



The role of invariant T cells in inflammation of the skin and airways

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Received: 15 February 2019 / Accepted: 21 March 2019 / Published online: 15 April 2019
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Abstract

Invariant and semi-invariant T cells are emerging as important regulators of host environment interactions at barrier tissues such as the airway and skin. In contrast to conventional T cells, invariant natural killer T (iNKT) cells and mucosal associated invariant T (MAIT) cells express T cell receptors of very limited diversity. iNKT and MAIT cells recognise antigens presented by the MHC class 1-like monomorphic molecules CD1d and MR1, respectively. Both iNKT cells and MAIT cells have been identified in the skin and airways and can rapidly produce cytokines after activation. Numerous studies have implicated iNKT cells in the pathology of both skin and airway disease, but conflicting evidence in human disease means that more studies are necessary to resolve the exact roles of iNKT in inflammation. The functions of MAIT cells in skin and lung inflammation are even less well defined. We herein describe the current literature on iNKT and MAIT cells in allergic and non-allergic skin diseases (dermatitis and psoriasis) and airway diseases (asthma, chronic obstructive pulmonary disease, rhinitis, and chronic rhinosinusitis).

Keywords Asthma · Chronic obstructive pulmonary disease · Rhinitis · Chronic rhinosinusitis · Dermatitis · Psoriasis · Invariant natural killer T · iNKT · Mucosal associated invariant T · MAIT

Introduction

In allergic individuals, T cells mount strong responses to environmental proteins called allergens (e.g. pollen, dust mites, food and animal fur). Allergen recognition occurs through the T cell receptor (TCR). Most T cells express a TCR consisting of an α and β chain, and a smaller proportion of T cells use γ and δ chains. Both $\alpha\beta$ and $\gamma\delta$ TCRs variably use interchangeable segments of DNA called V, D and J regions to generate their TCRs, one of the very few examples where changes to

the underlying DNA sequence occur as part of normal cellular development. This results in an enormous diversity of antigen specificities that allows the immune system to recognise a multitude of antigenic peptides. When a T cell recognises antigen, it undergoes clonal expansion, resulting in a population of cells with the same antigen specificity and VJ or VDJ sequence. After the antigen is cleared or removed, a clonal population of antigen-specific memory T cells remains that persist within an individual [1].

In addition to conventional T cells with polyclonal TCRs, populations of invariant or semi invariant T cells are known to exist, particularly at barrier surfaces such as the skin, airway and gut. Chronic inflammation at mucosal and skin surfaces involves both the adaptive and innate immune systems, often coupled with a breakdown of the host barrier system and infections. Invariant T cells have several features that are shared with both innate and adaptive immune cells. For example, they recognise discreet antigens via their TCRs, while also possessing the ability to respond directly to cytokine stimulation, a function that is typically reserved for cells of the innate immune system. Invariant T cells are capable of producing cytokines that are known to cause skin and airway inflammation, and recent studies show that these cell populations are altered in asthma, chronic obstructive pulmonary disease, atopic dermatitis and psoriasis. This review will first briefly describe invariant and semi-invariant T cells and then outline

This article is a contribution to the special issue on The Pathogenicity of Acquired Immunity in Human Diseases - Guest Editor: Kiyoshi Hirahara

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what is known about the role of these cells in inflammation of the skin and airway.

NKT cells

Natural killer T (NKT) cells rapidly produce cytokines and can be activated both through their TCR and via direct signals from cytokines. Invariant NKT (iNKT) cells express an invariant TCR α chain consisting of V α 14/J α 18 paired with a limited range of TCR β chains (V β 8.2, V β 7 or V β 2) in mice or V α 24/J α 18 paired with V β 11 in humans, and account for the majority of NKT cells [2–5]. NKT cells express the receptors for Interleukin (IL)-12 [6], IL-18 [7], IL-23 [8], IL-25 [9], and IL-33 [10], and CD4⁺ NKT cells express high levels of the lung-homing chemokine receptor CCR4 [11]. NKT cells are activated by endogenous and environmental glycolipid ligands presented in the context of the non-polymorphic major histocompatibility complex (MHC) class I-like antigen-presenting molecule, CD1d [12]. iNKT cells can be efficiently detected with CD1d tetramers loaded with the well-defined iNKT ligand alpha galactosylceramide (α -gal-cer). Fungal and bacterial antigens from *Sphingomonas* [13], *Aspergillus fumigatus* [14] and *Streptococcus pneumoniae* [15] have been shown to be recognised by NKT cells, implicating NKT cells in the recognition of environmental antigens. Interestingly, the NKT population is greatly expanded in germ-free (GF) mice [16], indicating that microbial signals are important to regulate their development.

