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Th9 cells and interleukin-9 in the pathogenesis of asthma

Células Th9 e Interlecuina-9 na patogenia da asma

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ABSTRACT
Objective: The aim of this study was to review the key information about the recent subtype of Th9 cells and interleukin-9 in the pathology of asthma.
Data source: It was surveyed in the databases Medline/Pubmed and OVID, original papers published between 1997 and 2012, in English and Spanish, using the selected descriptors.
Data synthesis: Asthma is a problem of public health, and its pathophysiology includes subtype of cells of the T helper family and their respective cytokines. The cytokine IL9 is produced by CD4 T cells by activation of transcription factors IRF4 and PU.1. Th9 mainly produce IL9, but Th2 can also secrete this cytokine. IL9 is involved of pathology of asthma by increasing of airway hyperresponsiveness and eotaxin release by lung epithelial cells. Moreover, inhibition of IL9 in asthma has been studied and reported as a preventive and inhibitory airway remodeling in mice.
Conclusion: Nowadays, the discovery of new treatments for allergic asthma is essential. Studying this new subtype of helper T cells and understanding its involvement in the development of asthma may provide a possibility of new treatments, such as inhibiting the production of IL9.

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Keywords: Interleukin-9, T helper cells, and TGF-β

RESUMO
Objetivo: O objetivo deste estudo foi revisar as principais informações sobre o recente subtipo de células Th9 e a interleucina-9 na patologia da asma.
Fonte dos dados: foram pesquisados nas bases de dados Medline / Pubmed e OVID, trabalhos originais publicados entre 1997 e 2012, em inglês e espanhol, utilizando os descritores selecionados.
Síntese dos dados: A asma é um problema de saúde pública e sua fisiopatologia inclui o subtipo de células da família T auxiliar e suas respectivas citocinas. A citocina IL9 é produzida pelas células T CD4 pela ativação dos fatores de transcrição IRF4 e PU.1. Th9 produz principalmente IL9, mas Th2 também pode secretar essa citocina. A IL9 está envolvida na patologia da asma, aumentando a hiper-responsividade das vias aéreas e a liberação de eotaxina pelas células epiteliais do pulmão. Além disso, a inibição da IL9 na asma foi estudada e relatada como remodelação preventiva e inibitória das vias aéreas em camundongos.
Conclusão: Atualmente, a descoberta de novos tratamentos para a asma alérgica é essencial. O estudo desse novo subtipo de células T auxiliares e a compreensão de seu envolvimento no desenvolvimento da asma podem proporcionar uma possibilidade de novos tratamentos, como inibir a produção de IL9.

Resumo: Interleucina-9, células T auxiliares e TGF-β

1 INTRODUCTION

Asthma is a public health problem worldwide, present in developed and developing countries, but the most deaths occur in low-income countries. Asthma is especially prevalent in children and it is characterized by airway hyperresponsiveness (AHR), recruitment of inflammatory leukocytes into the lungs and tissue remodeling (1). Asthma is divided into atopic asthma, non-atopic asthma, depending on the presence or absence of atopy (2). In the pathophysiology of asthma subtypes of T helper cell family which includes, Th1, Th2, Th17, Treg, Th22, Th25 and Th9, according to the production of cytokines may play a key role in disease development (3, 4) (Figure 1). CD4+ T cells differentiate into subsets functionally distinct after encountering antigen, and that functional heterogeneity of T cells is molded by many components such as the strength of the initial signal receivers of T cell antigens, cytokines and epigenetic factors (5).

Historically, it was believed that only two subtypes of T helper cells, Th1 and Th2, performed an important role in allergic diseases (6). Starting from this, the idea has changed from identifying other subset of T cells. And more recently, it was described a T cell that secrete interleukin 9 (IL-9) and it is distinct from Th1, Th2, Treg and Th17 (7, 8).

This new subtype was named Th9 cells thereby increasing the understanding of adaptive immunity (9). Changing the thought that Th2 cells were mainly producing IL-9, an interleukin which is a key in the development of asthma (10).

Based on such information, this review aims to clarify the influence of Th9 cells, which was recently described, and the interleukin secreted by these cells, the IL-9, to provide a better

understanding of their disease mechanism and consequently a better treatment conduction through this new pathophysiology.

