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Article

Biological Activity of Der p 1 and Der f 1 in Allergic Asthma and Their Contribution in Inflammation and the Role of Anti-inflammation in Allergic Asthma

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Julian[1], Anna Rozaliyani[1,2*], Heri Wibowo[1,2], Triya Damayanti[3]

[1]Master's Programme in Biomedical Science, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2]Department of Parasitology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[3]Departement of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Abstract. Asthma is a disease marked by chronic inflammation of the airways, with indications including wheezing, shortness of breath, and/or cough. As reported by GINA, the global prevalence of asthma is 1-18%. One type of asthma is Allergic asthma which is triggered by allergens, like Der p 1 and Der f 1 which upregulate type II immune response to secret IL-4 and IL-13 to upregulate IgE secretion. IgE binds to FcεRI in mast cells to release mediators that cause hypercontraction, this condition leads to asthma. Meanwhile, anti-inflammatory IL-10 manages IgE production by reducing inflammatory cytokine production and changing isotype switching. IgE Production is a crucial step. Therefore, it is essential to explore the cellular and molecular factors that trigger the regulated isotype-switching IgE and its suppressed mechanism, so this review will explore the biological activity of Der p 1 and Der f I and their contribution to inflammation and the role of anti-inflammation in allergic asthma especially isotype switching IgE We used PRISMA approaches, and tools (RSCB PDB, Uniprot, and SMART). The result appeared Der p 1, and Der f 1 activity have impacts on IL-4, IL-13, IL-10, and IgE secretion.

Corresponding Author :
Anna Rozaliyani
Department of Parasitology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
Email: anna.rozaliyani@ui.ac.id

1. Introduction

Asthma is a chronic inflammatory condition that causes airway hyperresponsiveness, which is still a worldwide issue. More than 350 million or 1-18% reported individuals who had asthma in 2020, and 260 million people had poorly controlled asthma in 2019. One type of asthma is allergic asthma [1-4].

Allergic asthma is caused by the exaggerated immune response to allergens, especially house dust mites. The major allergens in mites are Der p 1 and Der f 1 which contain enzymes to reduce antiprotease activity, cause tissue damage, and activate the immune system [5-6].

According to a recent study, *Dermatophagoides pteronyssinus* had the highest level of allergen sensitization, followed by *Dermatophagoides farinae*, *Blomia tropicalis*, and food allergens. Other research revealed that the group 1 allergen of Dermatophagoides, particularly Der p 1, had a significant prevalence of house dust mite sensitization [7-8].

This condition is a possibility to induce inflammation where innate lymphocytes-2 (ILCs-2) secrete alarmins and recruit dendritic cells (DCs) to capture allergen, but these mites have protease which downregulates type I and upregulates type II immune response to secrete some cytokines, especially IL-4 and IL-13 [9-10].

IL-4 and IL-13 are key roles in isotype switching to release IgE. IgE binds mast cell receptors. In secondary exposure allergens cause mast cells to degranulate by inducing cross-reaction complex IgE and their receptors to discharge mediators leading to bronchial contraction and causing asthma [9-10].

According to a recent study, asthmatic patients have greater levels of IL-4 and IL-13 than non-asthmatic individuals. An additional investigation has demonstrated a positive correlation between IL-4, IL-13, and IgE, particularly the specific IgE Der p and Der f [11-12].

To manage inflammation, the system immune has anti-inflammatory, particularly IL-10 which downregulates pro-inflammatory cytokines generation and changes isotype exchanging IgM to IgG to diminish IgE levels. A recent study has shown that IL-10 is important in managing allergic asthma. [13–16].

The Regulation of isotype switching IgE is a crucial stage, so It is essential to explore cellular and molecular mechanisms based on two sides, one side triggers upregulated isotype switching IgE, and the other side anti-inflammatory to manage biomechanism against allergen, especially Der p 1 and Der f 1 in allergic asthma, so it can be development therapy research for asthma based on inflammation and anti-inflammation side, so the objective of this review is exploring biological activity of Der p 1 and Der f 1 and their contribution in inflammation and the role of anti-inflammation in allergic asthma, especially in isotype switching IgE regulation

2. Materials and Methods

In this review, the PRISMA approach was used to select eligible articles in this literature review. We searched databases containing scientific publications, including PubMed, Science Direct, and Google Scholar. The search terms were (1) Asthma, (2) Der p 1 and Der f 1, (3) Inflammation and anti-inflammation in allergic asthma, (4) Regulation of Isotype switching IgE(5) Allergic asthma. Articles must be relevant, accessible by title, abstract, and relevant. The paper can be a literature review, an original article, or a case study covering the period 2019-2023. Exclusion criteria were duplicate and unrelated articles.