The transcription factor promyelocytic leukaemia zinc finger (PLZF, encoded by *Zbtb16*) is required for differentiation of the NKT lineage [17], and the transcription factors Egr1 and Egr2 have been shown to facilitate iNKT development in the thymus [18]. NKT cells can be differentiated into three subsets based on cytokine production and expression of the transcription factors PLZF, T-box 21 (T-bet), and RAR-related orphan receptor gamma (ROR γ t). NKT1 cells produce IFN- γ and express high levels of T-bet [19], NKT2 cells produce IL-4 and express high levels of PLZF [20], and NKT17 cells produce IL-17 and express high levels of ROR γ t [8, 20, 21]. NKT2 cells depend on the transcription factors PLZF, Gata3 and Irf4 for development [20, 22]. T-bet is required for differentiation of IFN γ -producing NKT1 cells [20], and ROR γ t expression is linked to production of IL-17 [23]. The microRNA Let 7 was recently shown to control development of NKT1 cells in the thymus [24].

It is becoming evident that further significant heterogeneity exists within the NKT cell subsets [25]. For example, Bcl-6-dependent follicular helper NKT (NKTfh) cells have been shown to promote antibody production and provide help for B cells via production of IL-21 [26]. iNKT cells are capable of activating B cells [27] and can provide help to B cells responding to CD1d-restricted antigens [28, 29]. In addition, NKT cells located in the interfollicular regions were recently

found to be required for initiation of antiviral B cell immunity [30]. This study also found that iNKT positioned close to the follicular borders rapidly produce IL-4 and are required for efficient formation of germinal centres and antibody production [30].

MAIT cells

Like iNKT cells, mucosal-associated invariant T (MAIT) cells are defined by their restriction to another non-classical MHC class I-related molecule MR1 [31]. MAIT cells are a subset of innate-like T cells that use a semi-invariant TCR that consists of V α 7.2 and J α 33, J α 12 or J α 20 [32–34] and predominately a V β 13 (TRBV6) and V β 2 (TRBV20) TCR β chain [33, 34] (Fig. 1). MAIT cells are found in high abundance in the gut lamina propria and are also found in circulation and in other tissues including the lung [35] and skin [36]. MAIT cells comprise 1–5% of peripheral blood T lymphocytes in humans, and their numbers increase after birth [37]. MAIT cells are predominately CD8⁺ and a smaller proportion are CD8 and CD4 double negative (DN) [37, 38]. Like most NKT cells, MAIT cells express high levels of CD161 and CCR6 [39] and the cytokine receptors IL-18R [40], IL-12R, IL-23R and IL-2R β , and have an effector-memory phenotype [41, 42]. MAIT cells show significant diversity and express the transcription factors PLZF and ROR γ t [43, 44], but MAIT cell subsets have not yet been fully defined. MAIT cell maturation is dependent on microbial signals [31], in contrast to NKT cells that appear to expand in GF mice [16]. MAIT cells recognise ligands from the riboflavin (vitamin B2) pathway [45]. Bacteria including *Staphylococcus aureus* and *Klebsiella pneumoniae*, and yeasts including *Candida albicans* and *Saccharomyces cerevisiae* that are capable of riboflavin synthesis are able to stimulate MAIT cells in an MR1-dependent manner [35].

