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New Insights into Asthma Inflammation: Focus on iNKT, MAIT, and $\gamma\delta$ T Cells

Jefferson Russo Victor, Guillaume Lezmi, Maria Leite-De-Moraes

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1 **New insights into asthma inflammation: focus on iNKT, MAIT and $\gamma\delta$ T cells**

2
3 **Short title: Innate-like T cells and asthma**

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5 Jefferson Russo Victor^{a, b} PhD, Guillaume Lezmi^{c, d} MD, PhD and
6 Maria Leite-de-Moraes^c PhD
7

8 **Affiliations:**

9 ^a-Laboratory of Medical Investigation LIM 56, Division of Clinical Dermatology, Medical
10 School, University of Sao Paulo, Sao Paulo, Brazil

11 ^b-Division of Environmental Health, FMU, Laureate International Universities, Sao Paulo,
12 Brazil

13 ^c-Laboratory of Immunoregulation and Immunopathology, INEM (Institut Necker-
14 Enfants Malades), CNRS UMR8253, INSERM UMR1151, and Université Paris Descartes,
15 Paris, France

16 ^d AP-HP, Hôpital Necker-Enfants Malades, Service de Pneumologie et d'Allergologie
17 Pédiatriques, Paris, France;
18
19

20 **Corresponding author:**

21 Maria Leite-de-Moraes, Laboratory of Immunoregulation and Immunopathology,
22 Institut Necker-Enfants Malades, CNRS UMR 8253, INSERM UMR 1151 and Université
23 Paris Descartes Sorbonne Paris Cité, 75015, Paris, France.

24 E-mail: maria.leite-de-moraes@parisdecartes.fr
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30 **Abstract**

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32 Asthma is a chronic immunological disease affecting all age groups, but often starting in
33 childhood. Although it has long been ascribed to a single pathology, recent studies have
34 highlighted its heterogeneity due to the potential involvement of various pathogenic
35 mechanisms. Here, we present our current understanding of the role of innate-like T
36 (ILT) cells in asthma pathogenesis. These cells constitute a specific family mainly
37 comprising $\gamma\delta$ T, invariant Natural Killer (iNKT) and Mucosal-Associated Invariant (MAIT)
38 T cells. They all share the ability to massively secrete a wide range of cytokines in a T cell
39 receptor (TCR)-dependent or -independent manner. ILT cells are prevalent in mucosal
40 tissues, including airways, where their innate and adaptive immune functions consist
41 primarily in protecting tissue integrity. However, ILT cells may also have detrimental
42 effects leading to asthma symptoms. The immune mechanisms through which this
43 pathogenic effect occurs will be discussed in this overview.

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45

46 **Key Words:** Asthma, $\gamma\delta$ T cells, iNKT cells, MAIT cells, children, patients, CD1d, MR1

47

48 INTRODUCTION

49

50 Asthma is now considered an umbrella term encompassing various conditions
51 characterized by wheeze, cough, shortness of breath, chest tightness and variable
52 degrees of airflow limitation. These symptoms are associated with different patterns of
53 inflammation [1-4]. For the sake of clarity, an allergic and a non-allergic type of asthma
54 are commonly distinguished. In the first case, inflammation is primarily caused by type
55 2 immune responses mediated through the Th2 cytokines IL-4, IL-5, and IL-13 and
56 associated with increased Th2 cells and eosinophils in the airways [5]. By contrast, non-
57 allergic asthma is mainly triggered by an inflammatory response to viral infections with
58 a major neutrophilic component [6]. There is mounting evidence that neutrophilic forms
59 of murine and human asthma are associated with IL-17A (hereafter referred to as IL-17)
60 [7-9]. This cytokine is involved in the induction and persistence of neutrophilic
61 inflammation[10] and can contribute to airway smooth muscle remodeling in
62 association with TGF- β [11].

63

64 Asthma can adopt diverse phenotypes associated with a number of endotypes[12,2,4].
65 Previous reports have implicated Th2 and Th17 cells in mechanisms favoring asthmatic
66 immune endotypes [13]. However, these two populations alone cannot account for the
67 great diversity of symptoms, mainly because other cell types present in the airways can
68 also contribute to the production of Th2- and Th17-type cytokines. The best potential
69 candidates for this purpose are “unconventional” T cells also currently named “Innate-
70 Like T (ILT) lymphocytes” that recognize non-peptide antigens presented by specialized
71 MHC class I-like molecules [14-16].

