoux, S., Genser, L., Torcivia, A., Soudais, C., Lantz, O., Boitard, C., Aron-wisnewsky, J., Larger, E., Clément, K., Lehuen, A., 2015. Mucosal-associated invariant T cell alterations in obese and type 2 diabetic patients. J. Clin. Invest. 125, 1–11. https://doi.org/10.1172/JCI78941.Results.

Meierovics, A.I., Cowley, S.C., 2016. MAIT cells promote inflammatory monocyte differentiation into dendritic cells during pulmonary intracellular infection. J. Exp. Med. 213, 2793–2809. https://doi.org/10.1084/jem.20160637.

Meyer, E.H., Goya, S., Akbari, O., Berry, G.J., Savage, P.B., Kronenberg, M., Nakayama, T., DeKruyff, R.H., Umetsu, D.T., 2006. Glycolipid activation of invariant T cell receptor + NK T cells is sufficient to induce airway hyperreactivity independent of conventional CD4 + T cells. Proc. Natl. Acad. Sci. 103, 2782–2787. https://doi.org/10.1073/pnas.0510282103.

Mirzaian, M., Kramer, G., Poorthuis, B.J., 2015. Quantification of sulfatides and lysosulfatides in tissues and body fluids by liquid chromatography-tandem mass spectrometry. J. Lipid Res. 56, 936–943. https://doi.org/10.1194/jlr.M057232.

Miyamoto, K., Miyake, S., Yamamura, T., 2001. A synthetic glycolipid prevents autoimmune encephalomyelitis by inducing TH2 bias of natural killer T cells. Nature 413, 531–534. https://doi.org/10.1038/35097097.

Montoya, C.J., Pollard, D., Martinson, J., Kumari, K., Wasserfall, C., Mulder, C.B., Rugeles, M.T., Atkinson, M.A., Landay, A.L., Wilson, S.B., 2007. Characterization of human invariant natural killer T subsets in health and disease using a novel invariant natural killer T cell-clonotypic monoclonal antibody, 6B11. Immunology 122, 1–14. https://doi.org/10.1111/j.1365-2567.2007.02647.x.

Motohashi, S., Nagato, K., Kunii, N., Yamamoto, H., Yamasaki, K., Okita, K., Hanaoka, H.,

Shimizu, N., Suzuki, M., Yoshino, I., Taniguchi, M., Fujisawa, T., Nakayama, T., 2009. A phase I-II study of alpha-galactosylceramide-pulsed IL-2/GM-CSF-cultured peripheral blood mononuclear cells in patients with advanced and recurrent non-small cell lung cancer. J. Immunol. 182, 2492–2501. https://doi.org/10.4049/jimmunol.0800126.

Nakai, Y., Iwabuchi, K., Fujii, S., Ishimori, N., Dashtsoodol, N., Watano, K., Mishima, T., Iwabuchi, C., Tanaka, S., Bezbradica, J.S., Nakayama, T., Taniguchi, M., Miyake, S., Yamamura, T., Kitabatake, A., Joyce, S., Van Kaer, L., Onoé, K., 2004. Natural killer T cells accelerate atherogenesis in mice. Blood 104, 2051–2059. https://doi.org/10.1182/blood-2003-10-3485.

Opal, S.M., Fisher, C.J., Dhainaut, J.F., Vincent, J.L., Brase, R., Lowry, S.F., Sadoff, J.C., Slotman, G.J., Levy, H., Balk, R.A., Shelly, M.P., Pribble, J.P., LaBrecque, J.F., Lookabaugh, J., Donovan, H., Dubin, H., Baughman, R., Norman, J., DeMaria, E., Matzel, K., Abraham, E., Seneff, M., 1997. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. Crit. Care Med. 25, 1115–1124. https://doi.org/10.1097/00003246-199707000-00010.

Palmer, J.L., Tulley, J.M., Kovacs, E.J., Gamelli, R.L., Taniguchi, M., Faunce, D.E., 2006. Injury-Induced Suppression of Effector T Cell Immunity Requires CD1d-Positive APCs and CD1d-Restricted NKT Cells. J. Immunol. 177, 92–99. https://doi.org/10.4049/jimmunol.177.1.92.