After selecting the articles as document types, they will discuss the biological activity of Der p 1 and Der f 1 and their impacts on the regulation of immunoglobulin E isotype switching. These keywords were used to search all databases, yielding a total of 21,803 articles. In addition, 17,201 items with irrelevant titles were eliminated. Some articles, spanning from abstract publishing to full text, may be reviewed. Because they did not match the inclusion requirements, 4,562 of the 4,602 possible articles were rejected. As a result, ten papers fulfilled the inclusion criteria and were ready for evaluation. The PRISMA plot of the papers chosen for this search is shown in Figure 1.

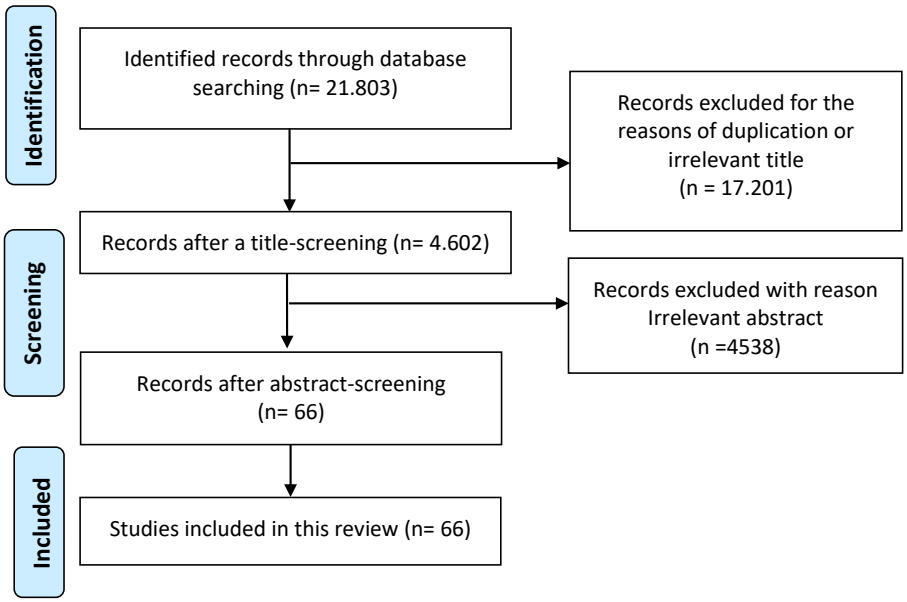

Figure 1. PRISMA workflow

We searched for structures of IgE, Interleukin 4, Interleukin 13, and Interleukin 10 using the homo sapiens criteria in Protein Data Bank (PDB) and Uniprot, but for searched for Der p 1 and Der f structure and active site using the criteria *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* species. Acari order or astigmata suborder keywords criteria were used to search the phylogenetic tree using Timetree (http://timetree.org). Utilizing Servier Medical Art (SMART), several of the icon illustrations were created.

3. Results and Discussion

3.1 Characteristics of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*

House dust mites are arachnid arthropods that weigh 5.8 g for females and 3.5 g for males and are 250–300 microns in length. Water constitutes 72–74% of their weight. This arthropod lacks antennae and has an eight-legged body with a striated cuticle. The body of the dust mite is divided into two parts: the idiosoma, which houses the body and legs, and the gnasthoma, which houses the bearing pedipalps and chelicerae [17-18].

Mites use the chemical and tactile sensors in the pedipalps to find food and detect environmental cues. A pair of three-segmented chelicerae that finish in the chela, a structure designed for grasping and gripping, make up the mouthpart. The idiosoma has been divided into other portions in the meantime. Both the anterior and posterior halves have what are known as "podosome" and "opisthosoma" legs, respectively. The prodosoma is the other component [17], [19].

When it is an adult or nymph, it has four pairs of legs; whereas it is a larva, it has just three. The coxa, trochanter, femur, genu, tibia, tarsus, and pretarsus are just a few of the parts that make up the mite's leg. The pretarsus typically consists of two claws, a single median empodium, and a membrane pulvillus that facilitates adherence to a variety of surfaces, including the host [17], [20].

House Dust Mites can reside in mattresses, carpets, curtains, and other areas of the home. Each adult excretes 0.5 to 1 gram of flakes every day, mostly in bed. This flake may feed 1 million dust mites. Ticks survive at a temperature of 15-35°C and a humidity of 70-80%, thus they cannot dwell in dry or cold environments. These mites come in a variety of species, but the most common allergens are *Dermatophagoides pteronyssinus* and *Dermatophagoides Farinae* [17], [21–23].

Dermatophagoides require higher indoor humidity (over 70% relative humidity) and a stable temperature (24 °C). These conditions are commonly observed in mattresses [20], [24], [25]. Dermatophagoides is a genus of the order Acari, which includes the species *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f). *Dermatophagoides farinae* lays eggs over 30 days, producing about one egg per day, whereas *Dermatophagoides pteronyssinus* lays approximately 80 eggs during 45 days.