Invariant T cells in airway inflammation

Asthma

Allergic asthma is a chronic inflammatory disease of the airways that develops due to aberrant immune responses to common environmental antigens including dust mites, pollens and fungi [46]. The type-2 cytokines IL-4, IL-5 and IL-13 produced by allergen-specific CD4⁺ T-helper (Th) cells contribute to the development of allergic responses including immunoglobulin E (IgE) production by B cells, cellular inflammation, and airway hyperreactivity (AHR) in asthmatics [1, 47, 48]. Glycolipid antigens from *Sphingomonas* [13], *Aspergillus fumigatus* [14] and *Streptococcus pneumoniae* [15] can be presented by the NKT antigen presentation molecule CD1d and are capable of inducing asthma-like symptoms in an NKT-dependent manner in mouse models [13–15]. The

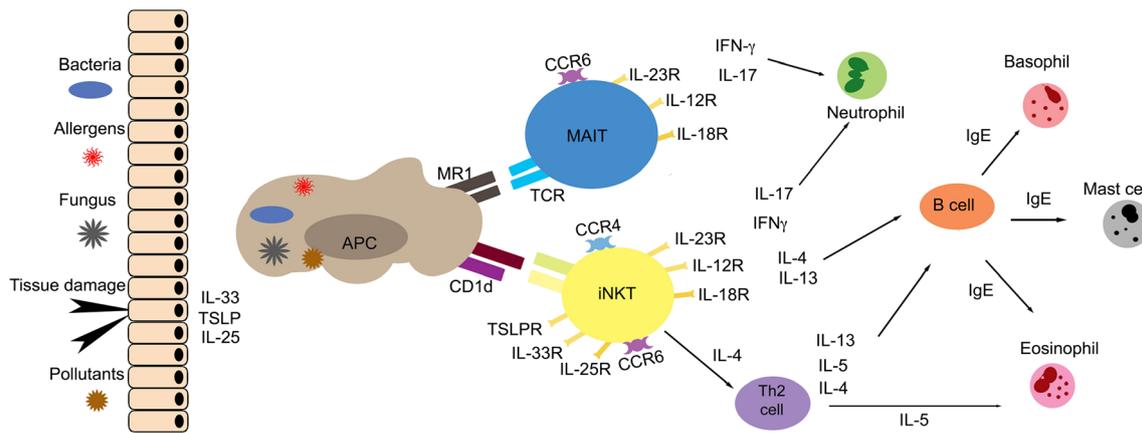


Fig. 1 Known activators and functions of iNKT and MAIT cells in the airway and skin. iNKT and MAIT cells express semi-invariant TCRs that recognise antigens presented by the MHC-like molecules CD1d and MR1, respectively. Both iNKT and MAIT cells can respond directly to cytokine stimulation. Rapid production of cytokines including IL-4, IL-

13, IL-17, and IFN- γ is capable of recruiting and activating effector cells such as eosinophils, neutrophils and altering conventional T cell function. IL-4 and IL-13 is also able to induce IgE production by B cells and potentiate antibody-mediated inflammatory responses

involvement of NKT cells in protein-allergen-induced asthma is more controversial. An early study using β 2 microglobulin knock out (KO) mice indicated that NKT cells were not required for development of airway inflammation [49]. Other studies using CD1d KO [50–52] also reported that loss of NKT cells did not diminish development of disease. However, other groups have reported significant reduction in inflammation and AHR in mice lacking NKT cells due to deletion of CD1d or $J\alpha$ 18 [53, 54]. Further implication for the involvement of iNKT cells in murine models of asthma comes from a recently developed mouse strain that has deletion of the invariant $J\alpha$ 18 region without disturbing recombination of downstream $J\alpha$ genes [55]. These mice do not develop cellular inflammation or AHR in an ovalbumin-induced lung inflammation model or cockroach antigen-induced AHR. Differences in mouse strain may provide a possible explanation for these divergent results. Initial experiments with CD1d KO mice were carried out on 129/SV or mixed S126/C57BL/6 backgrounds, and later experiments were done primarily with C57BL/6 or BALB/c background mice. Importantly, the type of stimulation of iNKT cells may be important in airway inflammation. Activation of iNKT cells in vitro with α -gal-cer, a potent ligand for iNKT cells, followed by adoptive transfer of these cells results in IFN- γ -dependent suppression of airway inflammation [56]. In contrast, intranasal exposure to α -gal-cer results in development of airway inflammation in mice and monkeys [57–59]. We found that the epigenetic repressor Ezh2 is an important regulator of the ability of iNKT cells to drive asthma-like airway pathology in mice [60]. Ezh2 KO C57BL/6 mice have markedly elevated levels of IL-4 and IL-13-producing NKT2 cells and spontaneously develop pathology resembling allergic asthma including elevated IgE, AHR airway mucus production and airway inflammation [60, 61]. Compared to WT mice, Ezh2 KO mice also develop