Rahimpour, A., Koay, H.F., Enders, A., Clanchy, R., Eckle, S.B.G., Meehan, B., Chen, Z., Whittle, B., Liu, L., Fairlie, D.P., Goodnow, C.C., McCluskey, J., Rossjohn, J., Uldrich, A.P., Pellicci, D.G., Godfrey, D.I., 2015. Identification of phenotypically and functionally heterogeneous mouse mucosal-associated invariant T cells using MR1 tetramers. J. Exp. Med. 212, 1095–1108. https://doi.org/10.1084/jem.20142110.

Reantragoon, R., Corbett, A.J., Sakala, I.G., Gherardin, N.A., Furness, J.B., Chen, Z., Eckle, S.B.G., Uldrich, A.P., Birkinshaw, R.W., Patel, O., Kostenko, L., Meehan, B., Kedzierska, K., Liu, L., Fairlie, D.P., Hansen, T.H., Godfrey, D.I., Rossjohn, J., McCluskey, J., Kjer-Nielsen, L., 2013. Antigen-loaded MR1 tetramers define T cell receptor heterogeneity in mucosal-associated invariant T cells. J. Exp. Med. 210, 2305–2320. https://doi.org/10.1084/jem.20130958.

Renukaradhya, G.J., Khan, M.A., Vieira, M., Du, W., Gervay-hague, J., Brutkiewicz, R.R., 2008. Type I NKT cells protect (and type II NKT cells suppress) the host' s innate antitumor immune response to a B-cell lymphoma. Hematology 111, 1–3. https://doi.org/10.1182/blood-2007-05-092866.The.

Rhee, R.J., Carlton, S., Lomas, J.L., Lane, C., Brossay, L., Cioffi, W.G., Ayala, A., 2003. Inhibition of CD1d activation suppresses septic mortality: a role for NK-T cells in septic immune dysfunction. J. Surg. Res. 115, 74–81.

Rogers, L., Burchat, S., Gage, J., Hasu, M., Thabet, M., Willcox, L., Ramsamy, T.A., Whitman, S.C., 2008. Deficiency of invariant V alpha 14 natural killer T cells decreases atherosclerosis in LDL receptor null mice. Cardiovasc. Res. 78, 167–174. https://doi.org/10.1093/cvr/cvn005.

Rouxel, O., Da Silva, J., Beaudoin, L., Nel, I., Tard, C., Cagninacci, L., Kiaf, B., Oshima, M., Diedisheim, M., Salou, M., Corbett, A., Rossjohn, J., McCluskey, J., Scharfmann, R., Battaglia, M., Polak, M., Lantz, O., Beltrand, J., Lehuen, A., 2017. Cytotoxic and regulatory roles of mucosal-associated invariant T cells in type 1 diabetes. Nat. Immunol. 18, 1321–1331. https://doi.org/10.1038/ni.3854.

Shaler, C.R., Choi, J., Rudak, P.T., Memarnejadian, A., Szabo, P.A., Tun-Abraham, M.E., Rossjohn, J., Corbett, A.J., McCluskey, J., McCormick, J.K., Lantz, O., Hernandez-Alejandro, R., Haeryfar, S.M.M., 2017. 2017. MAIT cells launch a rapid, robust and distinct hyperinflammatory response to bacterial superantigens and quickly acquire an anergic phenotype that impedes their cognate antimicrobial function: defining a novel mechanism of superantigen-induced immunopatho. PLoS Biol. https://doi.org/10.1371/journal.pbio.2001930.

Sharma, A.K., LaPar, D.J., Zhao, Y., Li, L., Lau, C.L., Kron, I.L., Iwakura, Y., Okusa, M.D., Laubach, V.E., 2011. Natural killer T cell-derived IL-17 mediates lung ischemia-reperfusion injury. Am. J. Respir. Crit. Care Med. 183, 1539–1549. https://doi.org/10.1164/rccm.201007-1173OC.

Sharma, A.K., LaPar, D.J., Stone, M.L., Zhao, Y., Kron, I.L., Laubach, V.E., 2013. Receptor for advanced glycation end products (RAGE) on iNKT cells mediates lung ischemia-reperfusion injury. Am. J. Transplant. 13, 2255–2267. https://doi.org/10.1111/ajt.12368.

Shi, K., Wood, K., Shi, F.D., Wang, X., Liu, Q., 2018. Stroke-induced immunosuppression and poststroke infection. Stroke Vasc. Neurol. 3, 34–41. https://doi.org/10.1136/svn-2017-000123.