2 PATHOPHYSIOLOGY OF ASTHMA

Asthma is a chronic inflammatory disorder, labeled "Th2 like" due the mainly differentiation of Th2 CD4 + T cells, which secrete cytokines such as IL-4, IL-5 and IL-13. The disease is caused by a combination of genetic, environmental and an inappropriate response to allergens, which usually has its onset early in life and emerges as the most common disease in children. It is physiologically characterized by bronchial hyperresponsiveness and infiltration of inflammatory cells in the airways, leading to intermittent airway obstruction (11-13).

The changes in the lungs present in asthma is caused by deposition of extracellular matrix protein such as fibronectin, collagen and mucus hypersecretion, and the proliferation of smooth muscle cells in the airways. A key feature of asthma is airway remodeling, which is associated with the up regulation of growth factors pro-fibrotic, in particular TGF-β (14). Remodeling is explained by excessive production of mucus epithelial (15).

These characteristics occur because there is an initial contact with an allergen mucosa, which initiates the production of IgE by B cells through the cooperation of Th2 cells. After challenged with allergen levels of Th2 cytokines IL-4 and IL-13 are found in the airways of subjects with asthma and eosinophil influx contribute to allergic inflammation in asthma (16).

The IFN-γ production by Th1 cells negatively regulates IgE synthesis, whereas IL-9 stimulates production of IgE and mast cell growth (16). The complex interaction between the cells leads to production of inflammatory mediators, including cytokines and chemokines, which plays a role in the pathogenesis of asthma (17).

3 IL-9, TH9 AND ASTHMA

Generally are involved in chronic inflammatory disorders of the cytokine Th2 cells, such as IL-5, IL-13 and IL-14. However, not long ago, Simonetta Baraldo cited that IL-9 might play an important role in allergic diseases of the airways. Initially, when it was described in the mid-year 1980, the IL-9 was identified in activated CD4+ T cells, and its production was associated with the family of Th2 cytokines (18-20). In this period of discovery of IL-9, it was characterized as a growth factor, involved in the differentiation of T cells and mast cells in murine models (19, 21).

IL-9 is a T cell derived cytokine with pleiotropic activities that promote the proliferation and differentiation of mast cells and erythroid progenitors, the survival of eosinophils, in vitro proliferation of activated T cells and differentiated immunoglobulin production B cell. In addition to

these activities, IL-9 also regulates the expression of IL-5 receptor on the cell surface, leading to hypersecretion of mucus by stimulation of calciform cell metaplasia and the expression of mucin gene (18, 22).

With the goal of greater clarification around IL-9, it was mapped along with other Th2 cytokines, such as IL-4, IL-5 and IL-13, and identified that its gene is located in the region 5q31-q33 chromosome 5 (23). In humans, IL-9 protein is comprised of 5 exons comprehending of 144 amino acids, which span approximately 4kB and has four potential glycosylation sites (21). From this, a new group of CD4+ T cells was designated Th9 by secrete IL-9. This new cell phenotype has attracted the attention of researchers worldwide, because IL-9 is associated with pleiotropic activity, which promotes allergic asthma (10).

Recently described, Th9 cells are considered the most consistent IL-9 secreting T cells, which are generated by the combined effects of the cytokines TGF-β and IL-4. These are pro-inflammatory cells and seem to be present in a broad spectrum of autoimmune and inflammatory diseases, and produce large amounts of IL-9, but also IL-10 (24). Because all the role of Th9 is not yet well understood in the immune system, some studies have shown that IL-9 can cause inflammation, particularly after re-stimulation of Th9, and the existence of Th9 cells occurs by the presence of transcription factor PU.1 (25).

According to the study of Horka, the data presented clarify that IL-9 secreted by Th9 is involved in the development of allergic inflammation of the lungs, besides confirming that the major source of IL-9 is the asthmatic bronchial mucosa (10, 26). As Th9 cells that secrete IL-9 affect the occurrence of allergic inflammation, studies on the development of these cells were performed. The data have the same order for these cells to develop Th9, requires multiple signals balance, such as transcription factors, Interferon regulatory factor (IRF4), PU.1, which are essential in addition to exposure to TGF-β and IL-4 (27).

TGF-β is described as a driver in the development of Th1 cells and Treg but its role is crucial in main characteristic of Th2 cells and Th9, which is to redirect the reprogramming of cells toward the Th2 phenotype to Th9 (7, 28). According to this author, in the deficiency in STAT6 prevent the development of Th9 cells (28).