72

73 Innate-like T (ILT) cells are unique unconventional T lymphocytes sharing features of
74 both innate and adaptive immunity. This population recognizes non-peptide antigens
75 presented by specialized MHC class I-like molecules. It includes invariant natural killer T
76 (iNKT), mucosal-associated invariant T (MAIT) and gamma-delta T ($\gamma\delta$ T) cells, all
77 characterized by a conserved and restricted T cell receptor (TCR) [14]. iNKT cells express
78 an antigen-specific semi-invariant TCR, V α 14-J α 18 (TRAV11-TRAJ18) and V α 24-J α 18
79 (TRAV10-TRAJ18) in mice and humans, respectively [17,16,14]. Similarly, MAIT cells
80 display V α 19-J α 33 (TRAV1-2-TRAJ33) in mice and V α 7.2-J α 33 (TRAV1-2-TRAJ33) in
81 humans [18-20]. The $\gamma\delta$ T cell population is not homogeneous, even though the V δ 2⁺
82 subset is predominant in human peripheral blood [21]. These cells can produce large
83 amounts of cytokines shortly after stimulation and play an important role in first-line
84 defense against microbial infections [22]. $\gamma\delta$ T, iNKT and MAIT cells are currently divided
85 into distinct subsets according to their cytokine profile (Table 1). They have all been
86 associated with a growing number of inflammatory diseases including asthma.

87

88 The next paragraphs will be focused on the development and functional properties of
89 ILT cells and their impact on the immune mechanisms leading to asthma.

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91

92 **INNATE-LIKE T CELLS**

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94 $\gamma\delta$ T cells

95

96 $\gamma\delta$ T cells constitute a distinct population of T lymphocytes in mice and humans, which
97 upon activation can promptly generate a number of cytokines and chemokines with
98 modulatory activities in innate and adaptive immunity [23-25]. Compared to other
99 unconventional T cells, they can readily perform effector functions in response to tissue
100 stress [22,23]. Furthermore, in epithelial tissues including lungs, $\gamma\delta$ T cells make up the
101 major resident T cell population and their functions, although still controversial, can be
102 related to tissue integrity and maintenance of host homeostasis [22].

103

104 $\gamma\delta$ T cells can be classified by the expression of their $\gamma\delta$ TCR chains. In humans, the
105 differential expression of δ (δ 1-3) and γ genes (γ 2-5, γ 8, γ 9, and γ 11) has been used to
106 this end, whereas in mice $\gamma\delta$ T cell subsets are defined by the expression of distinct γ
107 chains[26] (Table 1). Contrasting with conventional T cells, which recognize peptides
108 presented by MHC molecules, $\gamma\delta$ T cells can distinguish uncommon antigens, such as
109 stress molecules (MICA and MICB), heat-shock proteins or synthetic phosphoantigens
110 (pAg) [27,28]. It is clear by now that $\gamma\delta$ T cells do not interact directly with pAg but
111 require the presence of butyrophilin BTN3A as an intermediate [29]. This indicates the
112 usage of a fundamentally different mechanism of antigen detection whose molecular
113 basis remains to be elucidated.

114

115 Although $\gamma\delta$ T cells can produce several cytokines, two major murine subsets defined by
116 their capacity to produce IL-17 or IFN- γ have been described in recent years [30] (Table
117 1). Compared to conventional TCR $\alpha\beta$ ⁺ CD4 and CD8 T cells, $\gamma\delta$ T cells are more prompt in
118 producing significant amounts of IFN- γ [31], thus providing an early source of this factor
119 that could be protective in tumor immunity [32-34]. However, in some cases, such as
120 fulminant viral hepatitis in a murine model, the production of IFN- γ by $\gamma\delta$ T cells can
121 become deleterious [35]. $\gamma\delta$ T cells that produce substantial amounts of IL-17 are
122 frequently termed $\gamma\delta$ T17 and display a CD27⁻NK1.1⁺CCR6⁺ phenotype [30,36]. They can
123 take part in tissue surveillance and repair and mediate effective immune responses
124 against bacterial and fungal infections [37-40]. Conversely, they are potential promoters
125 of inflammation in type 1 autoimmune diseases, such as arthritis or colitis [41,42].
126 According to recent reports, $\gamma\delta$ T17 cells could also promote tumor progression in
127 experimental models [43].