Dermatophagoides farinae lacks Malpighian tubules. *Dermatophagoides pteronyssinus*, a closely related mite, is also thought to lack Malpighian tubules. The Malpighian tubules' role is to collect metabolic waste and discharge it into the gut lumen. This role must have been taken over by other tissues in the alimentary canal because dust mite feces contain a high concentration of the nitrogenous waste product guanine. A fecal pellet, as emitted by a dust mite, is made up of three to five food balls [17], [25], [26]. The taxonomic tree of *Dermatophagoides* is as follows.

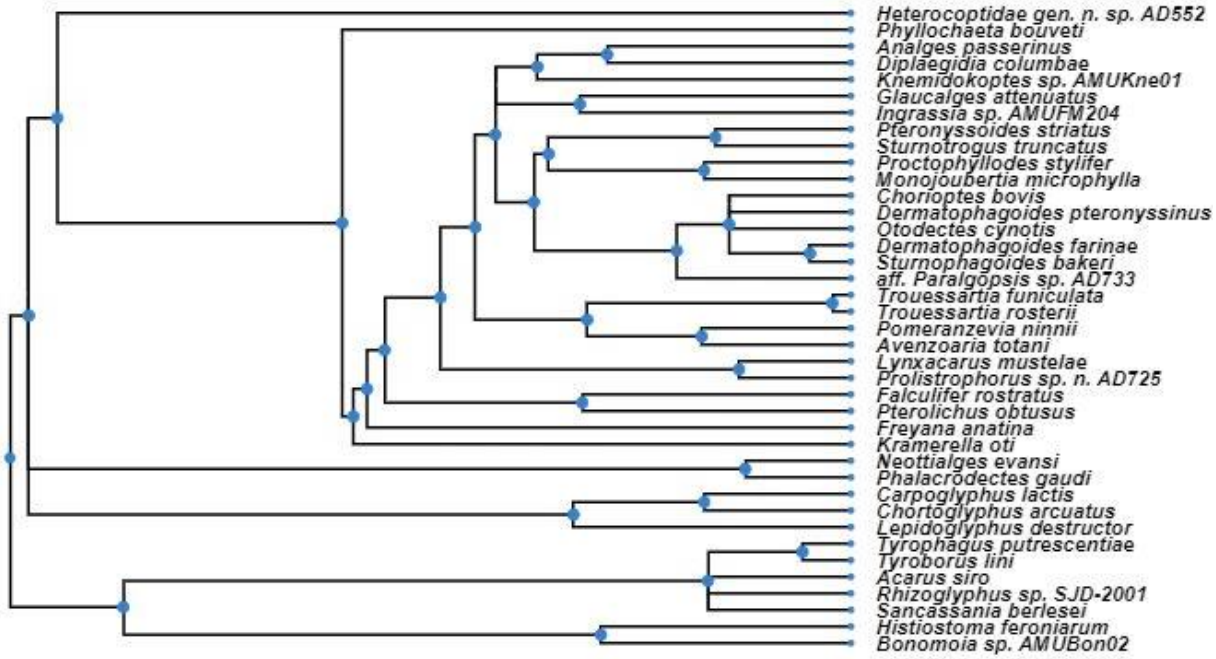

Figure 2. Phylogenetic tree of Astigmata suborder (http://timetree.org/)

3.2 Biological Activity of Group 1 Allergen *Dermatophagoides* (Der p 1, and Der f 1)

Dermatophagoides' feces and body parts include a wide range of allergens. Allergens have amino acid sequences that vary by 15-20%, which can cause cross-reactivity and act as epitopes, particularly Dermatophagoides Group I allergens (Der p 1 and Der f 1). The major allergens are Der p 1 and Der f 1, which have an IgE reactivity of 80-100 and a weight of 25 kDa [27-28].

Der p 1 is a *Dermatophagoides pteronyssinus* allergen in the form of a thiol protease with amino acid 320 and a hydrophobic region at position P2, also known as the basic residue, and active sites at positions 132,268 and 288, while Der f 1 is a *Dermatophagoides farinae* allergen with active sites at positions 132, 268, and 288. Hydrolase proteins containing 321 phenylalanine residues of amino acid length have an active site at positions 133, 269, and 288 [18], [29].