In addition to all the functions involved in development around the Th9 cells, TGF-β is suggested as an inhibitor of upregulation of IL-4 mediated by GATA-3, which depends on the expression of STAT6. Because of Th9 cells is an important inducer of asthma symptoms dependent on IL-4 (21), Goswami et al showed that IL-4 and STAT6 are required to activate IRF4 and enhance other factors, such as PU.1 the transcription factor Th9 cells , which binds directly to the IL-9 promoter in Th9 cells (28, 29).

STAT6 is not only capable to counteract the Foxp3-inducing capacity of TGF-B and directing the expression of IRF4, which is essential for the development of Th9 cells. This is remarkable in IRF4 deficient mice, are not able to expel *Nippostrongyrus brasiliensis*, suggesting that IL-9 protective, presumably by Th9 cells, is not present in the absence of IRF4, IRF4 may be a promising target for the treatment of chronic lung disease (30, 31).

According Goswami et al, the transcription factor IRF4 showed a pattern similar induction in Th2 and Th9 cells, although the expression of this factor was higher in Th9 cell differentiation (29). The IRF4 is essential for the development of Th2 cells, but is crucial for the development and function of IL-9 cells produced by Th9. In a study evaluating the contribution to the development of IRF4 Th9 cells, it was observed that Th9 cells expressed increased protein IRF4 Furthermore, this protein directs the development of Th9 cells by binding to the promoter of IL-9. In mice with heterozygous deficiency of IRF4, presented an intermediate phenotype, agreeing with asthma symptoms (30).

Although the transcription factor PU. 1 and IRF4 be associated with Th9, they are not specific to cells and Th9 are involved in the induction of other T cells, including Th2 cells. Thinking about it, a recent study by Xiao et al, a new co-stimulatory molecule was found, the call OX40, which promoted and potentiated the induction of Th9 cells. It was found that the binding of OX40 with TGF-β and IL-4 converted around 80% of CD4 + cells into Th9. It was also observed that OX40 is a support survival and proliferation of cells Th9, as well as inhibit Foxp3 + Treg cells through a variety of mechanisms for the control of immunity and immunopathology. It is associated with the pathogenesis of autoimmune colitis, encephalitis experimental autoimmune arthritis, asthma and graft rejection. Th9 cells were induced OX40 different from other cells Th9 reported that they had high expression of IL-9 expression without Th2 cytokines or other Th9 (32).

Thus, Th9 cells may play a regulatory role in the pathogenesis mechanism of protection versus immune responses (28, 33), and contributing to the pathology of asthma, being an important stimulator for infiltration of mast cells, as well as promoter tissue inflammation and mucus production (34, 35).

The hypothesis that IL-9 may play a harmful role in the pathology of asthma is reinforced by the fact that interleukin have the ability to increase hyperresponsiveness (15, 30). The action that IL-9 plays hyperresponsiveness occurs by the mechanism of interaction between the IL-9 receptor (IL-9R) and its own cognate associated with distinct receptors (36), suggesting a direct effect of IL-9 the muscles of the airways, and its influence in the release of eotaxin peas epithelial cells of the lungs. This is confirmed by the increased expression of IL-9 in patients with asthma compared to non-asthmatics, in addition to being involved in resistance to parasites, such as Trichurismuris (18, 34).

IL-9R is a heterodimer consisting of ligand-specific α chain subunit (IL-9Rα) and a common γ chain, which is shared with IL-2, IL-7 and IL-15 (7, 36). This receptor is located in the pseudo-autosomal region of the X and Y chromosome (Xq28 and yq12). IL-9R belongs to the superfamily hematopoetina receptor and is expressed in T cells, mast cells, macrophages, eosinophils and neutrophils and has also been implicated in asthma by these characteristics (18). According to Böttcher et al, IL-9 and IL-9R may be harmful to the human T cell differentiation, eosinophils, and mast cells. This receptor is expressed in tonsillar B cells, beyond the surface of bronchial smooth muscle cells from the human airway, which are synthesized by bronchial smooth muscle in asthma patients (16, 22, 36).

A specific feature of IL-9R is that it activates factors STATs and Janus Kinase, and this receptor has been shown to be crucial in the development of T cells and preventing apoptosis. However, its role is more specific in stimulating chemotactic factors by bronchial epithelial cells and smooth muscle cells. However processe derived from functional changes in IL-9R may arise from changes in the amino acid essential for activation of STAT and its signaling, such as tyrosine 116 and 336. These changes have an impact on allergic diseases, such as increased expression of IL-9 mRNA and enhance the immunoreactivity of IL-9 and IL-9R (37).