$\gamma\delta$ T cells in experimental models of asthma

The role of $\gamma\delta$ T cells in lung inflammation has been debated in the literature for more than 30 years. In 1998, one of the first publications supporting the requirement of $\gamma\delta$ T cells for promoting IgE production and Th2 airway inflammation in an IL-4-dependent manner came from experiments with $\gamma\delta$ T cell-deficient mice, which failed to develop the pathology [44]. One year later, another team reported that airway reactivity was increased in the absence of $\gamma\delta$ T cells, suggesting a protective role of these cells [45]. These controversial data could be explained by the distinct genetic backgrounds, namely BALB/c [44] and C57BL/6 [45] in these $\gamma\delta$ T cell-deficient mice. Indeed, these strains respond differently in the asthma protocol since BALB/c display more severe AHR than C57BL/6 mice, while airway eosinophilia is more pronounced in the C57BL/6 strain [46].

Further studies using blocking anti- $\gamma\delta$ TCR mAb administered during the resolution phase of OVA-induced allergic inflammation, provided evidence for an exacerbation of lung injury [47]. However, it turned out that GL3 mAb used in this study did not deplete $\gamma\delta$ T cells in vivo, but induced the downmodulation of their $\gamma\delta$ TCR [48].

The complexity of $\gamma\delta$ T cell regulation of asthmatic inflammation may be explained by the intervention of distinct subsets. In this line of evidence, it has been shown that the effect of $\gamma\delta$ T cells on IgE production in an OVA-induced allergic asthma model changed according to the phenotype of the $\gamma\delta$ T cell population involved [49]. Indeed V γ 1 $\gamma\delta$ T cells promoted an enhanced IgE response, while their V γ 4 counterpart suppressed this activity [50]. These non-overlapping functions of V γ 4 and V γ 1 $\gamma\delta$ T cell subsets were also observed in terms of AHR [51]. Consistent with this observation, it has been shown more recently that IL-4-producing V γ 1⁺ $\gamma\delta$ T cells promoted airway eosinophilia and AHR in experimental allergic asthma induced by the dust mite *Blomia tropicalis* [52].

$\gamma\delta$ T cells also produce IFN- γ and IL-17. It has been proposed that the IFN- γ thus generated might favor allergic inhibition by reducing IgE production [53], while IL-17-producing $\gamma\delta$ T cells could ameliorate AHR and accelerate the resolution of eosinophilic airway inflammation [47]. Furthermore, a relationship between reduced thymic maturation of IL-17-producing $\gamma\delta$ T cells and decreased lung inflammation has been described in a murine protocol of OVA-induced allergy [54].

$\gamma\delta$ T cells in asthmatic patients

In humans, peripheral $\gamma\delta$ T cells were reported to be decreased in difficult-to-control asthmatic patients compared to controls [55]. Further, a higher frequency of IL-4-producing versus a lower incidence of IFN- γ -producing $\gamma\delta$ T cells was described in patients with allergic asthma, as compared with healthy controls [56].

169

170 In another study $\gamma\delta$ T cells were found to be more frequent at the site of inflammation
171 in bronchoalveolar lavage fluid (BALF) of untreated asthmatic patients, as compared
172 with control volunteers [57]. Among the scarce data available on this issue, according to
173 another group, $\gamma\delta$ T cells occurred at similar levels in BALF or lung biopsies, whether the
174 donors were suffering from asthma or not [58], while another research confirmed that
175 the frequency of $\gamma\delta$ T cells in BALF from stable asthmatic subjects was not significantly
176 different from controls [59]. However, after *in vivo* allergen challenge, BALF $\gamma\delta$ T cells
177 increased their capacity to produce Th2-type cytokines, including IL-5 and IL-13, and
178 reduced their secretion of Th1-type cytokines, such as IFN- γ [59]. These findings suggest
179 that the $\gamma\delta$ T cytokine profile is flexible in BALF, ready to be skewed toward the Th2-type
180 in asthmatic patients [59].

181

182 Overall, the studies cited here reveal that $\gamma\delta$ T cells exert a highly complex control in lung
183 inflammation, possibly because of the contribution of various subsets whose
184 composition could differ according to the clinical status of asthmatic patients (Fig.1).