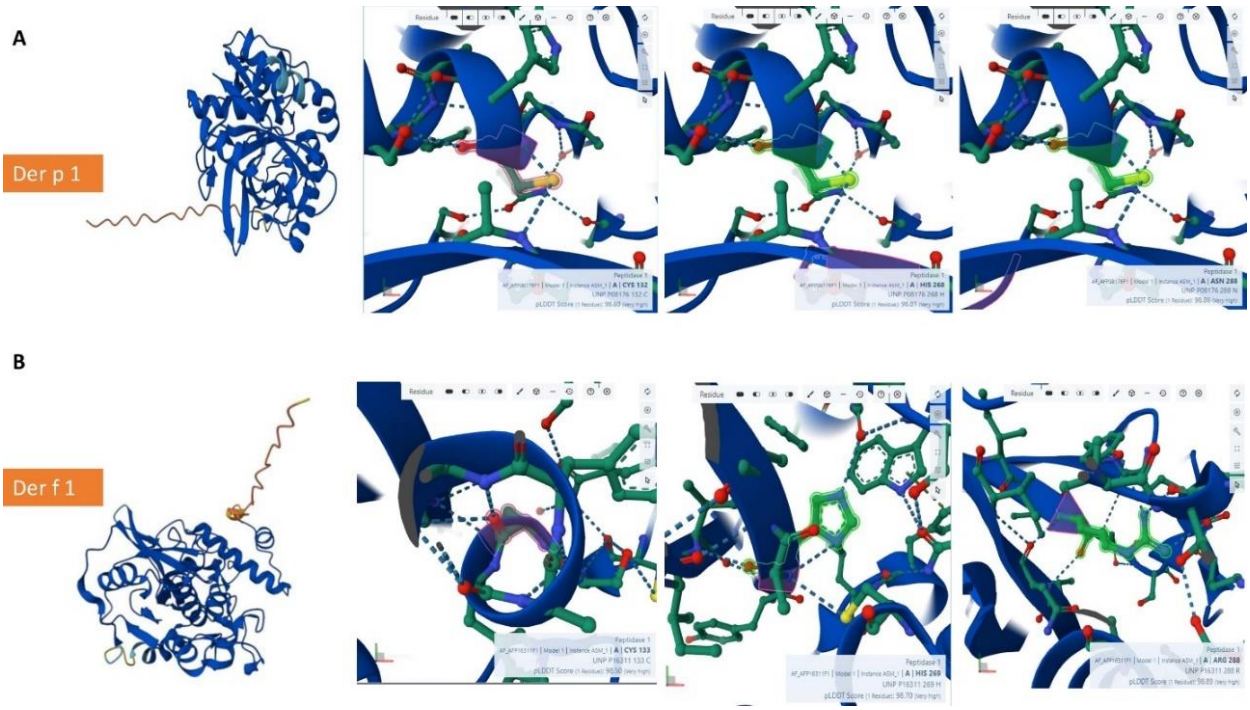

Figure 3. Structure and active sites of Group 1 *Dermatophagoides* Allergen: **(A)** Structure and Active sites of Der p 1 (Uniprot: https://www.uniprot.org/uniprotkb/P08176), **(B).** Structure and active sites of Der f 1 (Uniprot: https://www.uniprot.org/uniprotkb/P16311)

The proteolytic enzymes Der p 1 and Der f 1 can both harm tissues and boost the immune system, as illustrated in the table below.

Table 1. The activity of Der p 1 and Der f 1

Biological Activity	Results	Refferences
Mechanism of Cleavage Occludin and Claudin as tight junction protein	- Upregulation of the membrane permeability - The promotion mechanism of Innate Cell Tissues to release the alarmin cytokines IL-33, IL-25, and TSLP to recruit the host immune system	[30–32]
Cleavage of Co-Stimulatory Protein (CD40)	- Downregulation of IL-12, and IFN-γ - Downregulation of Th1 activity and changed to Th2	[33]
Dendritic Cell-Specific ICAM-grabbing non-integrin (DC-SIGN) Cleavage mechanism Interaction with Surfactan Protein (SP): SP-A and SP-D	-Inhibit opsonization and clearance mechanism	[34], [35]
Cleavage Mechanism of CD23	-Stimulation of upregulation IgE	[33],[36],
The downregulated mechanism of Antiprotease activity	- Downregulation of antiprotease	[37]

3.3 Inflammation Pathway

Allergens derived by dust mites Der p 1 and Der f 1 stimulate type II immune responses. When these mites are inhaled, they release Der p 1 and Der f 1, which contain proteolytic enzymes that cause tissue damage, leading to the release of signaling mediators and proteins such as interleukin 25 (IL-25), interleukin (IL-33) and thymic stromal lymphopoietin (TSLP), which leads to the mobilization of innate immune response cells such as dendritic cells [38], [39].

Protease activity cleaves the DC-SIGN and CD40 receptors, resulting in a decrease in type I immunological response and activation of the Th2-mediated type II immune activation pathway. This condition causes the secretion of IL-4, IL-5, IL-9, and IL-13, which raises IgE levels. Eosinophils are attracted to IL-5, which contributes to airway hyperresponsiveness, increased vascular permeability, airway remodeling, and the release of cytokines and chemokines like IL-4 [40], [41]. IL-9 attracts mast cells and basophils, IL-4 and IL-13 induce IgE isotype switching, and IL-13 modulates mucus secretion [33], [42].

IgE produced from mast cells or basophils can bind to the high-affinity IgE receptor (FcεRI). When secondary exposure to the allergen, a cross-linking mechanism takes place between the allergen and the IgE bound by mast cells. Mast cells and basophils respond by releasing vasoactive mediators such as histamine [43], [44]. These mediators promote smooth muscle contraction, increased vascular permeability and vasodilation, tissue injury, and even anaphylaxis. Furthermore, IL-13 promotes goblet cell metaplasia and increases mucus production, resulting in asthma-specific symptoms such as wheezing, shortness of breath, and a sense of heaviness in the chest, accompanied by intense coughing of varied duration, as well as restricted fluctuating airflow [45], [46]. The mechanism of allergic asthma is demonstrated in Figure 4.