Shichita, T., Sugiyama, Y., Ooboshi, H., Sugimori, H., Nakagawa, R., Takada, I., Iwaki, T., Okada, Y., Iida, M., Cua, D.J., Iwakura, Y., Yoshimura, A., 2009. Pivotal role of cerebral interleukin-17-producing T cells in the delayed phase of ischemic brain injury. Nat. Med. 15, 946–950. https://doi.org/10.1038/nm.1999.

Singer, M., Deutschman, C.S., Seymour, C.W., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G.R., Chiche, J.D., Coopersmith, C.M., Hotchkiss, R.S., Levy, M.M., Marshall, J.C., Martin, G.S., Opal, S.M., Rubenfeld, G.D., van der Poll, T., Vincent, J.L., Angus, D.C., 2016. The third international consensus definitions for Sepsis and septic shock (Sepsis-3). JAMA 315, 801–810. https://doi.org/10.1001/jama.2016.0287.

Singer, B.H., Dickson, R.P., Denstaedt, S.J., Newstead, M.W., Kim, K., Falkowski, N.R., Erb-Downward, J.R., Schmidt, T.M., Huffnagl, G.B., Standiford, T.J., 2018. Bacterial dissemination to the brain in sepsis. Am. J. Respir. Crit. Care Med. 197, 747–756. https://doi.org/10.1164/rccm.201708-1559OC.

Stax, A.M., Tuengel, J., Girardi, E., Kitano, N., Allan, L.L., Liu, V., Zheng, D., Panenka, W.J., Guillaume, J., Wong, C.H., van Calenbergh, S., Zajonc, D.M., van den Elzen, P., 2017. Autoreactivity to Sulfatide by Human Invariant NKT Cells. J. Immunol. 199, 97–106. https://doi.org/10.4049/jimmunol.1601976.

Szabo, P.A., Anantha, R.V., Shaler, C.R., McCormick, J.K., Haeryfar, S.M., 2015. CD1d- and MR1-Restricted t cells in Sepsis. Front. Immunol. 6, 401. https://doi.org/10.3389/fimmu.2015.00401.

Tavare, R., McCracken, M.N., Zettlitz, K.A., Knowles, S.M., Salazar, F.B., Olafsen, T., Witte, O.N., Wu, A.M., 2014. Engineered antibody fragments for immuno-PET imaging of endogenous CD8+ T cells in vivo. Proc. Natl. Acad. Sci. 111, 1108–1113. https://doi.org/10.1073/pnas.1316922111.

Toyama, M., Kudo, D., Aoyagi, T., Miyasaka, T., Ishii, K., Kanno, E., Kaku, M., Kushimoto, S., Kawakami, K., 2018. Attenuated accumulation of regulatory T cells and reduced production of interleukin 10 lead to the exacerbation of tissue injury in a mouse model of acute respiratory distress syndrome. Microbiol. Immunol. 62, 111–123. https://doi.org/10.1111/1348-0421.12564.

Tulley, J.M., Palmer, J.L., Gamelli, R.L., Faunce, D.E., 2008. Prevention of injury-induced suppression of T-cell immunity by the CD1d/NKT cell-specific ligand alpha-galactosylceramide. Shock 29, 269–277. https://doi.org/10.1097/shk.0b013e31811ff60c.

Uhel, F., Azzaoui, I., Gregoire, M., Pangault, C., Dulong, J., Tadie, J.M., Gacouin, A., Camus, C., Cynober, L., Fest, T., Le Tulzo, Y., Roussel, M., Tarte, K., 2017. Early expansion of circulating granulocytic myeloid-derived suppressor cells predicts development of nosocomial infections in patients with Sepsis. Am. J. Respir. Crit. Care Med. 196, 315–327. https://doi.org/10.1164/rccm.201606-1143OC.

VanderLaan, P.A., Reardon, C.A., Sagiv, Y., Blachowicz, L., Lukens, J., Nissenbaum, M., Wang, C.-R., Getz, G.S., 2007. Characterization of the natural killer T-Cell response in an adoptive transfer model of atherosclerosis. Am. J. Pathol. 170, 1100–1107. https://doi.org/10.2353/ajpath.2007.060188.

Venet, F., Pachot, A., Debard, A.L., Bohe, J., Bienvenu, J., Lepape, A., Powell, W.S., Monneret, G., 2006. Human CD4+CD25+ regulatory T lymphocytes inhibit lipopolysaccharide-induced monocyte survival through a Fas/Fas ligand-dependent mechanism. J. Immunol. 177, 6540–6547.