185

186 **invariant Natural Killer T cells**

187

188 Differentiation and maturation of iNKT cells occur in the thymus, where they appear
189 slightly later than MHC-restricted conventional T cells [60-63]. Thymic iNKT cell
190 differentiation requires a particular rearrangement between V α and J α gene segments
191 in the TCR α locus. This is believed to be a random process that occurs at very low
192 frequency leading to the characteristic iNKT cell invariant TCR α chain: V α 14J α 18
193 (TRAV11-TRAJ18) in mice and V α 24J α 18 (TRAV10-TRAJ18) in humans[64,65]. The TCR α
194 chain associates with a limited set of TCR β chains [66-68] (Table 1).

195

196 Once they have completed a tightly controlled thymic differentiation pathway, iNKT cells
197 migrate to peripheral organs as CD4⁺CD8⁻ and double-negative (CD4⁻CD8⁻) cells. In
198 humans, the CD4⁻CD8⁺ subset does likewise occur [69]. iNKT cells are mostly resident in
199 tissues, where they are believed to act as sentinels of tissue integrity by “patrolling” to
200 identify threats to the body [70]. They are rare in most peripheral sites (0.1-1% among
201 T lymphocytes) but numerous in the liver [16]. The invariant TCR α chains in mice and
202 humans are conserved, enabling iNKT cells to recognize the same glycolipids in both
203 species, as is the case for the glycolipid α -galactosylceramide (α -GalCer) [71,72].

204

205 iNKT cells are restricted by lipids and glycolipids loaded onto CD1d molecules present
206 on the surface of APCs [73]. Moreover, their cytokine production along with their
207 cognate interactions, enable them to modulate the activities of different immune cells
208 playing a pivotal role in the orchestration of the immune response [74].

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iNKT cells in experimental models of asthma

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In the nineties, several studies demonstrated that iNKT cells promptly and massively secreted IL-4 [75-78]. Consequently, it was proposed that their major role was to promote Th2 differentiation via this cytokine [79]. This has led a number of groups to test IL-4-producing iNKT cells in specific experimental models requiring Th2 cells, including allergic asthma models.

Initial studies using iNKT cell-deficient mice, namely β_2 microglobulin (β_2m)^{-/-} and CD1d^{-/-} strains, revealed no major differences in the severity of allergic airway inflammation [80-82]. More recently, other investigators using these same mutants concluded that NKT cells were dispensable for T cell-dependent allergic airway inflammation [83,84]. However, it turned out that both β_2m ^{-/-} and CD1d^{-/-} mice are also deficient for other T cell subsets (CD8⁺ T and CD1d-dependent T lymphocytes, respectively), thus masking a potential effect of iNKT cells. To solve this issue, two groups used more specific iNKT cell-deficient ($J\alpha 18$ ^{-/-}) mice, for which they reported attenuated asthma symptoms, including AHR, airway eosinophilia, Th2 inflammation and OVA-specific anti-IgE production relative to wild-type controls [85,86]. The adoptive transfer of wild type iNKT cells was sufficient to restore asthma severity in $J\alpha 18$ ^{-/-} mice. Of note, adoptive transfers of iNKT cells from IL-4^{-/-} or IL-13^{-/-} mice were much less effective and iNKT cells from double knockout IL-4^{-/-}IL-13^{-/-} mice had no effect at all [86]. This finding demonstrated that iNKT cells enhanced allergic asthma symptoms through the production of IL-4 and IL-13 [85,86].

Recently, a new mouse strain with the deletion of *Traja18* was created on a C57BL/6 genetic background [90]. These *Traja18*-deficient mice lack iNKT cells but have a normal $J\alpha$ -region repertoire. They display significantly less eosinophils and AHR in an airway hyper-reactivity model [90], thereby confirming the implication of iNKT cells in asthmatic airway inflammation. In further support of this conclusion, *Ezh2* (Enhancer of zeste homolog 2)-deficient mice spontaneously developed an asthma-like disease [91] associated with abnormally high iNKT cell counts, increased IL-4 and IL-13 production, AHR, lung inflammation and IgE levels, all consistent with a contribution of iNKT cells to asthma pathogenesis [91].