Recent analysis in animal models of the promoter region of the IL-9 gene, associated IgE and IL-9 and bronchial hyperresponsiveness, suggesting some genetic variations in the IL-9 gene may predispose to asthma (21). Playing a key role in the development of allergy, IL-9 may act directly on the IL-9R on B lymphocytes and regulate IgE synthesis. Therefore, IL-9 is suggested as a candidate for the pathology of asthma, based on the unbalance between total serum IgE and markers related with the expression of this gene (15, 37).

Produced in the airways of asthmatic patients, IL-9 was assessed by the same mRNAde detection of IL-9 in lung tissue after being challenged with allergen according Devos et al. In this study, 24 volunteers identified as asthma, using RAST and fluorenzima immunoassay specific IgE determinations were interleukins IL-5, IL-13 and IL-9 performed by ELISA. The results of this study suggested that IL-9 is specifically induced in PBMC by stimulation with hypersensitive adults and allergens associated with the titles of allergen specific IgE. It was found that the production of IL-9 was higher in atopic asthma patients than in those without asthma (38).

The study by Böttcher analyzed the PBMCs of 18 children identified as asthmatic, using criteria defined by the ISAAC (International Study of Asthma and Allergies in Childhood), and control children. Using the ELISA after stimulation of cells with allergens, cytokines IFN-γ, IL-4, IL-5, IL-9, IL-10 and IL-13 were determined (16). The results of this study corroborate the results obtained by Devos et al in the production of IL-9 showed higher levels in atopic children, is associated

only with atopic asthma, probably due to its inducing properties IgE (38). Having as axis the results of these two studies in humans, it was observed that IL-9 tends to be higher in asthmatics than in individuals without asthma (16, 38), reinforcing the interaction between the expression of IL-9 and atopy and asthma (8).

Several studies in mice were conducted surrounding the IL-9, suggesting their role in the predisposition to asthma. According Namkung et al, the reduction in IgE production was shown in transgenic mice due to a deficiency in IL-9 (21). Another study, in transgenic mice over-expressing and IL-9, suggested that this cytokine plays a role in the development of eosinophilia and airway hyperresponsiveness and mast cell hyperplasia (39). To emphasize that IL-9 is an important mediator in the pathogenesis of asthma, Chiba et al intratracheally administered recombinant IL-9 in naive mice after challenge with OVA, to evaluate the role of IL-9 IL-9 and correlate with UGRP1 a uteroglobin related protein secreted high expression in the trachea, bronchi and bronchioles, but its functional role in airway physiology is still unknown It is suggested that it possibly is involved in the pathogenesis of asthma. Besides involved in asthma, Chiba study showed that IL-9 is involved in the regulation of basic UGRP1 in the airways of mice and also regulates the expression UGRP1 these animals when IL-9 is administered intranasally. These results evidence that increased IL-9 is an important mediator in the pathogenesis of allergic bronchial asthma (17).

4 TREATMENT WITH IL-9

In asthma, allergic inflammation is caused by multiple cells, and changes in asthma include deposition of extracellular matrix proteins such as fibronectin, collagen, and tenascin, mucus hypersecretion and airway remodeling. However, currently the only treatment has potential effect on airway remodeling and is made with anti-inflammatory drugs such as corticosteroids. Besides the use of corticosteroids to treat asthma patients involves the use of antihistamines, anti-leukotrienes (40, 41).

Moreover, according to reports, which have been used in children's Omalizumab, a monoclonal recombinant humanized anti-IgE, recommended for the treatment of diseases mediated by IgE, which was approved in 2005 (42). In addition to these treatments has also been described therapy with cytokines, especially with IL5, which is an inhibitor of infiltration esosinófilos locked and it is the most commonly used, being secreted by chief cells involved in the pathology of asthma. However, it is still necessary to discover new therapeutic targets for asthma (40, 43). Thinking about the treatment and the fact that IL-9 is specifically over-regulated in the lungs after stimulation with allergens (23) all previous studies were limited to examining the effects by blocking IL-9 in acute inflammatory models. In the study by Kearley et al, after prolonged exposure to OVA, they found

that the levels of TGF-β, VEGF-β and FGF-2 were activated elevated in lung tissue and that neutralization of IL-9 expression markedly reduced these three cytokines, suggesting that this is one potential mechanism for modulating antifibrotic effect of pretreatment with anti-IL-9 11. Already Staudt et al suggest that neutralization of IL-9 can only revoke inducing properties related to asthma Th9 cells, whereas Th2 cell properties were only marginally affected (34).