Vincent, J.L., Marshall, J.C., Namendys-Silva, S.A., Francois, B., Martin-Loeches, I., Lipman, J., Reinhart, K., Antonelli, M., Pickkers, P., Njimi, H., Jimenez, E., Sakr, Y., investigators, I., 2014. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir. Med. 2, 380–386. https://doi.org/10.1016/S2213-2600(14)70061-X.

Wallace, K.L., Marshall, M.A., Ramos, S.I., Lannigan, J.A., Field, J.J., Strieter, R.M., Linden, J., 2009. NKT cells mediate pulmonary inflammation and dysfunction in murine sickle cell disease through production of IFN-gamma and CXCR3 chemokines. Blood 114, 667–676. https://doi.org/10.1182/blood-2009-02-205492.

Wisnoski, N., Chung, C.S., Chen, Y., Huang, X., Ayala, A., 2007. The contribution of CD4+ CD25+ T-regulatory-cells to immune suppression in sepsis. Shock 27, 251–257. https://doi.org/10.1097/01.shk.0000239780.33398.e4.

Wong, C.H.Y., Jenne, C.N., Lee, W.Y., Léger, C., Kubes, P., 2011. Functional innervation of hepatic iNKT cells is immunosuppressive following stroke. Science 334, 101–105. https://doi.org/10.1126/science.1210301. (80-.).

Yao, Y., Deng, H., Li, P., Zhang, J., Zhang, J., Wang, D., Li, S., Luo, Y., Wei, Z., Bi, G., Yang, X.-P.P., Tang, Z.-H.H., 2017. α-Lactose Improves the Survival of Septic Mice by Blockade of TIM-3 Signaling to Prevent NKT Cell Apoptosis and Attenuate Cytokine Storm. Shock 47, 337–345. https://doi.org/10.1097/SHK.0000000000000717.

Yang, S.H., Lee, J.P., Jang, H.R., Cha, R.H., Han, S.S., Jeon, U.S., Kim, D.K., Song, J., Lee, D.S., Kim, Y.S., 2011. Sulfatide-reactive natural killer T cells abrogate ischemia-reperfusion injury. J. Am. Soc. Nephrol. 22, 1305–1314. https://doi.org/10.1681/ASN.2010080815.

Yilmaz, G., Arumugam, T.V., Stokes, K.Y., Granger, D.N., 2006. Role of T lymphocytes and interferon-gamma in ischemic stroke. Circulation 113, 2105–2112. https://doi.org/10.1161/CIRCULATIONAHA.105.593046.

Yu, K.O., Im, J.S., Molano, A., Dutronc, Y., Illarionov, P.A., Forestier, C., Fujiwara, N., Arias, I., Miyake, S., Yamamura, T., Chang, Y.T., Besra, G.S., Porcelli, S.A., 2005. Modulation of CD1d-restricted NKT cell responses by using N-acyl variants of alpha-galactosylceramides. Proc. Natl. Acad. Sci. U. S. A. 102, 3383–3388. https://doi.org/10.1073/pnas.0407488102.

Zajonc, D.M., Maricic, I., Wu, D., Halder, R., Roy, K., Wong, C.-H., Kumar, V., Wilson, I.A., 2005. Structural basis for CD1d presentation of a sulfatide derived from myelin and its implications for autoimmunity. J. Exp. Med. 202, 1517–1526. https://doi.org/10.1084/jem.20051625.

Zhang, J., Han, C., Dai, H., Hou, J., Dong, Y., Cui, X., Xu, L., Zhang, M., Xia, Q., 2016. Hypoxia-inducible Factor-2alpha limits natural killer t cell cytotoxicity in renal Ischemia/Reperfusion injury. J. Am. Soc. Nephrol. 27, 92–106. https://doi.org/10.1681/ASN.2014121248.

Zhang, G., Nie, H., Yang, J., Ding, X., Huang, Y., Yu, H., Li, R., Yuan, Z., Hu, S., 2018. Sulfatide-activated type II NKT cells prevent allergic airway inflammation by inhibiting type I NKT cell function in a mouse model of asthma. Am. J. Physiol. Lung Cell Mol. Physiol. 975–984. https://doi.org/10.1152/ajplung.00114.2011.

