Available online on 15.06.2023 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

Open Access

Review Article

Involvement of iNKT Cells in Bronchial Asthma

Swarnima Kandari, Ratnakar, Abhishek Chandola
Department of Pharmacy practice, SGRRITS, Dehradun, India

A B S T R A C T

Background: Bronchial asthma is a prevalent inflammatory disease characterized by infiltration with eosinophils, lymphocytes, and mast cells in the airway leading to airway hypersensitivity and increased mucus secretion. T helper (Th) 2-based immune responses drive the inflammatory process. Numerous mechanisms are being studied to understand the progression of allergen induce asthma which subsequently led to the identification of a new population of T cells called the iNKT cells which showed promising results when experimented on murine models. iNKT cells are potent immune modulators involved in a variety of immunoregulations. This potency is the result of their ability to produce prime Th2 cytokines. The recognition of lipid antigens is required for the activation of iNKT cells. When an inflammation occurs due to Th2 cells and ozone, endogenous glycolipids become modified. This causes the activation of various subsets of iNKT cells and initiates airway hyperactivity. Infrequent human studies depict that the number of iNKT cells in BAL fluid ranges from 1 % of lung lymphocytes to 14 % which is a sign of dynamic fluctuation in the number of iNKT cells.

Methods: Selective literature review including primary and secondary sources of literature. Eg. Cochrane database, NCBI, MEDLINE database.

Key words: asthma, glycolipid ligand, iNKT cells, Th2 cytokine, airway hypersensitivity, α-galactosylceramide

A R T I C L E I N F O: Received 14 April 2023; Review Complete 10 May 2023; Accepted 25 May 2023; Available online 15 June 2023

Cite this article as:

Kandari S, Ratnakar, Chandola A, Involvement of iNKT Cells In Bronchial Asthma, Asian Journal of Pharmaceutical Research and Development. 2023; 11(3):67-75.DOI: http://dx.doi.org/10.22270/ajprd.v11i3.1256

*Address for Correspondence:
Swarnima Kandari, Department of Pharmacy practice, SGRRITS, Dehradun, India

INTRODUCTION

Bronchial asthma is a prevalent health problem affecting nearly one in every ten individual and is continuously escalating leading to a greater number of affected patients since the past two decades[1]. The pulmonary wards of the hospitals in the country are cramped with cases of bronchial asthma and the same site is evident in the majority of developing countries[2,3]. In general, Asthma is characterized by wheeze, cough, shortness of breath, chest congestion and any obstruction in the air pathway[4]. Not all symptoms lead to the main outcome i.e. asthma but are somehow linked to the dissimilar pattern of inflammation. The modulation of asthma occurs via epithelial cells, bronchial smooth muscle, fibroblasts and pulmonary nerves. Normally, asthma is classified into allergic and non-allergic types[5-7].

Endotypes classification

In allergic asthma, the primary cause of inflammation is the type 2 immune responses which are mediated through the Th2 cytokines including IL-4, IL5, and IL-13, produced by CD+4Th2 cells[8]. The interleukins enhance the growth, differentiation, and recruitment of eosinophils, basophils, mast cells, and IgE-producing B cells in asthma inflammation[9]. The Th2 cells produce Th2 cytokines, which increase allergen-specific IgE synthesis which further increase airway mucus production and differentiation of airway eosinophils. This leads to the development of airway hyper responsiveness (AHR) [10].

While, allergic asthma is the mostextensive form of asthma. The airways enclose eosinophils, allergen-specific CD4 Th2 cells, mast cells and basophils in huge numbers. Asthma affected patients from every age group have airway inflammation and airway hyper reactivity (AHR) as a common characteristic[11].

Non-allergic asthma is chiefly triggered by an inflammatory reaction caused due to viral infections with a major neutrophilic component[12, 13]. There is ample data to demonstrate that neutrophilic forms of murine and human asthma are linked with IL-17A[14, 15]. The cytokine IL-17A induces neutrophilic inflammation and in association with TGF-β contributes in airway smooth muscle remodelling [16].

Inflammation in Asthma

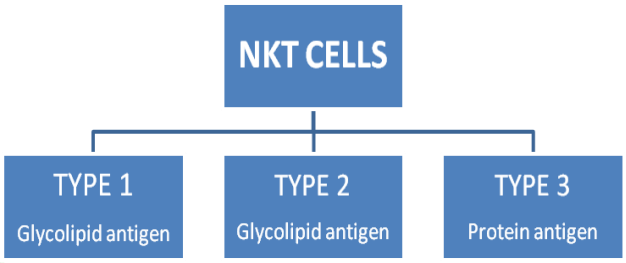
The fundamental characteristic of Asthma hyperresponsiveness is the reversible airway obstruction which does not occur in other non-asthmatic pulmonary inflammations like pneumonia and bronchiectasis[17]. Respiratory irritants like cold, fumes and smoke lead to extended clinical responses and further increase the severity of AHR. The increase in the concentrations of methacholine or histamine is a chief feature[18]. Airway inflammation cannot be concluded as the cause of airway hyper responsiveness but the inflammatory events increase airway responsiveness after exposure to allergens[19, 21]. There are also other causes of AHR for e.g., live influenza virus sources amplified bronchoconstriction involving cholinergic and non-cholinergic excitatory neural pathways. Other examples include epithelial necrosis and reduced production of epithelial relaxing factors such as PGE2 and neutral peptidases[22]. Some other studies imply that the levels of IgE antibodies are comparatively high in formative years which later on lead to the development of airway hyperresponsiveness[23].

To understand the mechanism of a asthma, experimentally induced allergic channel is studied and typically the inflammation follows the following pathways:

- Primarily identified as the early phase reaction, this step includes the release of pro inflammatory mediators like the histamine eicosanoids and reactive oxygen species. It is then followed by the activation of airway mast cells and macrophages[24, 25]. This causes contraction of the smooth muscles present in the airways encompassed with mucous secretion and vasodilatation[25]. The plasma gets exuded into the microvasculature after which the airway wall thickens and airway lumen narrows. This causes airway obstruction[26].
- The subsequent step is the late phase reaction which is characterised by Cellular events and release of proinflammatory mediators. In this step, because of the release of the cytokines previously, the early recruitment of mast cells occurs [27]. After the late phase reaction, non-specific bronchial hyperresponsiveness occurs.
- The maturation of inflammatory cells takes place in the bone marrow. Hematopoietic cells are also present in the airways [28, 29]. The travelling inflammatory and endothelial cells get adhered to the microvasculature. Further, the inflamed airways recruit the including eosinophils, lymphocytes, and monocytes (peripheral blood cells) [30, 31]. Along with pro inflammatory mediators, distinct adhesion molecules such as CD11a, CD11b, CD18, and intercellular adhesion molecule-1 (ICAM-1) or vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells also catalyses the induction of the inflammatory response[32, 33].