Even though iNKT cells do not recognize OVA as an antigen, their ability to promote lung inflammation is TCR-dependent since the injection of blocking anti-CD1d antibodies reduced the effect, indicating that endogenous lipidic antigens stimulated the iNKT cells [85]. Indeed, in this setting we cannot exclude that commensal microbial antigens present in the lung could take part in the activation of iNKT cells. In the same line of evidence, an elegant study by Blumberg's team showed that iNKT cells accumulated in the lung and in the colonic lamina propria in germ-free (GF) mice, rendering these

251 animals more susceptible to OVA-induced asthma and oxazolone-induced colitis [87].
252 The colonization of neonatal GF mice with a normal flora or *Bacteroides fragilis*
253 decreased the number of iNKT cells and protected the mice against these diseases,
254 clearly establishing a link between iNKT cells and the microbiota [87,88]. Knowing that
255 a bacterial community is present in the airways and that this microbiota could be altered
256 in the case of asthma [89], we postulate that some bacterial antigens might activate
257 iNKT cells in the lung, thus promoting inflammation. Further studies are required to test
258 this hypothesis.

259

260 For asthma that is not associated with pro-Th2 allergic immune responses, it has been
261 reported that i.n. administration of α -GalCer activates IL-17-secreting iNKT cells, which,
262 in turn, promote airway neutrophilia [92]. IL-17-secreting iNKT cells are also required for
263 the pathogenic mechanisms leading to AHR after exposure to ozone, a major component
264 of air pollution [93]. Hence, iNKT cells may promote asthma inflammation in different
265 ways, depending on their cytokine profile (Fig. 2).

266

267 **iNKT cells in asthmatic patients**

268

269 Analysis of the incidence of iNKT cells in the peripheral blood of adult asthmatic patients,
270 revealed no significant differences when compared to control subjects [94]. Further
271 studies suggested however that IL-4-producing iNKT cells were more frequent in these
272 cases and that they were associated with lung functions [95]. In children with asthma,
273 the percentage of peripheral blood iNKT cells did not differ significantly between
274 asthmatic children classified as exacerbators (1 or more severe exacerbations in the last
275 12 months) and non-exacerbators [96]. Similarly, no relationship was observed between
276 the frequency of circulating iNKT cells and IL-4- or IFN- γ -producing iNKT cells in one-
277 year-old children and asthma-related clinical outcomes at the age of seven years [97].

278

279 In addition to peripheral blood analysis, a number of studies have evaluated iNKT cells
280 in BALF or bronchial biopsies of asthmatic patients. The first data in adult asthmatic
281 patients revealed that about 60% of the pulmonary CD4⁺CD3⁺ T cells in the group with
282 moderate-to-severe persistent asthma were iNKT cells [98]. These results were not
283 reproduced by others [99,100], who found that up to 2% of the T cells recovered from
284 airway biopsies, BALF and sputum induction from subjects with mild or moderately
285 severe asthma were iNKT cells. Umetsu and collaborators reported later that only a
286 small fraction of T cells in the lung of adult asthmatic patients were iNKT cells [101],
287 which accounted for less than 1% of T cells in BALF from children with severe asthma
288 [102]. The discrepancies between these studies could be explained by the limited
289 number of samples, the heterogeneity of the cohorts, or by non-specific staining of cells
290 in BALF, as suggested by the study of Thomas *et al* [100].

291

292 Taken together, these findings show that large adult and children cohorts composed of
293 asthmatic patients with well-defined symptoms and grades of severity (controlled, non-
294 controlled and severe asthma) associated with relevant controls are required to
295 definitely assess whether iNKT cells are involved in asthma pathology or not.

296

297 Mucosal-Associated Invariant T cells

298

299 MAIT cells are restricted by the MHC class I-related molecule MR1 and recognize
300 microbial-derived vitamin B2 (riboflavin) metabolites [103] (Table 1). Riboflavin
301 metabolites are not present in mammalian cells but occur in several bacteria and yeast
302 [104], which suggests that MAIT cells can sense antigens displayed by a limited number
303 of microbes.