enhanced AHR in response to house dust mite challenge that is dependent on iNKT cells [60]. iNKT cells may also participate in other types of asthmatic pathology including ozone-induced asthma; IL-17-producing iNKT cells were also found to be required for the development of AHR in an ozone-induced model of AHR development [62].

iNKT cells have been shown to respond directly to cytokine signals and in this way can participate in inflammatory pathways independently of specific antigen recognition. IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) are produced by epithelial cells in response to cell stress and damage [63]. IL-25 signals through IL-17RB that is expressed on iNKT2 and iNKT17 cells [9, 64]. IL-25 administration results in increased iNKT-dependent IgE, airway inflammation and AHR [9, 64]. IL-33 signals through the ST2 receptor that is also expressed on iNKT cells and can induce production of cytokines from iNKT cells [10, 65]. iNKT cells also express the receptor for TSLP, and TSLP overexpression results in increased AHR that was also found to be dependent on iNKT cells [66]. PolyI:C is a synthetic analogue of double-stranded RNA that stimulates toll-like receptor 3 (TLR3). Double-stranded RNA is found in some viruses, and TLR3 is an important sensor of viral infection. PolyI:C was found to induce IL-1b and IL-23 production by dendritic cells and increase IL-17-production from iNKT cells [67]. This pathway was shown to enhance iNKT-dependent neutrophilia and AHR [67]. These data indicate cellular stress, and viral signals may indirectly result in iNKT activation and the contribution of iNKT cells to development of asthma-like lung pathology. Overall, these data indicate that iNKT cells are capable of driving development of asthma-like disease in animal models.

In human asthmatics, increased numbers of NKT cells in bronchoalveolar lavage (BAL) samples [68–70], and an increase in NKT cells after allergen challenge [71] have been

reported; however, some studies have failed to detect a difference in lung NKT cell numbers between asthmatics and non-asthmatics [72, 73]. The majority of these studies detected iNKT cells in BAL and sputum samples at around 1–2% of T cells. There does not appear to be a clear relationship between the total numbers of iNKT cells in the blood and asthma phenotypes [69, 74, 75]. However, one study has identified an increase in the proportion of IL-4-expressing iNKT cells in asthma patients compared to controls [76]. As outlined above, three subsets of iNKT cells have been defined in mice; IFN- γ -producing iNKT1 cells [19], IL-4-producing iNKT2 cells [20], and IL-17-producing iNKT17 cells [21]. In the context of disease pathogenesis and response to therapy, it will therefore be important to define iNKT cell subsets in human inflammatory diseases.

Decreased MAIT cell frequency has been observed in the peripheral blood, sputum and tissue biopsy specimens from asthma patients [77]. In the same study, a significant reduction in the number of MAIT cells in peripheral blood and sputum was also observed in severe asthmatics compared with mild asthmatics. MAIT cell frequency also negatively correlated with the dose of inhaled corticosteroids and positively correlated with forced expiratory volume in one second (FEV1) [77]. Another recent study found that MAIT cell frequency in peripheral blood at 1 year of age was associated with less risk of asthma at 7 years of age [74]. Though, the frequency of MAIT cells at 3 years of age was not found to be associated with risk of aeroallergen sensitization or wheezing at 3 years [74]. The frequency of MAIT cells was also shown to correlate with increased production of IFN- γ by conventional CD4⁺ T cells [74]. In addition, the proportion of IL-17-producing MAIT cells and conventional CD4⁺ T cells positively correlates with asthma exacerbations [75]. It is therefore possible that cytokine production from activated MAIT cells contributes to a skewing of the immune system away from Th2 responses that promote common allergic inflammatory phenotypes, such as eosinophilic inflammation and production of IgE.