Role of NKT cells in Asthma inflammation

The progression of asthma is suggested to be by the contribution of NKT cells. NKT cells which are only 1% of the total Lymphocytes (WBCs) are responsible for the expression of both T cells (T-cell receptor) and NK cells (e.g., NK1.1, NKG2D)[34]. NKT cells are sometimes confused with Natural killer cells and cytotoxic T cells (cytotoxic T cells). Natural killer cells are critical part of the innate immune system and are a type of cytotoxic lymphocyte belonging to the ILC family or innate lymphoid cells. And cytotoxic T cell is a T lymphocyte (a form of white blood cell) that inhibits cancer cells or other transmuted cells[35]. NKT cells are classified into three subtypes, following the basis of their TCR.



a. TYPE I NKT CELLS

They are the invariant NKT (iNKT) cells that express invariant TCR alpha chains including V α24 – J α18 in humans and V α 14 – J α18 in mice together with a restricted selection of Vβ chains (Vβ8, Vβ7, Vβ2 in mice and Vβ11 in humans). Type 1 NKT rely on the glycolipid antigens of the non-polymorphic major histocompatibility complex (MHC) class I-like molecule CD1d such as the glycolipid α-galactosylceramide (α-GalCer) [36, 37]. Type I NKT cells respond and express a pattern recognition receptor. For instance, the development of allergen induced AHR demands the presence of CD1d-restricted or type 1 NKT cells. Type 1 NKT cells contribute to AHR and asthma more apparently [38].

b. TYPE II NKT CELLS

They are responsible for the expression of the non-invariant TCRs and simultaneously identify glycolipid antigens presented by CD1d. They have diverse TCR range because of which they can't be recognized using α-GalCerloaded CD1d tetramers [39].

c. TYPE III NKT CELLS

Type 3 NKT cells are restricted to MHC (major histocompatibility complex) class I and class II molecules other than CD1d. The non-invariant TCRs are a component of their expression.They also recognize antigen in a CD1d-independent manner[40, 41].

Type 1 and type 2 NKT cells recognize glycolipid antigens whereas type 3 cells recognize protein antigens. CD1D present on type1 and 2 is expressed by the mucosal epithelial cells of the airway tract, hepatocytes, T cells, B cells, macrophages and dendritic cells [42, 43].

Different subsets of iNKT

iNKT cells can be CD4+, CD4−CD8− or CD8+ in humans. The human CD4+ produces larger amounts of IL-4, IL-13, IFN-γ and Th2 cytokines[44], and in mice the same CD4+ iNKT cells produce larger amounts of IL-4 but is less effective in tumour immunity[45]. Other important immunoregulatory cytokines are also produced by CD4+ cells such as the IL-2, GM-CSF, IL-6 and IL-10. One of the e.g. is of phorbol 12-myristate 13-acetate (PMA)/ionomycin and α-GalCer-pulsed dendritic cells[46]. On the other hand, CD4-CD8- iNKT cell subset showcase greater cytotoxicity and only produce IFN-γ and TNF-α [47].

An additional subset of iNKT cells, NK1.1 has been studied whose function is not yet clear. It produces IL-17 but not IL-4. Every subset of iNKT cells expresses distinct receptors dependable for specific organs [48, 49]. According to a study that was performed on the participation of IL-17 in airway neutrophilia resulting from exposure to α-GalCer, PBS-57 (another iNKT cell ligand), it was verified that pulmonary iNKT cells could produce IL-17 upon activation[50, 51].

Studies propose that human Vα24 iNKT cells, defined by staining with CD1d tetramers or dual staining with Vα24 and Vβ11 monoclonal antibodies[52], are functionally and phenotypically heterogeneous in their expression of CD4/8 and their capacity for cytokine production [53, 54]. CD1d-restricted T cells have been acknowledged equally in mice as well as humans, and possess consideration for their unusual ability to secrete both Th1 and Th2 cytokines quickly upon stimulation[55 – 57]. iNKT cells are consistent for the development of AHR and airway inflammation. The suppression of OVA-induced AHR can be caused by the administration of anti-CD1d antibodies or a CD1d-dependent antagonist [58]. Other than this, lately, another subset of iNKT cells has been identified that meticulously releases high concentrations of IL-17 within definite time period (say 2-3 hours) from TCR stimulation during the lack of Th17 priming cytokineor IL-23. This iNKT cell subset is particularly distinct and has predefined cytokine secretion phenotype with discharge of IL-17 and IL-22 but no other Th1 or Th2 cytokines[59, 60].

Summary point:

1. Airway inflammation cannot be concluded as the cause of airway hyper responsiveness but the inflammatory events increase airway responsiveness after exposure to allergens.
2. The Th2 cells produce Th2 cytokines, which increase allergen-specific IgE synthesis which further increase airway mucus production and differentiation of airway

Lipid antigens in correlation with pulmonary iNKT cells

The recognition of lipid antigens is deemed significant for the activation of iNKT cells. Inflammatory environment base the expression of endogenous glycolipids [61]. When an inflammation occurs due to Th2 cells and ozone, endogenous glycolipids become modified. This causes the activation of various subsets of iNKT cells and initiates airway hyperactivity. An example is of Disialoganglioside GD3 which is a tissue specific glycolipid from tumour cells[62]. Other than the endogenous lipids, exogenous lipids mainly derived from microorganisms and plants can also be found for the activation of pulmonary iNKT cells[63]. A study concludes the activation of pulmonary iNKT cells and progression of AHR by other pathogens as well. Examples that were provided to support it include diacylglycerol antigens from the causative agent of Lyme disease and Borrelia burgdorferi glycolipid II. In addition, mycobacterium cell wall possesses phosphatidylinositol mannoside, which binds to CD1d and activates mouse and human iNKT cells[64–67]. Other organisms, such as Salmonella typhimurium, Listeria monocytogenes, Staphylococcus aureus, Escherichia coli, and cytomegalovirus, also bear the ability to activate iNKT cells but have an obliqueapproach. They work by stimulating DC production of cytokines such as IL-12, which then activate iNKT cells. E.g. of Cellular phospholipids include, phosphatidylcholine, phosphatidylinositol, phosphatidylglycerol, and phosphatidylethanolamine[68]. NKT cell development demands CD1d trafficking to lysosomal compartments in conjunction with lipid transfer function of saposins[69]. Isoglobotrihexosylceramide which is a lysosomal glycosphingolipid is another example of endogenous glycolipids. It can stimulate both human as well as mice iNKT cells. In a study from 2004, Hexb (lysosomal glycosphingolipid degrading enzyme b-hexosaminidase) cells were incapable stimulating Vα14 NKT hybridomas thus suggesting that iGb3 (Isoglobotrihexosylceramide) may perhaps alone characterize the chief natural ligand of NKT cells[70, 71]. Previously, two different mechanisms were proposed for the activation of Vα14 iNKT cells. They were proposed particularly by microbial products that do not enclose a ligand for the invariant TCR[72]. It has also been made known that Vα14 iNKT cells can also be stimulated by the collective action of IL-12 from dendritic cells, macrophages and endogenous GSL Ag(s) (glycosphingolipids) presented by CD1d [73].