304

305 MAIT cells develop in the thymus, where they become functionally competent and able
306 to promptly produce Th1 (IFN- γ , TNF- α) and Th17 (IL-17 and IL-22) cytokines in response
307 to stimulation [105]. In contrast, MAIT cells produce only low to moderate levels of Th2
308 (IL-4 and IL-13) cytokines [106-109]. Similarly to iNKT cells, MAIT precursors undergo a
309 positive selection of MR1⁺ double-positive (CD4⁺CD8⁺) thymocytes [110,111]. Previous
310 reports have stressed the key role of the microbiota in MAIT cell expansion since these
311 cells are nearly absent in germ-free mice [20]. Recently, Lantz's team made a major
312 breakthrough in this field by demonstrating that microbial metabolites control the
313 thymic development of MAIT cells [112]. This finding paved the way for revisiting the
314 concept of exogenous and self-antigens.

315

316 Human MAIT cells express high levels of CD161 and IL-18R α and are mainly CD8⁺ [113].
317 A smaller proportion among these is double-negative (CD4⁻CD8⁻) and some CD4⁺ cells
318 have been described in the literature [114]. MAIT cells can be activated in a TCR-
319 dependent and -independent manner. They account for up to 10% of peripheral blood
320 T cells and are numerous in the gut, lung, and liver [115,113,20]. Their abundance in
321 mucosal tissues supports their involvement in antimicrobial responses [20].

322

323 Because of the scarce pieces of evidence for a role of MAIT cells in experimental models
324 of asthma, we will not discuss this issue, but pass on directly to studies with asthmatic
325 patients.

326

327 **MAIT cells in asthmatic patients**

328

329 As indicated by their name, MAIT cells are preferentially associated with mucosal tissues
330 including lungs, where they promote antimicrobial defenses through the secretion of
331 IFN- γ , TNF- α , IL-17, perforin and granzyme B [116-120]. Evidence for MAIT cell expansion
332 in the lungs of MAIT cell-enriched V α 19iC α ^{-/-}MR1^{+/+} mice experimentally infected with

333 *Mycobacterium tuberculosis* supports their role during pulmonary infection [121]. This
334 proliferative response was rapid and depended on the MR1 presentation of riboflavin
335 biosynthesis-derived bacterial ligands [121]. In line with these experimental data it has
336 been reported that adult patients suffering from active pulmonary tuberculosis (TB) had
337 more MAIT cells in BALF and lung parenchyma than uninfected controls [122]. However,
338 in children with similar symptoms, reduced MAIT cell counts were found both in
339 peripheral blood and BALF [123]. This discrepancy might be due to clinical differences
340 between pediatric and adult active TB, calling for further studies to ascertain the role of
341 MAIT cells in in this infectious disease.

342

343 The data gained from lung infections prompted several groups to address the
344 involvement of MAIT cells in other lung pathologies like asthma. Pioneer studies by
345 Hinks et al. reported that the frequency of MAIT cells was significantly lower in
346 peripheral blood, sputum and bronchial biopsy samples of asthmatic patients, relative
347 to control subjects [124]. This deficiency was correlated with clinical severity and the
348 use of oral corticosteroids [124].

349

350 A recent study provided evidence for a relationship between a high frequency of
351 circulating MAIT cells in one-year-old children and a lower risk of developing asthma by
352 the age of seven years [97]. Furthermore, these high MAIT cell levels were correlated
353 with higher frequency of IFN- γ -producing CD4⁺ T cells, suggesting a possible protective
354 effect of MAIT cells as children grow older [97]. IL-17 production by MAIT cells did not
355 correlate with asthma in this study. In children with mild asthma, the frequency of
356 circulating MAIT cells did not differ between exacerbators and non-exacerbators [96].
357 However, the proportion of MAIT cells producing IL-17 correlated positively with the
358 number of severe exacerbations and negatively with the asthma control test score in
359 these children, which was not the case for their IFN- γ -producing counterpart [96]. More
360 recently, the same team showed that MAIT cells, including their IL-17-producing subset,
361 were present in BALF from children with severe asthma [125]. It is noteworthy that when
362 this group was divided into two according to the frequency of their IL-17-producing
363 MAIT cells in BALF into MAIT17-low and MAIT17-high, the latter presented more severe
364 exacerbations than their MAIT17-low counterpart [125].

365

366 Overall, the results of these studies suggest that IL-17-producing MAIT cells may be
367 associated with asthma symptoms, whereas the pro-Th1 subset might provide
368 protection [97,96,125] (Fig. 3).