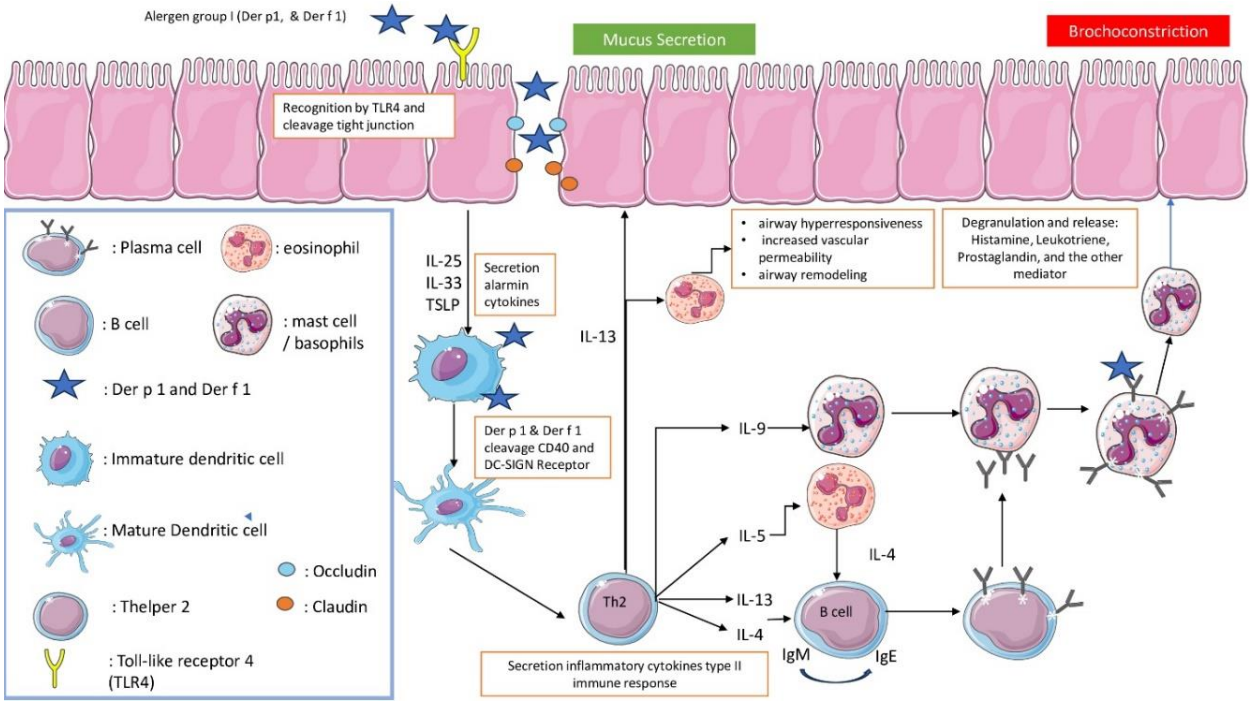

Figure 4. Allergic Asthma Pathway. Parts of the figure were created using Servier Medical Art images. Servier Medical Art is distributed under a Creative Commons Attribution 3.0 Unported License. (https://creativecommons.org/licenses/by/3.0/)

3.3.1 Isotype Switching

Isotype switching is the key mechanism in allergic asthma. The inflammatory cytokines IL-4 and IL-13 are essential for type II immune response. IL-4 and IL-13, which are generated by Th-2 cells, play a crucial role in asthma inflammation, as this cytokine is implicated in IgE isotype switching [47], [48].

The IL-4 gene is found in the 5th exon of the 5q31.1 locus, and the IL-13 gene is placed in the 6th exon of the 5q31.1 locus. Isotype switching begins with transcription at the constant heavy chain (CH) via cytokine activation of the C germline transcription (CGLTs) inducers IL-4 and IL-13 on B cells. IL-4 binding to IL-4R recruits and activates Janus-activated kinase-1 (JAK 1), JAK-3, and TYK-1. STAT6 (signal transducer and activator of transcription) is then activated. CD40L also interacts with CD40, activating tumor necrosis factor receptor-associated factors (TRAFs) and causing nuclear translocation of transcription factors nuclear factor kappa Beta (NF-κB) and activator protein 1 (AP1)[5], [49].

The synergistic interaction of IL-4R and CD40 induces of Ig germ-line epsilon (GLepsilon) transcription(CεGLTs) and Activation-induced cytidine deaminase (AID) via NF-κB, and STAT6 is required for isotype switching [47], [50], [51]. The mechanism of isotype switching and crystal structure of IL-4 and IL-13 binding with its receptors is demonstrated in Figure 5.