The results of the T Horka and colleagues suggest that inhibition of IL-9 is a more suitable for the treatment of asthma. Another study on the treatment of Kearley et al reported that mice pretreated with anti-IL-9 were completely protected against the increase in the total resistance of the airways and tissue resistance caused by the disease, suggesting that inhibition of remodeling airways is associated with OVA (10, 23). These data suggest that the prolonged inhibition of IL-9 is required to reduce the activity of mast cells and mediate significant beneficial effects on the lungs. The pre-treatment with anti IL-9 also protected mice induced chronic remodeling in HDM and inhibited mast cell numbers, which is the axis which regulates airway fibrosis (40).

However, new treatments have been studied around the IL-9, and the new group of T cells, since in Horka et al study, the data clearly show that IL-9 is derived from Th9 prominently involved in the development of allergic inflammation the lungs (10).

5 CONCLUSION

The identification of this new subtype of T cells and their role and influence on the development of asthma brought a greater understanding of its mechanism. In addition, clarified on the plasticity of Th2 cells and Th9. Another positive aspect is the suggestion of new treatments through inhibition with anti-IL-9 to the blockade of airway inflammation.

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FIGURE: 1 AND 2

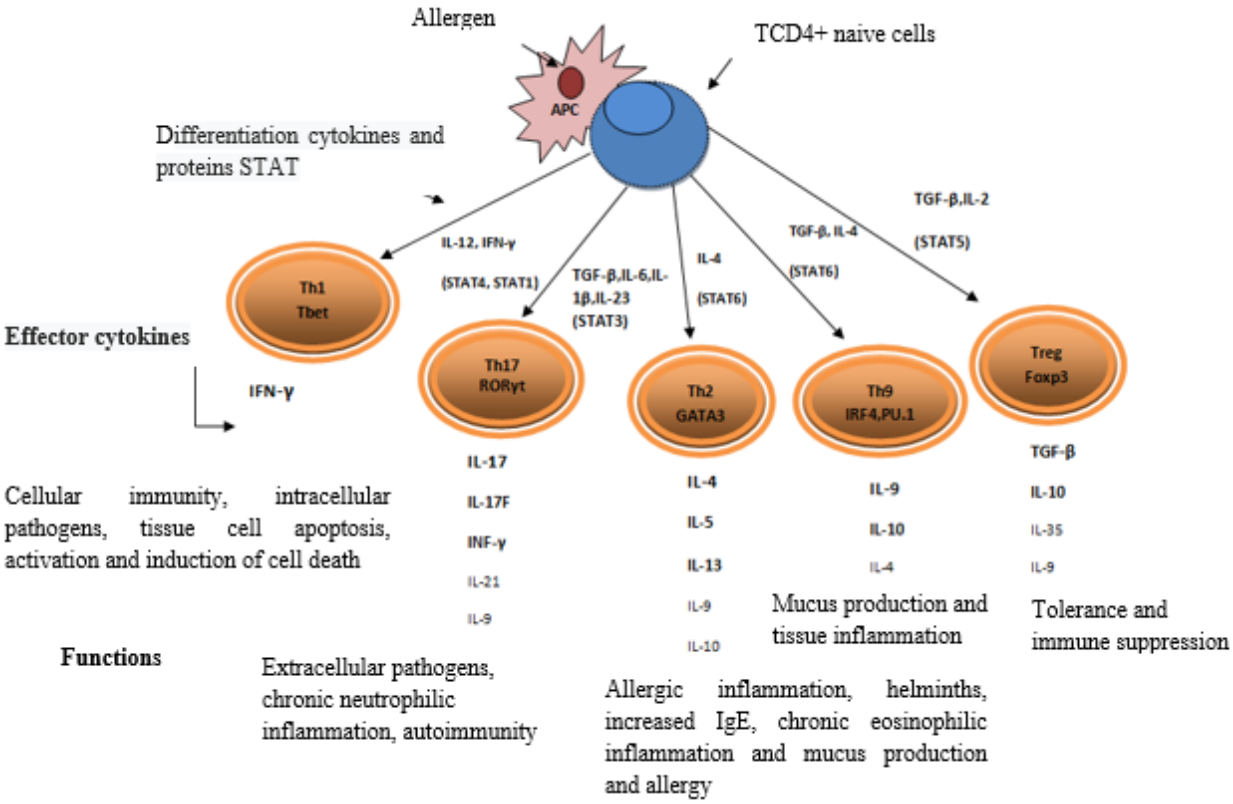

Fig.1. The differentiation of T naïve cells. After stimulation with allergen, state of cells and microenvironment, T naïve cells differentiate between T helper cells of different subtypes, Th1, Th2, Th17, Treg and Th9. Each of these subtypes has transcription factors and STATs specific to their differentiation target, as well as their respective effectors cytokines and their functions