α- galactosylceramide as an iNKT cell ligand

Discovered in the year 1997, α-galactosylceramide is a glycolipid presented by the monomorphic MHC class I-like CD1d molecule[74]. It was thought that the iNKT cell ligand should encompass both hydrophobic and hydrophilic properties to bind with both CD1d pockets and Vα14 antigen receptor respectively [75]. Activation of iNKT cells with α -GalCer promotes vigorous IFN- production by bystander cells such as NK cells. The common example being of exogenous glycolipid, α-GalCer which activates iNKT cells in mice and has been repeatedly studied. It causes rapid progression of severe AHR characterized by neutrophils, eosinophils, and lymphocytes. When glycolipids which resemble α-GalCer structurally were isolated from gram-negative α-proteobacteria sphingomonas, the response was similar [76]. In a study conducted in 1999, it was demonstrated that α-GalCer first binds to CD1d molecules on DCs followed by the recognition of α-GalCer bound DCs by NKT cells and their interaction with TCRs. After this, the endogenously produced IL-12 stimulates IFN-g production by NKT cells and IFN-g produced by NKT cells up regulates IL-12R on NKT cells [77, 78].

Do iNKT cells have an effect on human asthma?

A substantial number of studies have examined endobronchial biopsies; bronchoalveolar (BAL) fluid and sputum samples obtained from asthmatic patients and have found the presence of iNKT cells[79]. Out of the 7 studies that have been reviewed for this paper, 5 studies suggest that iNKT cells were present in the lung of patients with asthma [80 – 84] but the remaining of the studies did not find iNKT cells in samples of the asthma patients which have questioned the significance of iNKT cells in asthma[85]. Although the fact that every study conducted followed somewhat different protocol can't be ignored. For example, the major α- GalCer loaded CD1d tetramer or the anti-invariant NKT TCR or even the arrangement of 24 / V 11, which are the prominent means for identifying iNKT cells were either omitted in some of the studies or replaced[86]. Some studies replaced BAL fluid samples with sputum samples which may have led to discrepancies and thus questioning the broader objective, the role of iNKT in Asthma. According to a study that was performed on patients with broad range of asthma severity and non-asthmatic controls, using α-GalCer-loaded CD1d tetramers with appropriate unloaded CD1d tetramer as a control to identify iNKT cells, showed that patients who had severe but poorly controlled asthma had greater number of iNKT cells in their BAL samples[87]. The iNKT cells present in the BAL fluid varied largely (from 1 % up to 60 % of the T cells). Thus leading to the conclusion of not all asthma patients have increased number of iNKT cells [83, 84]. This again supports the fact that the iNKT cells as a factor can't be ignored in asthma. The results that vary are also affected by the type of the patient population undergoing the study, the different techniques used to identify the iNKT cells and even the tissues that were used for analysis. The studies are difficult to perform in humans but are regularly performed on murine models. But the outcomes of the infrequent human studies depict that the number of iNKT cells in BAL fluid ranges from 1 % of lung lymphocytes to 14 % which is a sign of dynamic fluctuation in the number of iNKT cells [88].

Studies conducted on mice and other non-human primates provide strong evidences concerning the importance of iNKT cells in asthma. With reference to the study performed in 2007 which was approved by the Institutional Review Boards at Children's Hospital Boston and Brigham and Women's and Connolly Hospitals, it was suggested that the number of iNKT cells matter less as compared to their potency. The small number of iNKT cells present in asthmatic patients suggests that iNKT cells might be more actively potent as they are rather considered [89]. The experiment induced asthma in mice by 3 distinct ways including allergens, viruses and exposure to ozone thus creating three models of the disease. Each of these models required an unlike subset of iNKT cells for the development of AHR.

iNKT cells in allergen induced asthma

According to a study published in 2003, it was shown that iNKT cells are in association with Th2 responses, eosinophils, and AHR. Both J α18 and CD1d mice, which lack iNKT cells, failed to develop allergen-induced AHR. The study showed the requirement of iNKT cells for the development of allergen-induced AHR. This study indicates that both Th2 cells (necessary for allergen-specific responses) and iNKT cells producing IL-4 and IL-13 are required for the development of allergen-induced AHR[90-92].

iNKT cells in ozone induced asthma

Studies conducted on mouse models who have been induced with asthma with air pollution, developed severe AHR and airway inflammation. Unlike allergen-induced AHR, which is associated with airway eosinophils, ozone-induced AHR was associated with airway neutrophils and macrophages[90]. Significantly, both CD1d and J α18 were unsuccessful in developing ozone-induced AHR, demonstrating that iNKT cells were required in the development of ozone-induced AHR. Moreover, IL-17A mice failed to develop ozone-induced AHR, although they developed severe allergen-induced AHR, indicating that IL-17 was specifically required for ozone but not for allergen-induced AHR[91, 81 – 83].

iNKT in virus induced asthma

The experiment that was conducted to identify the presence of iNKT cells in this model utilized Sendai virus to induce the symptoms of asthma. [92]. Using Sendai virus it was demonstrated that viral infection induced acute bronchiolar inflammation, chronic mucous cell metaplasia and increased AHR. In this model, the iNKT cells induced alternatively activated macrophages, which produced IL-13, which in turn drove increased mucus production and AHR [83, 93].

Summary points:

1. Inflammation occurs due to Th2 cells and ozone and endogenous glycolipids become modified.
2. Isoglobotrihexosylceramide which is a lysosomal glycosphingolipid is an example of endogenous glycolipids.
3. α-galactosylceramide is a glycolipid presented by the monomorphic MHC class I-like CD1d molecule.
4. Th2 cells and iNKT cells producing IL-4 and IL-13 are required for the development of allergen-induced AHR

Can Asthma be treated via iNKT cells?

The NKT cells, which express both NK receptors and TCR are encoded by the Vα14 and Jα281 gene segments, and are suggested to conduct an imperative function in the regulation of immune responses [93]. Cytokines such as IL-12 are capable of stimulating NKT cells to release IFN- and demonstrate natural cytotoxicity. This IFN- release by NKT cells in response to α-GalCer is primarily mediated by IL-12 produced by dendritic cells. NKT cells which are chiefly stimulated by α-GalCer inhibit antigen-induced allergic responses by the production of IFN-γ [94]. Because of their presence in Asthma, iNKT cells provide as a striking objective for asthma therapy[95]. Studies suggest that targeting iNKT cells may perhaps involve:

- Direct removal of iNKT cells or paralyzing iNKT cell function,
- Preventing theactivation of iNKT cells by blocking CD1d, or
- Altering iNKT cell function by reducing Th2 cytokine production [81, 96]

Experiments to support these ideas include the following:

When a-GalCer was intranasally administered to already sensitized mice there was seen inhibition of AHR and eosinophilia along with BALF Th2 cytokine production[97]. Furthermore, the reduction of IL-4 was associated with an increase of IFN-c indicated that a shift from a pro asthmatic Th2 to a protecting Th1 response had occurred in the airways[96]. Many studies in cancer field used α-GalCer or DCs loaded with α-GalCer, and showed hopeful efficacy in animal models.A known C-glycoside analog of α-GalCer has been shown to induce iNKT cells to produce distorted Th1 cytokines, and were shown to be more potent than α-GalCer in both antitumor and antimalarial efficacy[98 -100]. In autoimmune disease field, another analog of α-GalCer, an OCH compound, has been shown to induce distorted Th2 response and to protect mice against a Th1 disease like autoimmune encephalitis and collagen induced arthritis[101 – 104]. α-GalCer can bind CD1 d of both mice and human species and activate NKT cells of both species[97]. Thus there lies the scope for immunotherapy with α-GalCer for human asthma. Single injection of α-GalCer may provide protection against airway inflammation. Some of the limited data propose a realistic use of α-GalCer for therapeutic intervention in asthma. According to the research paper published in 2005, α-GalCer has differing effects on allergen induced eosinophilic airway inflammation and the degree of eosinophil infiltration and the IgE levels remained unchanged by both method of a-GalCer administration in Jα-281mice[105, 106].

This therapeutic advancement with α-GalCer is still debatable though as α-GalCer can also function as an adjuvant to develop allergen sensitization, and can induce AHR on its own. So other ways of treatment counting iNKT cells need to be explored to bring about the essential optimization of asthma treatment. IL-17BR is expressed in cultured primary fibroblasts and that IL-17E stimulates the production of the Eosinophil associated mediators CCL-5, CCL-11, GM-CSF, and CXCL-8 in these cells[42]. In a study it was showed that IL17E is expressed in the bronchial submucosa in asthma, and that the cytokines TNF-a and TGF-b1 which are involved in the pathogenesis of the disease have the ability to modulate the fibroblast response to IL-17E [43].

Other functions of iNKT cells

- As an immunomodulator

iNKT cells comprise of evolutionallyconserved subpopulation of T lymphocytes that express both T cell receptor (TCR) and NK receptors[107].iNKT cells recognize glycolipid antigens by an invariant TCRα chain composed of Vα14-Jα18 segments in mice and Vα24-Jα18 segments in humans[108]. Experimentally, activated iNKT cells are one amongst the primary potent immune modulators through an enormous production of a various cytokines including IL-4 and IFN-γ and were the major source of cytokines among TCR-bearing cells after stimulation with anti-CD3 antibody in vivo[33, 36].

- In the development of allergic responses

The link between allergic responses and iNKT cells includes treatment with α-GalCer induced IL-4 and IL-10 which provided protection against colitis [109]. BALB/c or C57BL/6J mice mixed Th1 and Th2 type colitis was shown and treatment with α-GalCer exacerbates the disease [110]. These results clearly indicate that iNKT cells situated in the gut mucosa can influence the type of colitis observed and can contribute to allergic colitis.

- iNKT cells in human SLE

Humans that are genetically susceptible to autoimmune diseases, including systemic lupus erythematosus (SLE) have reduced numbers and functional defects in iNKT cells[111]. A few human studies have investigated the presence and function of iNKT cells in peripheral blood in lupus patients and healthy control subjects [112]. The authors concluded that approximately 50% of autoimmune diseases react to α-GalCer treatment. In non-responders a functional defect of the iNKT cells can be suspected[113]. Another group investigated different rheumatic disease patients including SLE. In SLE patients CD8+ iNKT cell number was significantly reduced in the peripheral blood as compared to healthy controls. The authors suggest that a reason for this reduced iNKT cell number could be that the iNKT cells migrate into inflamed tissues. The immunoregulatory function of iNKT cells seems to be quite well supported by data [114].

CONCLUSION

The studies and papers reviewed for this article did not include any new discoveries and were partially based on ideas and theoretical approaches. Robust data and evidences are required to support the fact that the presence of iNKT cells influence asthma in some way or other. Further studies involving the researches on iNKT cells as potential treatment approach are required to comprehend and conclude the theory. The fact that iNKT cells participate in AHR and airway modulation is enough to carry out dedicated researches. New treatment approaches are required other than immunosuppressive therapies and iNKT cells ensembles substantial data.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

No funding was received for this work.

Ethical statement

No ethical approval was required as this study did not involve human participants or laboratory animals.

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

REFERENCES

1. Matangkasombut P, Marigowda G, Ervine A, Idris, L., Pichavant, M., Kim, H. et al. Natural killer T cells in the lungs of patients with asthma. J Allergy Clin Immunol 2009; 123(5):1181-1185. DOI:10.1016/j.jaci.2009.02.013
2. Umetsu D, McIntire J, Akbari O, Macaubas C, DeKruyff R. Asthma: an epidemic of dysregulated immunity. Nat Immunol 2002; 3,715–720. DOI:10.1038/ni0802-715