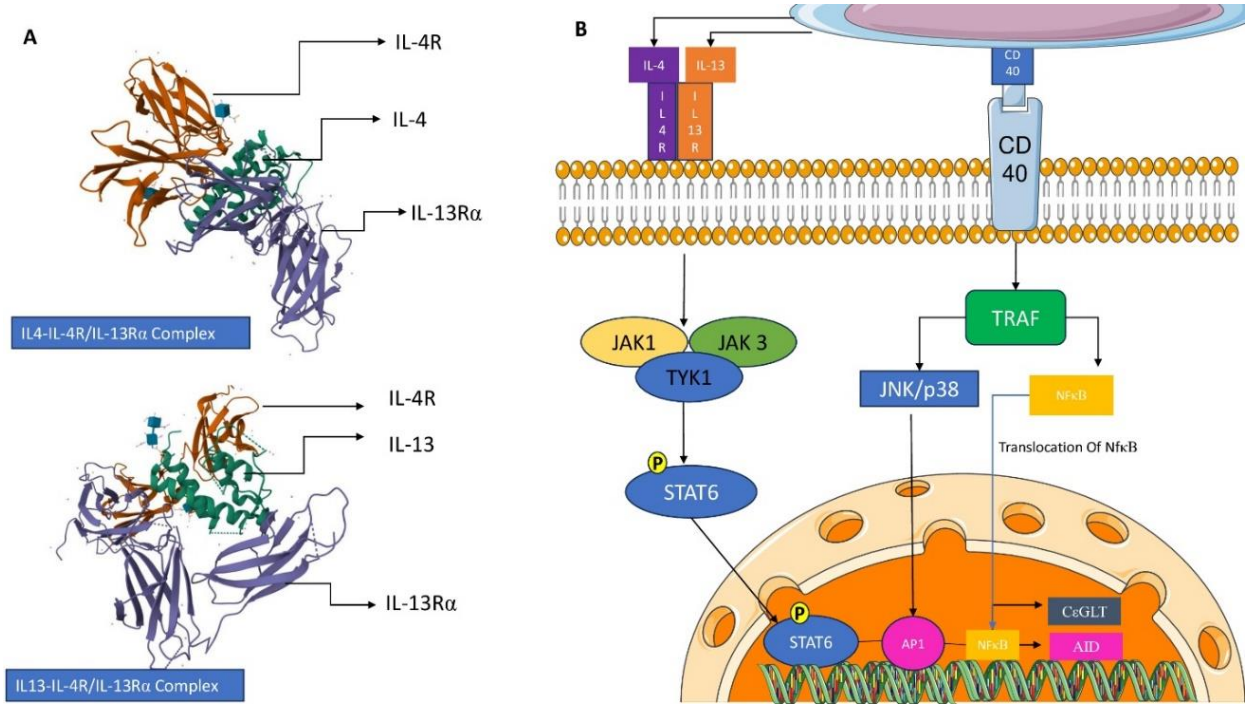

Figure 5. Crystal Structure of binding IL-4 and IL-13 with its receptors and Isotype Switching Signaling Pathway (A) Crystal Structure of IL4R-IL-4-IL13Rα Complex, and IL4R-IL-13 - IL13Rα Complex (https://www.rcsb.org/). (B) Signaling Pathway of Isotype Switching IgE mechanism. Parts of the figure were drawn using pictures from Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/)

3.3.2 Immunoglobulin E and Their Receptor

Immunoglobulin E is a kind of antibody with two light chains and one heavy chain. Disulfide linkages connect the 110 amino acids that make up each chain. The heavy chain has a structure that is identical to the IgM heavy chain and is made up of four constant region domains (Cε1–Cε4). The Cε2 and Cε3 domains of the IgG antibody isotype and the Cε3 and Cε4 domains are identical[52], [53].

Two heavy chains and two light chains make up the antibody IgE, which can bind two antigens. Four Cε dimers, designated Cε1-4, make up the Cε-terminal portion of the heavy chain. The particular IgE binding capacity for the cellular receptors Fc RI and CD23 is determined by the specific molecular structure of this dimer. IgE is more flexible when engaging with its receptors since it has a Cε-2 domain but no hinge region [54–56].

Only heavy chains with the ability to bind to cellular receptors, such as low-affinity FcεRII or CD23 receptors and high-affinity FcεRI receptors, are present in the Fc IgE component. Mast cells and basophils both express FcεRI as a tetramer [56], [57].

The extracellular domain, transmembrane helical domain, and cytoplasmic sequence are all parts of the subunit portion. The extracellular domains that separate IgE binding from IgE receptors are two. Tyrosine-based activation motifs of immunoreceptors (ITAMs) are present in the subunits. [57], [58].

In type I hypersensitivity, there is a cross-reactivity between IgE antigen and FcεRI, a surface tetramer, which can activate Syk, Lyn, and Fyn, which in turn phosphorylates LAT, PLC-1, and lymphocyte cytosolic protein 2 (LCP-2) or SH2 domain containing leukocyte protein of 76 kDa (SLP-76). When LAT binds to Grb2 and Gads, VAV and SOS are released. Asthma can be brought on by active mediators including histamine, prostaglandins, and leukotrienes that are present in the mast cell granules due to the ability of VAV and SOS to bind to PI3K and MAPK[45], [59].