369

370

371

372 **CONCLUDING REMARKS**

373

374 Much progress has been achieved in understanding the physiological and pathological
375 role of $\gamma\delta$ T, iNKT and MAIT cells, which have by now acquired a lasting position among
376 the complex immune mechanisms leading to distinct asthma phenotypes and
377 endotypes. Nonetheless, major uncertainties remain. For instance, asthma often begins
378 early in childhood, at a time when the amount and functional properties of lung $\gamma\delta$ T,
379 iNKT and MAIT cells are about to be established. However, very few studies have
380 addressed the evolution of these populations in the airways with age. The cross-talk
381 between lung $\gamma\delta$ T, iNKT and MAIT cells needs likewise to be investigated in more detail,
382 as well as the influence of microorganisms present in the lung. In sum, studies of
383 experimental models and pediatric asthma will be crucial for the comprehension of
384 these complex interactions and the development of new therapeutic approaches.

385

386

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390

391 **Compliance with Ethical Standards**

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

393 **Ethical Approval and Informed Consent**

394 No approvals or informed consents were obtained, as this manuscript does not contain
395 primary research data.

396

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853 **Figure Captations**

854

855 **Figure 1: $\gamma\delta$ T cell immune response in asthma.** In experimental asthma models (left) IL-
856 4-producing $\gamma\delta$ T cells could enhance Th2 inflammation, IgE production, airway
857 eosinophilia and airway hyperreactivity (AHR), while IL-17-producing $\gamma\delta$ T17 cells could
858 have an opposite effect. In BALF (bronchoalveolar lavage fluid) from asthmatic patients
859 (right), the frequency of $\gamma\delta$ T cells was elevated. These $\gamma\delta$ T cells improved their ability to
860 secrete IL-5 and IL-13 following allergen challenge. The main effects resulting from the
861 activation of $\gamma\delta$ T are listed within the lung figure.

862 \uparrow = induction/augmentation; \downarrow = reduction/inhibition.

863

864 **Figure 2: iNKT cell immune response in asthma.** In experimental asthma models (left)
865 IL-4-and IL-13-producing iNKT2 cells will enhance IgE production, airway eosinophilia
866 and airway hyperreactivity (AHR), while IL-17-producing iNKT17 cells could promote
867 airway neutrophilia and AHR. The frequency of iNKT cells in BALF (bronchoalveolar
868 lavage fluid) from asthmatic patients (right) rang from 0.1% to 10%. The main effects
869 resulting from the activation of iNKT cells are listed within the lung figure.

870 \uparrow = induction/augmentation; ? = no functional effects described.

871

872 **Figure 3: MAIT cell immune response in asthma.** The studies concerning the implication
873 of MAIT cells in experimental asthma models (left) are currently in progress. IL-17-
874 producing MAIT cells are associated with severe exacerbations in asthmatic patients
875 (right) while their IFN γ -producing counterpart maybe involved in protection.

876 ? = no functional effects described.

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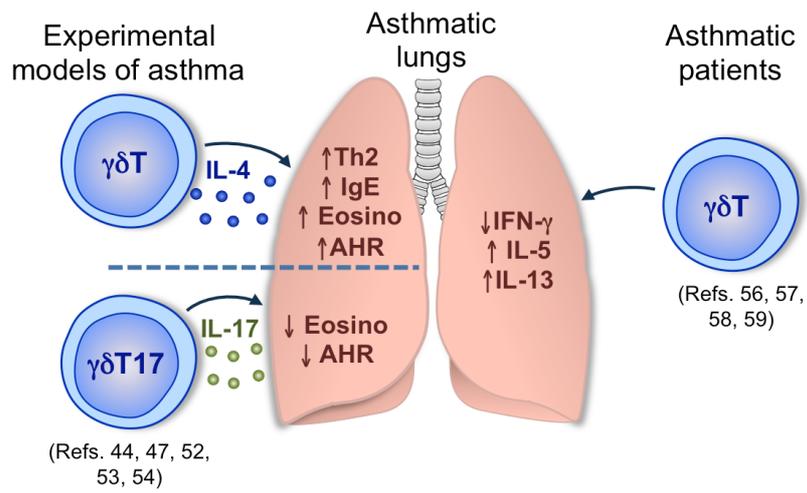