3. BusseWW, Lemanske RF. Advances in immunology: asthma. N. Engl. J. Med 2001; 344:350–62. DOI:10.1056/nejm200102013440507
4. Victor, J.R, Lezmi, G, Leite-de-Moraes. New Insights into Asthma Inflammation: Focus on iNKT, MAIT, and γδT Cells. Clinic Rev Allerg Immunol 2020; 59, 371–381. DOI:10.1007/s12016-020-08784-8
5. Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol 2011; 127(2):355–360. DOI:10.1016/ j.jaci.2010.11.037
6. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. J Allergy Clinical Immunol 2019; 144(1):1–12. DOI:10.1016/j.jaci.2019.05.031
7. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet 2018; 391(10118):350–400. DOI:10.1016/S0140-6736 (17) 30879-6
8. Wenzel SE. Asthma: defining of the persistent adult phenotypes. Lancet 2006; 368(9537):804–813. DOI:10.1016/S0140-6736(06)69290-8 6
9. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet 2008;372:1107-19. DOI:10.1016/S0140-6736(08)61452-X
10. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, et al. GINA 2019: a fundamental change in asthma management: treatment of asthma with short acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J 2019;53(6). DOI:10.1183/ 13993003.01046-2019
11. DeKruyff R, Umetsu D, Pichavant M, Akbari O, Yasumi T, Savage P, et al. Activation of nonclassical CD1d-restricted NK T cells induces airway hyperreactivity in beta 2-microglobulin-deficient mice. J Immunol 2008;181(7):4560-4569. DOI:10.4049/jimmunol.181.7.4560
12. Le´tuve´ S, Kadoch S, Audusseau S, Rothenberg ME, Fiset PO, Ludwig MS, et.al. IL-17E up regulates the expression of proinflammatory cytokines in lung fibroblasts. J Allergy Clin Immunol 2006; 117(3):590-6. DOI:10.1016/j.jaci.2005.10.025
13. Papotto PH, Ribot JC, Silva-Santos B. IL-17 + γδ T cells as kick-starters of inflammation. Nat Immunol 2017;18(6):604–611. DOI:10.1038/ni.3726
14. Humbles AA, Lloyd CM, McMillan SJ, Friend DS, Xanthou G, McKenna EE, et al. A critical role for eosinophils in allergic airways remodelling. Science 2004;305:1776-9. DOI:10.1126/science.1100283
15. Nocker RE, Schoonbrood DF, van de Graaf EA, Hack CE, Lutter R, Jansen HM, et al. Interleukin-8 in airway inflammation in patients with asthma and chronic obstructive pulmonary disease. Int Arch Allergy Immunol 1996;109:183-91. DOI:10.1159/000237218
16. Yousefi S, Hemmann S, Weber M, Holzer C, Hartung K, Blaser K, et al. IL-8 is expressed by human peripheral blood eosinophils: evidence for increased secretion in asthma. J Immunol 1995;154:5481-90. DOI:10.3389/fimmu.2014.00570
17. Sears MR, Greene JM, Willan AR, Wiecek E, Taylor D.R, Flannery E.M, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N. Engl. J. Med 2003;349:1414–22. DOI:10.1056/NEJMoa022363
18. Brusasco V, Crimi E, Pellegrino R. Airway hyperresponsiveness in asthma: not just a matter of airway inflammation. Thorax 1998;53(11):992-998. DOI:10.1136/thx.53.11.992
19. Durham SR, Craddock CF, Cookson WO, Benson MK, et al. Increases of airway responsiveness to histamine precede allergen induced late asthmatic responses. J Allergy Clin Immunol 1988; 82:764–70. DOI:10.1016/0091-6749(88)90077-2
20. Rossi GA, Crimi E, Lantero S, Gianiorio P, Oddera S, Crimi P, et al. The late-phase asthmatic reaction to inhaled allergen is associated with an early recruitment of eosinophils in the airways. Am Rev Respir Dis 1991;143:379–83. DOI:10.1164/ajrccm/144.2.379
21. Kava T. Acute respiratory infections, influenza vaccination and airway reactivity in asthma. Eur J Respir Dis 1987; 70(Suppl 150):7–38.
22. Martinez DF. Viral infections and the development of asthma. Am J Respir Crit Care Med 1995; 151:1644–8. DOI:10.1164/ajrccm/151.5_Pt_1.1644
23. Grunberg K, Smits HH, Timmers MC, Klerk EP, Dolhain RJ, Dick EC, et al. Experimental rhinovirus 16 infection. Effects on cell differentials and soluble markers in sputum in asthmatic subjects. Am J Respir Crit Care Med 1997;158:609–16. DOI:10.1164/ajrccm.156.2.9610079
24. 21. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma From Bronchoconstriction to Airways Inflammation and Remodelling. Am J Respir Crit Care Med. 2000; 161(5):1720-45. DOI:10.1164/ajrccm.161.5.9903102
25. Liu MC, Hubbard WC, Proud D, Stealey BA, Galli SJ, Sobotka AK, et al. Immediate and late inflammatory responses to ragweed antigen challenge of the peripheral airways in allergic asthmatics: cellular, mediator, and permeability changes. Am. Rev. Respir. Dis 1991;144(1):51–58. DOI:10.1164/ajrccm/144.1.51
26. Tonnel Ab, Joseph M, Gosset P, Fournier E, Capron A. Alveolar Macrophage And Its Participation In The Inflammatory Processes Of Allergic Asthma. Lancet 1986;22 Suppl 7:70-7.
27. Gounni AS, Lamkhioued B, Ochiai K, Tanaka Y, Delaporte E, Capron A, et al. High-affinity IgE receptor on eosinophils is involved in defence against parasites. Nature 1994;367: 183–186. DOI:10.1038/367183a0.
28. Greiff L, Erjefalt I, Svensson C, Wollmer P, Alkner U, Andersson M, et al. Plasma exudation and solute absorption across the airway mucosa. Clin. Physiol 1993;13:219–233. DOI:10.1111/j.1475-097X.1993.tb00322.x
29. Georas SN, Liu MC, Newman W, Beall LD, Stealey BA, Bochner BS. Altered adhesion molecule expression and endothelial cell activation accompany the recruitment of human granulocytes to the lung after segmental antigen challenge. Am. J. Respir. Cell Mol. Biol 1992;7(3):261–269. DOI:10.1165/ajrcmb/7.3.261.
30. Bentley AM, Meng Q, Robinson DS, Hamid Q, Kay AB, Durham SR. Increases in activated T lymphocytes, eosinophils, and cytokine mRNA expression for interleukin-5 and granulocyte/macrophage colony-stimulating factor in bronchial biopsies after allergen inhalation challenge in atopic asthmatics. Am. J. Respir. Cell Mol. Biol 1993;8(1):35–42. DOI:10.1165/ajrcmb/8.1.35
31. Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. J. Allergy Clin. Immunol 1987;79:734–740. DOI:10.1016/0091-6749(87)90204-1
32. Granger DN, Kubes P. The microcirculation and inflammation: modulation of leukocyte–endothelial cell adhesion. J. Leukoc. Biol 1994;55(5):662–675.
33. Bochner B, Schleimer R. The role of adhesion molecules in human eosinophil and basophil recruitment. J. Allergy Clin. Immunol 1994;94:427–439. DOI:10.1016/0091-6749(94)90195-3
34. Matangkasombut P, Pichavant M, DeKruyff RH, Umetsu DT. Natural killer T cells and the regulation of asthma. Mucosal Immunol. 2009;2(5):383-92. DOI:10.1038/mi.2009.96
35. 35.Ronchi F, Falcone M. Immune regulation by invariant NKT cells in autoimmunity . Front. Biosci 2008; 13:4827 – 4837. DOI:10.2741/3042
36. Rhijn IV , Koets AP, Jin IS, Piebes D, Reddington F, Besra GS, et al. The bovine CD1 family contains group 1 CD1 proteins, but no functional CD1d. J. Immunol 2006; 176(8):4888 – 4893. DOI:10.4049/jimmunol.176.8.4888
37. Kawano T, Cui J, Koezuka Y, Toura I, Kaneko Y, Motoki K, et al. CD1d-restricted and TCR-mediated activation of valpha14 NKT cells by glycosylceramides. Science 1997;278(5343):1626-9. DOI:10.1126/science.278.5343.1626
38. Thomas SY, Lilly CM, Luster AD. Invariant natural killer T cells in bronchial asthma . N. Engl. J. Med. 2006; 354(24):2613-6; author reply 2613-6. DOI:10.1056/nejmc066189

39. Umetsu DT, DeKruyff RH. Opinion—a role for natural killer T cells in asthma. Nat. Rev. Immunol 2006; 6(12):953-8. DOI:10.1038/nri1968

40. Godfrey DI, MacDonald HR, Kronenberg M, Smyth MJ, Kaer LV. NKT cells: What's in a name? Nat. Rev. Immunol 2004;4(3):231–7. DOI:10.1038/nri1309

41. Lisbonne M, Diem S, Keller AD, Lefort J, Araujo LM, Hachem P, et al. Cutting edge: Invariant V alpha 14 NKT cells are required for allergen-induced airway inflammation and hyperreactivity in an experimental asthma model. J. Immunol 2003; 171(4):1637-41. DOI:10.4049/jimmunol.171.4.1637

42. Akbari O, Stock P, Meyer E, Kronenberg M, Sidobre S, Nakayama T, et al. Essential role of NKT cells producing IL-4 and IL-13 in the development of allergen-induced airway hyperreactivity. Nat. Med 2003;9(5):582-8. DOI:10.1038/nm851

43. Brennan PJ, Brigl M, Brenner MB. Invariant natural killer T cells: an innate activation scheme linked to diverse effector functions. Nat Rev Immunol 2013;13(2):101–117. DOI:10.1038/ nri3369.