Zhou, D., Mattner, J., Cantu, C., Schrantz, N., Yin, N., Gao, Y., Sagiv, Y., Hudspeth, K., Wu, Y.P., Yamashita, T., Teneberg, S., Wang, D., Proia, R.L., Levery, S.B., Savage, P.B., Teyton, L., Bendelac, A., 2004. Lysosomal glycosphingolipid recognition by NKT cells. Science 306, 1786–1789. https://doi.org/10.1126/science.1103440. (80-.).

Zimmerman, J.E., Kramer, A.A., Knaus, W.A., 2013. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. Crit. Care 17. https://doi.org/10.1186/cc12695.

Further reading

Dusseaux, M., Martin, E., Serriari, N., Peguillet, I., Premel, V., Louis, D., Milder, M., Le Bourhis, L., Soudais, C., Treiner, E., Lantz, O., 2011. Human MAIT cells are xenobiotic resistant, tissue-targeted, CD161hi IL-17 secreting T cells. Blood 117, 1250–1260. https://doi.org/10.1182/blood-2010-08-303339.

Eberl, G., Lees, R., Smiley, S.T., Taniguchi, M., Grusby, M.J., MacDonald, H.R., 1999.

Tissue-specific segregation of CD1d-dependent and CD1d-independent NK t cells. J. Immunol. 162, 6410–6419.
Funda, D., Stenvang, J.P., Buschard, K., 1995. Age-related changes in T gamma delta cells of NOD mice. Immunol. Lett. 45, 179–184.
Groh, B.Y.V., Porcelli, S., Fabbi, I.M., Lanier, L.L., Picker, L.J., Anderson, T., Warnke, R.A., Bhan, A.K., Strominger, J.L., Ii, M.B.B., 1989. Human Lymphocytes Bearing T Cell Receptor Y/S Are Phenotypically Diverse and Evenly Distributed Throughout the Lymphoid System Two Structurally Distinct Types of CD3-associated TCR Exist. The Majority of Pe-ripheral T Lymphocytes and a Sizeable Portio. pp. 169.
Hinks, T.S.C., Wallington, J.C., Williams, A.P., Djukanovic, R., Staples, K.J., Wilkinson, T.M.A., 2016. Steroid-induced deficiency of mucosal-associated invariant T cells in the chronic obstructive pulmonary disease lung implications for nontypeable haemophilus influenzae infection. Am. J. Respir. Crit. Care Med. 194, 1208–1218. https://doi.org/10.1164/rccm.201601-0002OC.
Kenna, T., Mason, L.G., Porcelli, S.A., Koezuka, Y., Hegarty, J.E., O'Farrelly, C., Doherty, D.G., 2003. NKT cells from normal and tumor-bearing human livers are phenotypically and functionally distinct from murine NKT cells. J. Immunol. 171, 1775–1779. https://doi.org/10.4049/jimmunol.171.4.1775.
Kenna, T., Golden-Mason, L., Norris, S., Hegarty, J.E., O'Farrelly, C., Doherty, D.G., 2004. Distinct subpopulations of γδ T cells are present in normal and tumor-bearing human liver. Clin. Immunol. 113, 56–63. https://doi.org/10.1016/j.clim.2004.05.003.
Kita, H., Naidenko, O.V., Kronenberg, M., Ansari, A.A., Rogers, P., He, X.S., Koning, F., Mikayama, T., Van de Water, J., Coppel, R.L., Kaplan, M., Gershwin, M.E., 2002. Quantitation and phenotypic analysis of natural killer T cells in primary biliary cirrhosis using a human CD1d tetramer. Gastroenterology 123, 1031–1043. https://doi.org/10.1053/gast.2002.36020.
Konishi, J., Yamazaki, K., Yokouchi, H., Shinagawa, N., Iwabuchi, K., Nishimura, M., 2004. The characteristics of human NKT cells in lung cancer - CD1d independent cytotoxicity against lung cancer cells by NKT cells and decreased human NKT cell response in lung cancer patients. Hum. Immunol. 65, 1377–1388. https://doi.org/10.1016/j.humimm.2004.09.003.
Matsuda, J.L., Naidenko, O.V., Gapin, L., Nakayama, T., Taniguchi, M., Wang, C.R., Koezuka, Y., Kronenberg, M., 2000. Tracking the response of natural killer T cells to a glycolipid antigen using CD1d tetramers. J. Exp. Med. 192, 741–754. https://doi.org/10.1084/jem.192.5.741.