Figure 1

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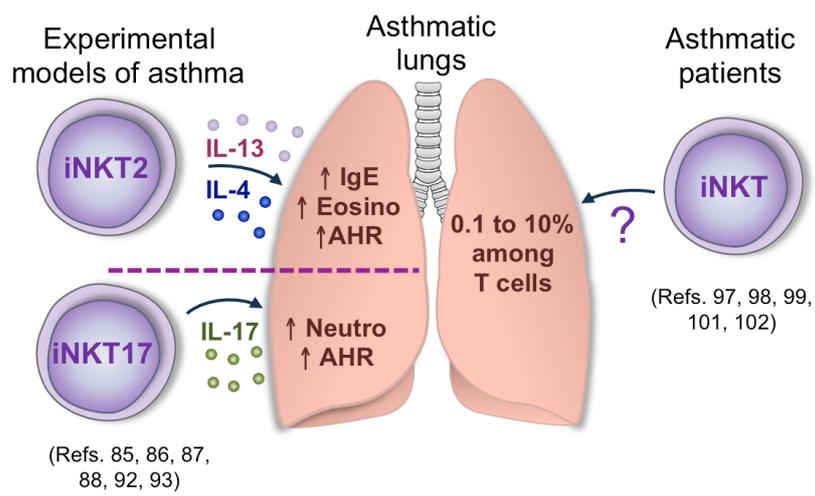


Figure 2

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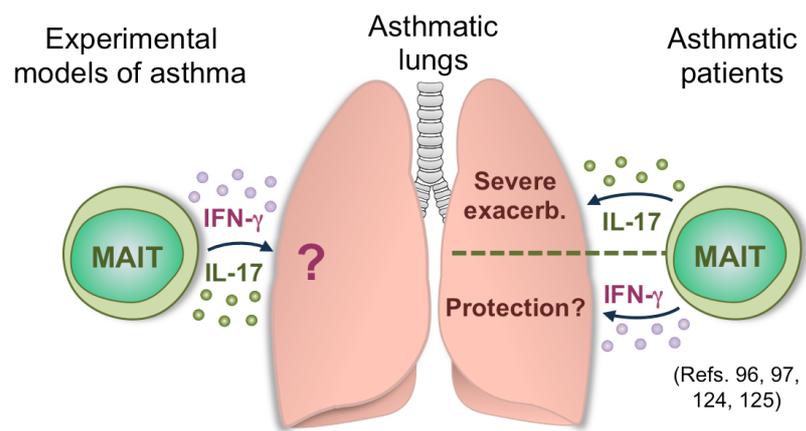


Figure 3

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Table 1. Major features of $\gamma\delta$ T, iNKT and MAIT cells.

| | $\gamma\delta$ T | | iNKT | | | MAIT | |
|------------------------------|---|--------------------|--|-------------|--------|---|--------|
| TCR | <ul style="list-style-type: none"> • Mice: Vγ1, Vγ4, Vγ5, Vγ7 (TRGV1, 4, 5, 7). • Humans: Vδ1-3 (TRDV1-3), Vγ2-5, Vγ8, Vγ9, Vγ11 (TRDV2-5, 8, 9, 11). | | <ul style="list-style-type: none"> • Mice: Vα14-Jα18 (TRAV11-TRAJ18). • Humans: Vα24-Jα18 (TRAV10-TRAJ18). | | | <ul style="list-style-type: none"> • Mice: Vα19-Jα33 (TRAV1-2-TRAJ33). • Humans: Vα7.2-Jα33 (TRAV1-2-TRAJ33). | |
| Antigen-presenting molecules | BTN3A (as an intermediate) | | CD1d | | | MR1 | |
| Antigens | stress molecules (MICA and MICB), heat-shock proteins or synthetic phosphoantigens (pAg) | | glycolipids (α -GalCer, iGb3, others) | | | Riboflavin derivatives (5-OP-RU) | |
| Major subsets | $\gamma\delta$ T IFN- γ ⁺ | $\gamma\delta$ T17 | iNKT1 | iNKT2 | iNKT17 | MAIT1 | MAIT17 |
| Transcription factors | Tbet | RORC | Tbet, GATA-3 | GATA-3 | RORC | Tbet | RORC |
| Major cytokines produced | IFN- γ | IL-17 | IFN- γ , IL-4 | IL-4, IL-13 | IL-17 | IFN- γ | IL-17 |