44. Hinks TS, Zhou X, Staples KJ, Dimitrov BD, Manta A, Petrossian T, et al. Innate and adaptive T cells in asthmatic patients: relationship to severity and disease mechanisms. J Allergy Clin Immunol 2015;136(2):323–333. DOI:10.1016/j. jaci.2015.01.014

45. Kim CH, Butcher EC, Johnston B. Distinct subsets of human V alpha 24-invariant NKT cells: cytokine responses and chemokine receptor expression. Trends Immunol 2002; 23:516–19. DOI:10.1016/s1471-4906(02)02323-2

46. Gumperz JE, Miyake S, Yamamura T, Brenner MB. Functionally distinct subsets of CD1drestricted natural killer T cells revealed by CD1d tetramer staining. J. Exp. Med 2002; 195:625– 36. DOI:10.1084/jem.20011786

47. Crowe NY, Coquet JM, Berzins SP, Kyparissoudis K, Keating R, Pellicci DG, et.al. Differential antitumor immunity mediated by NKT cell subsets in vivo. J Exp Med. 2005;202(9):1279-1288. DOI:10.1084/jem.20050953

48. Umetsu DT, DeKruyff RH. Immune dysregulation in asthma. Curr. Opin. Immunol 2006; 18:727–32. DOI:10.1016/j.coi.2006.09.007

49. Cui J, Shin T, Kawano T, Sato H, Kondo E, Toura I, et al. Requirement for V14 NKT cells in IL-12-mediated rejection of tumors. Science 1997; 278:1623–1626. DOI:10.1126/science.278.5343.1623

50. Michel M., Keller AC, Paget C, Fujio M, Trottein F, Savage PB, et al. Identification of an IL-17-producing NK1.1(neg) iNKT cell population involved in airway neutrophilia. J Exp Med. 2007;204(5):995-1001. DOI:10.1084/jem.20061551

51. Liu Y, Goff RD, Zhou D, Mattner J, Sullivan BA, Khurana A, et al. A modified alpha-galactosyl ceramide for staining and stimulating Natural Killer T cells. J. Immunol. Methods 2006; 312:34–39. DOI:10.1016/j.jim.2006.02.009

52. Kim CH, Butcher EC, Johnston B. Distinct subsets of human Vα24-invariant NKT cells: cytokine responses and chemokine receptor expression. Trends Immunol. 2002;23(11):516-9. DOI:10.1016/s1471-4906(02)02323-2

53. Tumes D, Hirahara K, Papadopoulos M, Shinoda K, Onodera A, Kumagai J, et al. Ezh2 controls development of natural killer T cells, which cause spontaneous asthma-like pathology. J Allergy Clin Immunol 2019;144(2):549-560.e510. DOI:10.1016/j. jaci.2019.02.024.

54. Lee PT, Benlagha K, Teyton L, Bendelac A. Distinct functional lineages of human Vα24 natural killer T cells. J. Exp. Med.2002; 195(5):637-41. DOI:10.1084/jem.20011908

55. Takahashi T, Chiba S, Nieda M, Azuma T, Ishihara S, Shibata Y, Takeo Juji et al. Analysis of human Vα24+CD8+ NKT cells activated by α-glycosylceramide-pulsed monocyte-derived dendritic cells.J.Immunol.2002;168(7):3140-4.

56. Bendelac A, Lantz O, Quimby ME, Yewdell JW, Bennink JR, Brutkiewicz RR. CD1 recognition by mouse NK1 T lymphocytes. Science 1995; 268(5212):863-5. DOI:10.1126/science.7538697

57. Exley M, Garcia J, Balk SP, Porcelli S. Requirements for CD1d recognition by human invariant V 24CD4CD8 T cells. J. Exp. Med. 1997;186:109–120. DOI:10.1084/jem.186.1.109

58. Chandra S, Zhao M, Budelsky A, de Mingo PA, Day J, Fu Z, et al. A new mouse strain for the analysis of invariant NKT cell function. Nat Immunol 2015;16(8):799–800. DOI:10.1038/ni.3203.

59. Pietro CD , FalconeM. The role of invariant NKT cells in organ-specific autoimmunity. Front Biosci (Landmark Ed). 2014;19:1240-50. DOI:10.2741/4279

60. Coquet JM, Chakravarti S, Kyparissoudis K, McNab FW, Pitt LA, McKenzie BS, et al. Diverse cytokine production by NKT cell subsets and identification of an IL-17-producing CD4- NK1.1.- NKT cell population. Proc Natl Acad Sci U S A 2008;105(32):11287-92. DOI:10.1073/pnas.0801631105

61. ZhouD, Mattner J, Cantu C, Schrantz N, Yin N, Gao Y, et al. Lysosomal glycosphingolipid recognition by NKT cells . Science 2004; 306(5702):1786-9. DOI:10.1126/science.1103440

62. Rauch J, Gumperz J, Robinson C, Sköld M, Roy C, Young DC, et al. Structural features of the acyl chain determine self phospholipid antigen recognition by a CD1d-restricted invariant NKT (iNKT) cell . J. Biol. Chem. 2003; 278(48):47508-15. DOI:10.1074/jbc.m308089200

63. Wu DY, Segal NH, Sidobre S, Kronenberg M, Chapman PB. Cross-presentation of disialoganglioside GD3 to natural killer T cells. J. Exp. Med. 2003; 198(1):173-81. DOI:10.1084/jem.20030446

64. Meyer EH, Goya S, Akbari O, Berry GJ, Savage PB, Kronenberg M,et al. Glycolipid activation of invariant T cell receptor+ NK T cells is sufficient to induce airway hyper reactivity independent of conventional CD4+ T cells . Proc. Natl. Acad. Sci. USA 2006; 103(8):2782-7. DOI:10.1073/pnas.0510282103

65. Kinjo Y, Wu D, Kim G, Xing GW, Poles MA, Ho DD, et al. Recognition of bacterial glycosphingolipids by natural killer T cells . Nature 2005; 434(7032):520-5. DOI:10.1038/nature03407

66. Mattner J, Debord KL, Ismail N, Goff RD, Cantu C 3rd, Zhou D, et al. Exogenous and endogenous glycolipid antigens activate NKT cells during microbial infections. Nature 2005; 434(7032):525-9. DOI:10.1038/nature03408

67. Tsuji, M. Glycolipids and phospholipids as natural CD1d-binding NKT cell ligands. Cell. Mol. Life Sci. 2006; 63(16):1889-98. DOI:10.1007/s00018-006-6073-z

68. Kinjo Y, Tupin E, Wu D, Fujio M, Navarro RG, Benhnia MI, et al. Natural killer T cells recognize diacylglycerol antigens from pathogenic bacteria. Nat. Immunol. 2006; 7(9):978-86. DOI:10.1038/ni1380

69. Pniewska E, Pawliczak R, "The Involvement of Phospholipases A2 in Asthma and Chronic Obstructive Pulmonary Disease", Mediators of Inflammation, vol. 2013. DOI:10.1155/2013/793505.