Allergic rhinitis and chronic rhinosinusitis

Conventional CD4⁺ [78] and CD8⁺ [79] T cells are present in airway tissue from chronic rhinosinusitis (CRS) patients. In particular, effector-memory CD8⁺ T cells are present in significantly higher proportions in CRS with nasal polyps, a more severe form of CRS inflammation. iNKT has been described in the nasal mucosa of asthma patients with CRS with nasal polyps [80]. Interestingly, the same study did not detect iNKT cells in the nasal mucosa of non-asthmatic CRS or allergic rhinitis (AR) patients [80]. At present, the roles of MAIT cells within tissues from AR and CRS patients are unknown. Overall, the participation of iNKT and MAIT cells in upper airway inflammation remains to be defined.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterised by inflammatory cellular infiltration and remodelling of the airways. Repeated intranasal administration of the iNKT-ligand α -gal-cer was reported to induce a COPD-like disease in mice [81], and acute lung infection with mouse Sendai virus was found to induce chronic iNKT cell-dependent lung pathology similar to COPD and asthma [82]. Decreased numbers of iNKT cells in peripheral blood and sputum of COPD patients compared to healthy controls have been reported [83]. Interestingly, the same study found a decrease in DN iNKT cells and an increase in CD4⁺ iNKT cells in the blood of COPD patients, indicating that more detailed analysis of iNKT subtypes in COPD may be warranted.

Reduced numbers of both CD8⁺ and DN MAIT cells have been found in the peripheral blood of COPD patients [83, 84]. Furthermore, similar to asthma patients, a reduced number of MAIT cells were associated with worse FEV1 and increased severity of COPD [84]. It was subsequently shown that MAIT cells are significantly reduced in blood and bronchial tissue from steroid-treated, but not steroid-naive, COPD patients [85]. The authors also show that MAIT cells respond to *Haemophilus influenzae* infected macrophages in an MR1-dependent manner, suggesting that MAIT cell dysfunction may contribute to the markedly increased prevalence of *Haemophilus influenzae* infection in COPD [86].

Invariant T cells in skin inflammation

The skin is an essential barrier to infection. Its function is achieved by a well-coordinated system of structural and immune cells that ensures adequate immune responses to microbial pathogens and environmental factors, while maintaining self-tolerance that prevents allergy and autoimmunity [87, 88]. Tissue-resident memory CD8⁺ T cells are an important first line of defence against re-infection and are involved in various chronic skin inflammatory diseases, including psoriasis [89]. The CD4⁺ T cell population in the skin consists of Th cell-subsets and immunosuppressive regulatory T cells. IFN- γ and IL-2-producing Th1 cells have been shown to mediate delayed-type hypersensitivity reactions such as contact hypersensitivity (CHS) and psoriasis. Th2 cells secrete IL-4, IL-5 and IL-13 and are involved in the pathophysiology of allergic skin diseases. Th17 cells protect the skin by promoting neutrophil and T cell recruitment. In contrast, Th22 cells have limited inflammatory properties but promote skin homeostasis by inducing keratinocyte proliferation and maintaining skin integrity. An imbalance in the number and/or function of skin-resident or infiltrated conventional T cells has been associated with chronic skin inflammation and skin pathology

[90]. We will now review the current literature on iNKT and MAIT cells in inflammatory skin diseases.

Atopic dermatitis

Atopic dermatitis (AD) is a highly pruritic, chronic relapsing inflammatory skin disease characterised by skin barrier dysfunction that results in dry skin and allergic sensitisation to antigens. It is the most common chronic skin disease, affecting 15 to 30% of the population in industrialised countries, especially in young children and commonly precedes the onset of other atopic conditions (i.e., allergic rhinitis or asthma). Most patients with AD have an allergic form (allergic AD), characterised by high serum or local IgE levels and positive skin prick test reactions to common environmental allergens such as food or aeroallergens. The remaining patients have non-allergic AD, with normal total IgE levels and negative serum allergen-specific IgE, reflecting multiple different pathogenic mechanisms and indicating that AD represents a collection of heterogeneous groups [91].