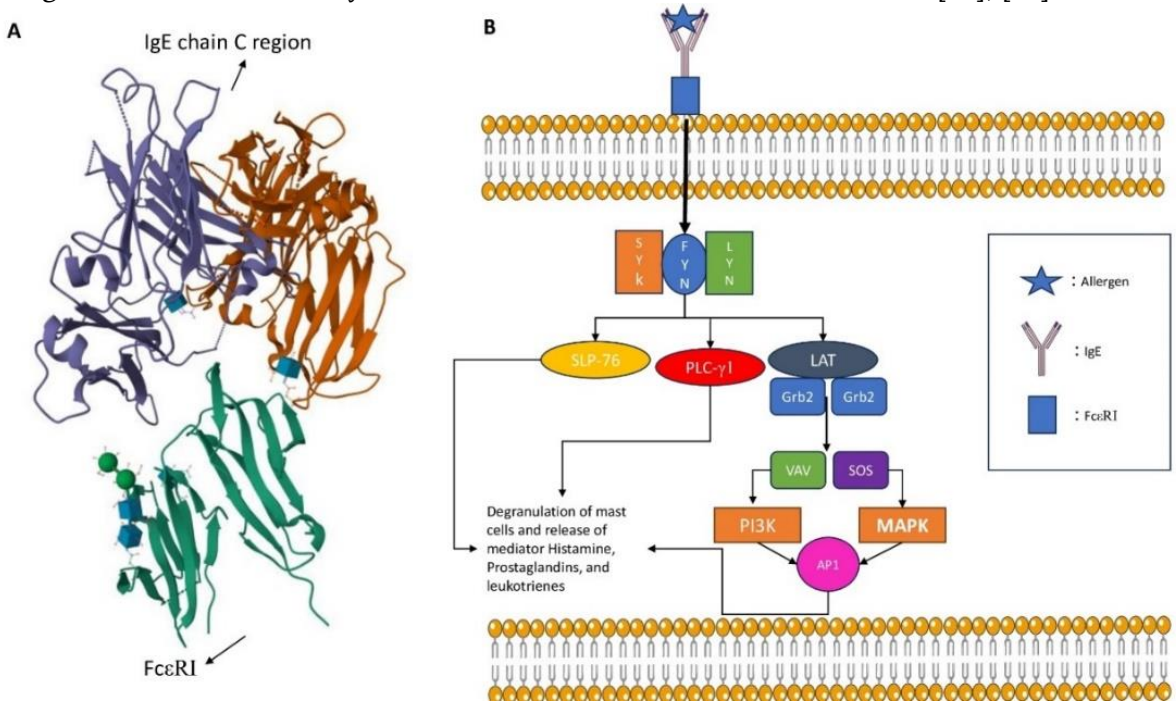

Figure 6. Crystal Structure and Signaling Pathway of Mast Cell Degranulation. (A) Crystal Structure of IgE-FcεRI complex (https://www.rcsb.org/). (B) Signaling Pathway Mast Cell Degranulation. The figure's components were created using images from Servier Medical Art. Under the terms of a Creative Commons Attribution 3.0 Unported License, Servier Medical Art is published. (https://creativecommons.org/licenses/by/3.0/)

The type II integral membrane protein known as CD23 or the low-affinity IgE receptor (FcRII) controls the production of IgE by B cells and aids in the presentation of antigens by presenting IgE immune complexes. Leucine-zipper oligomers in the shape of trimers are formed by CD23, which has a head that contains lectins and a stalk-like segment at the N-terminus. As a result of the CD23 region's susceptibility to proteolytic enzymes such as Der p 1 protease, the synthesis of IgE is increased [37], [45].

3.3 Anti-Inflammation Role to Suppress Inflammation

Anti-inflammatory cytokines are cytokines that regulate pro-inflammatory cytokines produced by particular cells, like Tregs. To regulate allergies, T regulators are activated when dendritic cells catch pathogens and release IL-10 and TGF-β [6], [60]. Transforming Growth Factor β (TGF-β) and IL-10 are cytokines that are produced by T regulators and function as immune system inhibitors. TGF-β promotes the generation and release of vascular endothelial cell growth factor and plasminogen activator inhibitor, which contributes to vascular remodeling in the asthmatic airway [61], [62].