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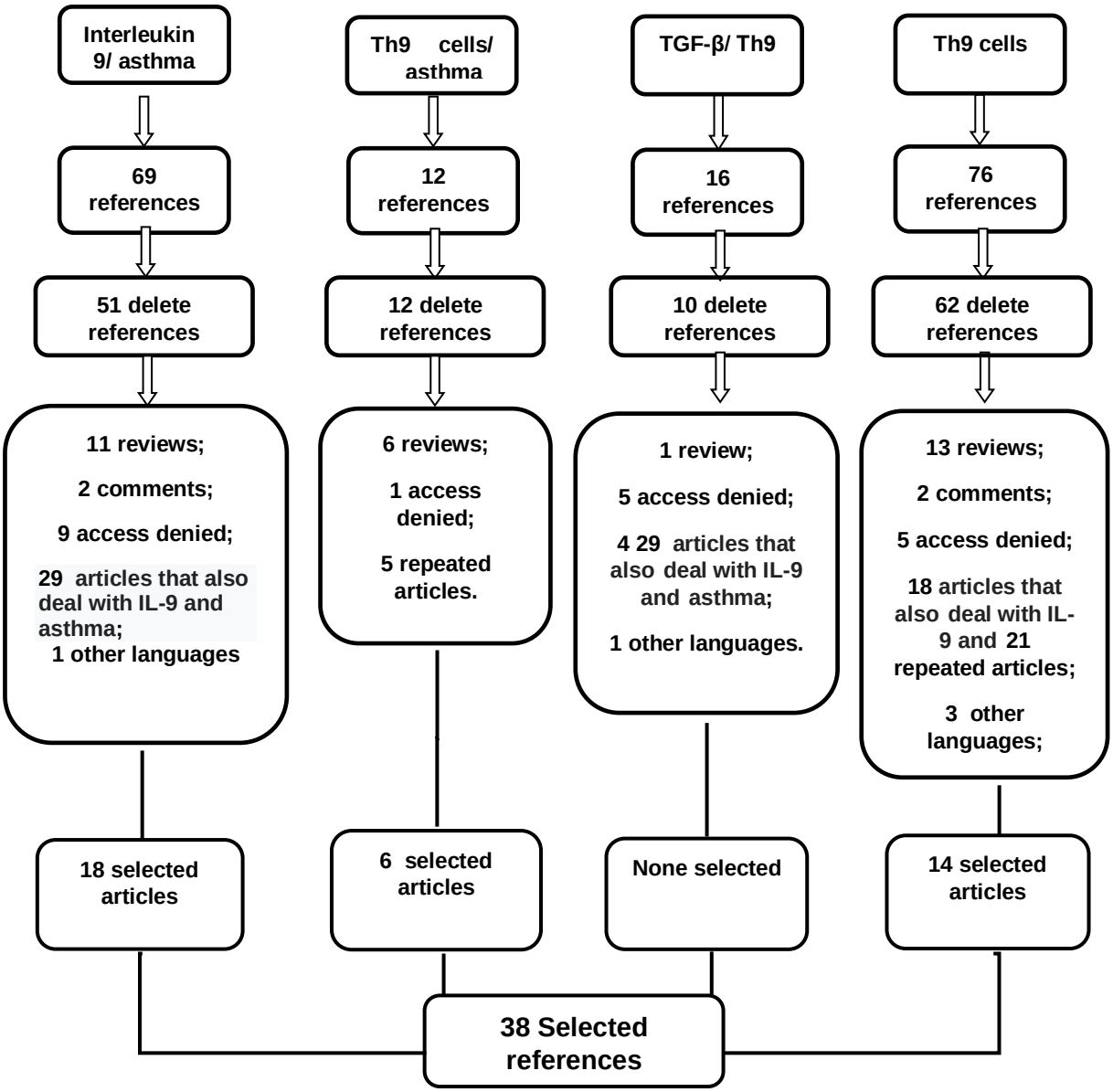

Fig.2 Layout of the search and selection os references for the review article