In the last decade, despite their small number in the peripheral blood, iNKT cells have entered into the focus of immunological investigations in AD. However, the exact roles of iNKT cells in AD have not been completely defined. Contradictory results in iNKT cell numbers in the peripheral blood of patients with AD have been reported. A significant increase has been reported in iNKT cells in peripheral blood mononuclear cells (PBMCs) of patients with moderate to severe AD compared to mild AD and healthy controls [92]. Furthermore, the same study suggested that TSLP-induced IL-4 and IL-13 secretion from iNKT cells contributed to the innate allergic immune response in AD [92]. In contrast, other research groups found a lower number of iNKT cells in peripheral blood of AD patients [93, 94]. These conflicting findings may in part be explained by their use of different cell surface markers to define iNKT cells in different studies. A decrease in iNKT cells in peripheral blood could also reflect their recruitment into the skin. iNKT cells were detected as dermal infiltrating cells in skin lesions of AD, allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD), and they were predominantly found in areas with dense perivascular infiltrates [95, 96]. iNKT cells are able to produce large amounts of Th1 or Th2 cytokines upon activation, depending on their subset. CD4⁺ iNKT cells release the most Th2 cytokines and CD8⁺ and DN iNKT cells predominantly exhibit Th1 phenotypes and cytotoxic activity [97]. In the functional analysis of NKT cells in AD patient's blood, it was reported that overall IL-4 production was increased in the iNKT cells from AD patients compared with those from healthy controls. Particularly in the DN iNKT population, the significant increase in IL-4 was accompanied by a

significant decrease in IFN- γ levels [94]. However, in skin lesions from AD patients, such bias on Th2 responses was not observed [95].

ACD is an eczematous, inflammatory skin disease. ACD can be divided into distinct phases: sensitisation, elicitation and inflammatory regulation. Sensitisation is the immunologic priming response following the initial topical exposure to the allergen. Subsequent exposures at the same or distant sites on the skin result in a more vigorous secondary immune response at the point of contact, referred to as elicitation, followed by the immune resolution stage. The extent and severity of these hypersensitivity responses are controlled by different inflammatory regulation pathways. The presence of a significant number of iNKT cells at elicitation sites of ACD as well as in an experimental model of CHS has been reported [96].

In mice, NKT cells were reported to play important roles in the regulation of CHS in different phases. NKT cell-deficient CD1d KO and iNKT cell-deficient J α 18 knock-out mice on BALB/c [98–100], C57BL/6 [98] and B10.PL(H-2u) [101] backgrounds were reported to have a significantly impaired CHS response. In the sensitisation phase, iNKT cells can recognise and be activated by highly conserved endogenous and microbial glycolipids, presented on CD1d molecules [98]. Furthermore, iNKT cells activated and colocalised with dendritic cells in the draining lymph nodes after sensitisation. iNKT were also reported to promote the survival and maturation of dendritic cells that contribute to CHS establishment [99]. In the early elicitation phase, activated iNKT cells in the liver were suggested to secrete IL-4 and activate B-1 B cells to produce of hapten-specific immunoglobulin M (IgM) [102, 103]. At the challenge site in the skin, the IgM forms immune complexes with the antigen to activate complement C5a generation, which increases vascular permeability and facilitates the local recruitment of effector CD8⁺ T cells into the extravascular tissues [104]. While the above observations support an effector role of iNKT cells in CHS responses, some studies demonstrated a suppressive role of iNKT cells in CHS. It was reported that NKT cells suppress the CD8⁺ T cell response, which results in an enhancement of the CHS response in C57BL/6 CD1d KO mice [105]. Furthermore, a pronounced infiltration of mononuclear cells in the skin, reduced frequencies of IL-10 releasing B cells in the spleen and peritoneal cavity, was detected in CD1d KO mice of the same genetic background [106]. The relative importance of these two opposite functions during CHS may depend on the mouse strain or differences in experimental protocols between studies. Wild-type BALB/c mice develop a higher CHS response than of wild-type C57BL/6 mice [98]. BALB/c mice have been shown to have significantly more IL-4-producing iNKT2 cells compared to C57BL/6 mice [20]. This

indicates that iNKT cells may have a pivotal role in CHS to DNFB in BALB/c but not in C57BL/6 mice.