In this review, we focused on IL-10, because Inflammatory cytokine production is inhibited by IL-10. When IL-10 binds to its receptor, IL-10R, it activates JAK1, Tyrosine Kinase 2 (TyK-2), and Signal Transducer and Activator of Transcription 3 (STAT3), which then moves to the nucleus. IL-1 receptor antagonist (IL-1RN) and suppressor of cytokine signaling 3 (SOCS-3) are two examples of suppressor genes that are produced as a result of STAT3 binding to STAT-binding areas [63], [64]. On the other hand, IL-1RN blocks IL-1 from attaching to its receptor, reducing pro-inflammatory signals. Furthermore, STAT3 can inhibit STAT6, which stops the synthesis of IL-4 and IL-13. This may lessen the generation of Th2-secreting proinflammatory cytokines like IL-4, which might lead to isotype switching and increase IgE synthesis [64], [65].

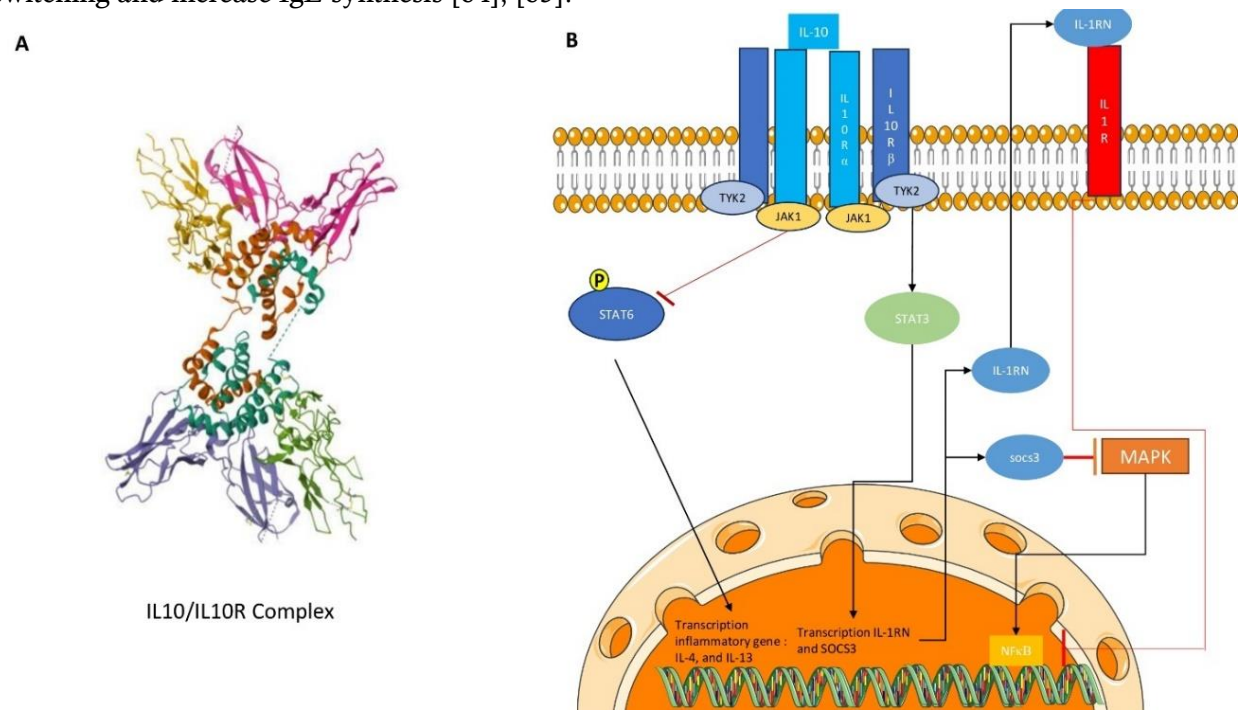

Figure 8. IL-10 and Its Mechanism of Action. (A) Crystal Structure of IL-10/IL-10R complex (https://www.rcsb.org/). (B) Mechanism of action IL-10. The figure's components were created using images from Servier Medical Art. Under the terms of a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/)

Another mechanism of IL-10 can induce a more dominant isotype switching to Immunoglobulin G4 (IgG4). When IL-10 attaches to B cell receptors, B cells develop into plasma cells and change their isotype to IgG4, which suppresses the release of mediators from mast cells like histamine and prevents hypersensitive reactions [15], [66].

4. Conclusion

Asthma is a complex disease characterized by chronic inflammation in the airways. It is therefore defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough of varying severity and duration as well as the degree of airway obstruction. Allergic asthma is a type of asthma that is very easy to recognize. Allergens, such as the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. This species has group 1 Allergens (Der p 1, and Der f 1) which contain protease. This enzyme cleavages DC-SIGN and CD40 which can downregulate Th1 response and induce Th2 response. Th2 releases cytokines that produce hypersensitivity, especially IL-4, and IL-13 which can induce B cells to release Immunoglobulin E. Immunoglobulin E binds to its receptor in mast cell to activate degranulation mechanism. Degranulation of mast cells releases mediators like histamine, prostaglandin, etc. causing hyper muscle contraction. Inflammatory mechanisms can lead to allergic asthma, but inflammation can be inhibited in the presence of IL-10-releasing Tregs that can suppress type 2 immune responses and alter phenotype switching of IgG4 in B cells.

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