70. Porubsky S, Speak AO, Luckow B, Cerundolo V, Platt FM, Gröne HJ. Normal development and function of invariant natural killer T cells in mice with isoglobotrihexosylceramide (iGb3) deficiency. Proc Natl Acad Sci U S A 2007; 104(14):5977-82. DOI:10.1073/pnas.0611139104

71. Moody D, Porcelli S. Intracellular pathways of CD1 antigen presentation. Nat Rev Immunol 2003; 3(1):11-22. DOI:10.1038/nri979

72. Nagarajan N, Kronenberg M. Invariant NKT cells amplify the innate immune response to lipopolysaccharide. J Immunol. 2007; 178(5):2706-13. DOI:10.4049/jimmunol.178.5.2706

73. Brigl M, Bry L, Kent SC, Gumperz JE, Brenner MB. Mechanism of CD1d-restricted natural killer T cell activation du. ring microbial infection. Nat. Immunol. 2003; 4(12):1230-7. DOI:10.1038/ni1002

74. Zhang Y, Springfield R, Chen S, Li X, Feng X, Moshirian R, et al. α-GalCer and iNKT Cell-Based Cancer Immunotherapy: Realizing the Therapeutic Potentials. Front Immunol, 2019; 10:1126. DOI:10.3389/fimmu.2019.01126

75. Taniguchi M, Harada M, Kojo S, Nakayama T, Wakao H. The regulatory role of V alpha14 NKT cells in innate and acquired immune

response. Annu. Rev. Immunol. 2003; 21:483-513. DOI:10.1146/annurev.immunol.21.120601.141057

76. Sullivan BA, Kronenberg M. Activation or anergy: NKT cells are stunned by alpha-galactosylceramide. J Clin Invest 2005; 115(9):2328-9. DOI:10.1172/jci26297

77. Kitamura H, Iwakabe K, Yahata T, Nishimura S, Ohta A, Ohmi Y, et al. The natural killer T (NKT) cell ligand galactosylceramide demonstrates its immunopotentiating effect by inducing interleukin (IL)-12 production by dendritic cells and IL-12 receptor expression on NKT cells. J. Exp. Med. 1999; 189(7):1121-8. DOI:10.1084/jem.189.7.1121

78. Cohen NR, Garg S, Brenner MB. Antigen presentation by CD1 lipids, T cells, and NKT cells in microbial immunity. Adv Immunol 2009;102:1-94. DOI:10.1016/s0065-2776(09)01201-2

79. Spinozzi F, Porcelli SA. Recognition of lipids from pollens by CD1-restricted T cells. Immunol. Allergy Clin. North Am.2007; 27(1):79-92. DOI:10.1016/j.iac.2006.11.004

80. Pham-Thi N, Blic J, Bourgeois M, Dy M, Scheinmann P, Leite-de-Moraes M. Enhanced frequency of immunoregulatory invariant natural killer T cells in the airways of children with asthma. J. Allergy Clin. Immunol. 2006;117(1):217-8. DOI:10.1016/j.jaci.2005.09.052

81. Hamzaoui A, Cheik Rouhou S, Graïri H, Abid H, Ammar J, Chelbi H, Hamzaoui K. NKT cells in the induced sputum of severe asthmatics. Mediators Inflamm. 2006; 2006(2):71214. DOI:10.1155/MI/2006/71214

82. Sen Y, Yongyi B, Yuling H, Luokun X, Li H, Jie X,et al. Vα24-invariant NKT cells from patients with allergic asthma express CCR9 at high frequency and induce Th2 bias of CD3+ T cells upon CD226 engagement. J. Immunol. 2005; 175 (8) 4914-4926. DOI:10.4049/jimmunol.175.8.4914

83. Kim EY, Battaile JT, Patel AC, You Y, Agapov E, Grayson MH, et al. Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease . Nat. Med. 2008; 14(6):633-40. DOI:10.1038/nm1770

84. Matangkasombut P, Marigowda G, Ervine A, Idris L, Pichavant M, Kim HY, et al. Natural killer T cells in the lungs of patients with asthma . J. Allergy Clin. Immunol. 2009; 123(5):1181-5. DOI:10.1016/j.jaci.2009.02.013

85. Mutalithas K, Croudace J, Guillen C, Siddiqui S, Thickett D, Wardlaw A, et al. Bronchoalveolar lavage invariant natural killer T cells are not increased in asthma . J. Allergy Clin. Immunol. 2007; 119(5):1274-6. DOI:10.1016/j.jaci.2007.02.021

86. Vijayanand P, Seumois G, Pickard C, Powell RM, Angco G, Sammut D, et al. Invariant natural killer T cells in asthma and chronic obstructive pulmonary disease . N. Engl. J. Med. 2007; 356(14):1410-22. DOI:10.1056/NEJMoa064691

87. Pichavant M, Goya S, Meyer EH, Johnston RA, Kim HY, Matangkasombut P, et al. Ozone exposure in a mouse model induces airway hyperreactivity that requires the presence of natural killer T cells and IL-17. J Exp Med 2008; 205(2):385-93. DOI:10.1084/jem.20071507

88. Akbari O, Faul JL, Hoyte EG, Berry GJ, Wahlstrom J, Kronenberg M, et al. CD4+ invariant T-cell-receptor1 natural killer T cells in bronchial asthma. N Engl J Med 2006; 354(11):1117-29. DOI:10.1056/nejmoa053614

89. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol 2007; 119(2):405-13. DOI:10.1016/j.jaci.2006.11.639

90. Gern JE, Busse WW . The role of viral infections in the natural history of asthma . J. Allergy Clin. Immunol. 2000;106(2):201-12. DOI:10.1067/mai.2000.108604

91. Sigurs N , Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13 . Am. J. Respir. Crit. Care Med. 2005;171(2):137-41. DOI:10.1164/rccm.200406-730oc

92. Hamelin ME, Prince GA, Gomez AM, Kinkead R, Boivin G. Human metapneumovirus infection induces long-term pulmonary inflammation associated with airway obstruction and hyperresponsiveness in mice . J. Infect. Dis. 2006; 193(12):1634-42. DOI:10.1086/504262

93. Yoshimoto T, Min B, Sugimoto T, Hayashi N, Shikawa Y, Sasaki Y, et al. Nonredundant roles for CD1d-restricted natural killer T cells and conventional CD4+ T cells in the induction of immunoglobulin E antibodies in response to interleukin 18 treatment of mice. J Exp Med. 2003; 197(8):997-1005. DOI:10.1084/jem.20021701

94. Bendelac A, Rivera MN, Park SH, Roark JH. Mouse CD1-specific NK1 T cells: development, specificity, and function. Annu. Rev. Immunol. 1997; 15:535–562. DOI:10.1146/annurev.immunol.15.1.535

95. Takeda K, Seki S, Ogasawara K, Anzai R, Hashimoto W, Sugiura K, et al. Cytotoxic NK1.1 Ag+ alpha beta T cells with intermediate TCR induced in the liver of mice by IL-12. J. Immunol 1995; 154(9):4333-40.