Psoriasis

Psoriasis is a chronic inflammatory skin condition characterised by erythematous scaling plaques that can affect any area of the skin and the nails, affecting approximately 3% of the population worldwide [107]. Psoriasis is driven by activated Th cells that stimulate proinflammatory cytokine production (IFN- γ , IL-2 and TNF α) and abnormal keratinocyte hyperproliferation. Psoriasis has long been recognised as a Th1/Th2 disease and recently challenged by the detection of abundant and active CD4⁺ Th17 cells and Th22 in psoriatic skin lesions. Their corresponding cytokines IL-17 and IL-22 have been shown to be important for the pathogenesis of psoriasis [108].

The potential role of iNKT cells in psoriasis was first demonstrated in xenograft animal studies where iNKT cells from the psoriatic patient were shown to induce psoriasis in normal human skin transplanted onto immunodeficient (SCID) mice [109, 110]. Furthermore, a constant finding observed by independent laboratories is that iNKT cells are detected in greater numbers in lesional skin of psoriatic patients than in normal healthy skin and/or nonlesional skin [111, 112]. The direct interaction of iNKT cells with CD1d-bearing keratinocytes and consequent induction of keratinocyte hyperproliferation is suggested to be a major pathogenic role of NKT cells in psoriasis [111].

MAIT cells have been recently found in normal and psoriatic human skin [36]. They are uniquely activated by riboflavin metabolites that are presented in the context of MR1, which is ubiquitously expressed by dendritic cells and keratinocytes [113]. MAIT cells have been shown to account for the majority of the IL-17-producing CD8⁺ T cells in the blood [39]. It was also reported that the IL-17⁺CD8⁺ cells were highly enriched in psoriatic skin and represent an additional source of IL-17, IFN- γ and TNF α leading to strong inflammatory responses [114]. The number of IL-17-producing IL-17⁺CD8⁺ cells in the blood correlates with psoriasis disease severity, and IL-17⁺CD8⁺ cells in the dermis and epidermis of psoriatic plaques consist of both conventional and MAIT cells [36]. There is therefore strong evidence to support the involvement of MAIT cells in psoriasis.

Conclusions

Invariant T cells, including iNKT and MAIT cells, are key sensors and immune regulators at the host-environment interface and are likely to play important roles in chronic inflammatory diseases of the airway and skin. It is intriguing that iNKT cells are expanded in the absence of microbial signals,

but MAIT cells have an absolute requirement for microbial signals for their maturation. These differences most likely underpin the roles of iNKT and MAIT cells in environmental signalling and immune function, and their importance in regulating microbial tolerance and infection.

iNKT cells recognise glycolipid ligands from *Sphingomonas*, *Aspergillus fumigatus* and *Streptococcus pneumoniae* and can rapidly produce cytokines upon ligand recognition. It is therefore tempting to speculate that NKT cells drive inflammatory disease in humans. iNKT cells have been shown to participate in a number of inflammatory diseases of the airway and skin. The majority of studies have found that iNKT cells can promote inflammation of the airway and skin, but immunoregulatory roles for iNKT cells have also been reported. More detailed analysis of the functionally different subsets of iNKT will likely yield important insights into their contribution to human disease. MAIT cells are also implicated in both positive and negative regulation of airway and skin inflammation; however, studies on the association between MAIT cells and airway diseases are limited. Further research on the functional heterogeneity of iNKT and MAIT cells, and identification of additional environmental and endogenous ligands, is warranted to determine their role and therapeutic potential in airway and skin inflammation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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