Ohteki, T., Abo, T., Seki, S., Kobata, T., Yagita, H., Okumura, K., Kumagai, K., 1991. Predominant appearance of γ/δ T lymphocytes in the liver of mice after birth. Eur. J. Immunol. 21, 1733–1740. https://doi.org/10.1002/eji.1830210722.
Parker, C.M., 1990. Evidence for extrathymic changes in the T cell receptor gamma/delta repertoire. J. Exp. Med. 171, 1597–1612. https://doi.org/10.1084/jem.171.5.1597.
Pons, J., Sauleda, J., Ferrer, J.M., Barceló, B., Fuster, A., Regueiro, V., Julia, M.R., Agusti, A.G.N., 2005. Blunted γδ T-lymphocyte response in chronic obstructive pulmonary disease. Eur. Respir. J. 25, 441–446. https://doi.org/10.1183/09031936.05.00069304.
Scanlon, S.T., Thomas, S.Y., Ferreira, C.M., Bai, L., Krausz, T., Savage, P.B., Bendelac, A., 2011. Airborne lipid antigens mobilize resident intravascular NKT cells to induce allergic airway inflammation. J. Exp. Med. 208, 2113–2124. https://doi.org/10.1084/jem.20110522.
Tang, X.-Z., Jo, J., Tan, A.T., Sandalova, E., Chia, A., Tan, K.C., Lee, K.H., Gehring, A.J., De Libero, G., Bertoletti, A., 2013. IL-7 Licenses Activation of Human Liver Intrasinusoidal Mucosal-Associated Invariant T Cells. J. Immunol. 190, 3142–3152. https://doi.org/10.4049/jimmunol.1203218.
Thomas, S.Y., Scanlon, S.T., Griewank, K.G., Constantinides, M.G., Savage, A.K., Barr, K.A., Meng, F., Luster, A.D., Bendelac, A., 2011. PLZF induces an intravascular surveillance program mediated by long-lived LFA-1–ICAM-1 interactions. J. Exp. Med. 208, 1179–1188. https://doi.org/10.1084/jem.20102630.
Tilloy, F., Treiner, E., Park, S.-H., Garcia, C., Lemonnier, F., de la Salle, H., Bendelac, A., Bonneville, M., Lantz, O., 1999. An Invariant T Cell Receptor α Chain Defines a Novel TAP-independent Major Histocompatibility Complex Class Ib–restricted α/β T Cell Subpopulation in Mammals. J. Exp. Med. 189, 1907–1921. https://doi.org/10.1084/jem.189.12.1907.
Uezu, K., Kawakami, K., Miyagi, K., Kinjo, Y., Kinjo, T., Ishikawa, H., Saito, a., 2004. Accumulation of T Cells in the Lungs and Their Regulatory Roles in Th1 Response and Host Defense against Pulmonary Infection with Cryptococcus neoformans. J. Immunol. 172, 7629–7634. https://doi.org/10.4049/jimmunol.172.12.7629.
Urboniene, D., Babusyte, A., Lötvall, J., Sakalauskas, R., Sitkauskiene, B., 2013. Distribution of γδ and other T-lymphocyte subsets in patients with chronic obstructive pulmonary disease and asthma. Respir. Med. 107, 413–423. https://doi.org/10.1016/j.rmed.2012.11.012.
van Wilgenburg, B., Scherwitzl, I., Hutchinson, E.C., Leng, T., Kurioka, A., Kulicke, C., de Lara, C., Cole, S., Vasanawathana, S., Limpitikul, W., Malasit, P., Young, D., Denney, L., Moore, M.D., Fabris, P., Giordani, M.T., Oo, Y.H., Laidlaw, S.M., Dustin, L.B., Ho, L.P., Thompson, F.M., Ramamurthy, N., Mongkolsapaya, J., Willberg, C.B., Screaton, G.R., Klenerman, P., 2016. MAIT cells are activated during human viral infections. Nat. Commun. 7, 11653. https://doi.org/10.1038/ncomms11653.
Wu, J., Xu, L., Han, X., Hu, H., Qi, F., Bai, S., Chai, R., Teng, Y., Liu, B., 2017. Role of γδ T cells in exacerbated airway inflammation during reinfection of neonatally primed mice in adulthood. J. Med. Virol. 89, 2108–2115. https://doi.org/10.1002/jmv.24914.