96. Hachem P , Lisbonne M, Michel M, Diem S, Roongapinun S, Lefort J, et al. Alpha-galactosylceramide-induced iNKT cells suppress experimental allergic asthma in sensitized mice: role of IFNgamma . Eur. J. Immunol. 2005;35(10):2793-802. DOI:10.1002/eji.200535268

97. Matsuda H, Suda T, Sato J, Nagata T, Koide Y, Chida K, et al. α-Galactosylceramide, a ligand of natural killer T cells, inhibits allergic airway inflammation . Am. J. Respir. Cell Mol. Biol. 2005;33(1):22-31. DOI:10.1165/rcmb.2004-0010oc

98. Kawano T, Cui J, Koezuka Y, Toura I, Kaneko Y, Sato H, E Kondo, et al. Natural killer-like nonspecifi c tumor cell lysis mediated by specifi c ligand-activated Valpha14 NKT cells . Proc. Natl. Acad. Sci. USA 1998;95(10):5690-3. DOI:10.1073/pnas.95.10.5690

99. Nagaraj S, Ziske C, Strehl J, Messmer D, Sauerbruch T, Schmidt-Wolf I G. Dendritic cells pulsed with alpha-galactosylceramide induce anti-tumor immunity against pancreatic cancer in vivo . Int. Immunol. 2006; 18(8):1279-83. DOI:10.1093/intimm/dxl059

100. Fujii S, Shimizu K, Kronenberg M, Steinman RM. Prolonged IFN-gamma-producing NKT response induced with α-galactosylceramide-loaded DCs . Nat. Immunol. 2002;3(9):867-74. DOI:10.1038/ni827

101. Ishikawa A, Motohashi S, Ishikawa E, Fuchida H, Higashino K, Otsuji M, et al. A phase I study of alpha-galactosylceramide (KRN7000)-pulsed dendritic cells in patients with advanced and recurrent non-small cell lung cancer . Clin. Cancer Res. 2005; 11(5):1910-7. DOI:10.1158/1078-0432.ccr-04-1453

102. Uchida T, Horiguchi S, Tanaka Y, Yamamoto H, Kunii N, Motohashi S, et al. Phase I study of alpha-galactosylceramide-pulsed antigen presenting cells administration to the nasal submucosa in unresectable or recurrent head and neck cancer . Cancer Immunol. Immunother. 2008; 57(3):337-45. DOI:10.1007/s00262-007-0373-5

103. Fujii SI, Shimizu K, Hemmi H, Fukui M, Bonito AJ, Chen G, et al. Glycolipid alpha-C-galactosylceramide is a distinct inducer of dendritic cell function during innate and adaptive immune responses of mice . Proc. Natl. Acad. Sci. USA 2006; 103(30):11252-7. DOI:10.1073/pnas.0604812103

104. Oki S, Chiba A, Yamamura T, Miyake S . The clinical implication and molecular mechanism of preferential IL-4 production by modifi ed glycolipid-stimulated NKT cells. J. Clin. Invest. 2004; 113(11):1631-40. DOI:10.1172/jci20862

105. Bryan SA, O'Connor BJ, Matti S, Leckie MJ, Kanabar V, Khan J, et al. Effects of recombinant human interleukin-12 on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 2000; 356(9248):2149-53. DOI:10.1016/s0140-6736(00)03497-8

106. Morishima Y, Ishii Y, Kimura T, Shibuya A, Shibuya K, Hegab A, et al. Suppression of eosinophilic airway inflammation by treatment with a-galactosylceramide. Eur J Immunol. 2005; 35(10):2803-14. DOI:10.1002/eji.200525994

107. Oki S, Miyake S. Invariant Natural Killer T (iNKT) Cells in Asthma: A Novel Insight into the Pathogenesis of Asthma and the Therapeutic

Implication of Glycolipid Ligands for Allergic Diseases. Allergol Int. 2007; 56(1):7-14. DOI:10.2332/allergolint.r-06-137

108. Kronenberg M. Toward an understanding of NKT cell biology: progress and paradoxes. Annu. Rev. Immunol. 2005;23:877-900. DOI:10.1146/annurev.immunol.23.021704.115742

109. Heller F, Fuss IJ, Nieuwenhuis EE, Blumberg RS, Strober W. Oxazolone colitis, a Th2 colitis model resembling ulcerative colitis, is mediated by IL-13- producing NK-T cells. Immunity 2002;17(5):629-38. DOI:10.1016/s1074-7613(02)00453-3

110. Saubermann LJ, Beck P, Jong YP, Pitman RS, Ryan MS, Kim HS, et al. Activation of natural killer T cells by alphagalactosylceramide in the presence of CD1d provides protection against colitis in mice. Gastroenterology 2000; 119(1):119-28. DOI:10.1053/gast.2000.9114

111. Godó M, Sessler T, Hamar P. Role of Invariant Natural Killer T (iNKT) Cells in Systemic Lupus Erythematosus. Curr Med Chem. 2008; 15(18):1778-87. DOI:10.2174/092986708785132988

112. Kojo S, Adachi Y, Keino H, Tanaguchi M, Sumida T. Dysfunction of T cell receptor AV24AJ18+, BV11+ double-negative regulatory natural killer T cells in autoimmune diseases. Arthritis Rheum 2001; 44(5):1127-38. DOI:10.1002/1529-0131(200105)44:5<1127::AID-ANR194>3.0.CO;2-W.

113. Van der Vliet HJ, Blomberg BM, Nishi N, Reijm M, Voskuyl AE, Bodegraven AA et al. Circulating V(α24+) Vβ11+ NKT cell numbers are decreased in a wide variety of diseases that are characterized by auto reactive tissue damage. Clin. Immunol., 2001;100(2):144-8. DOI:10.1006/clim.2001.5060

114. Mitsuo A, Morimoto S, Nakiri Y, Suzuki J, Kaneko H, Tokano Y, et al. Decreased CD161+CD8+ T cells in the peripheral blood of patients suffering from rheumatic diseases. Rheumatology (Oxford). 2006; 45(12):1477-84.DOI:10.1093/rheumatology/kel119.