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The Impact of Forkhead Box Protein P3 (FOXP3) on Allergic Asthma: Review Article

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ABSTRACT
Background: Asthma is a major health problem. Increases the price tag as well as the number of people affected by it. The pathogenesis of allergic asthma has been linked to a number of genes. The FOXP3 gene have recently been studied for their potential relevance in the protection against development of allergic asthma.
Objective: Assessment of possible importance of Forkhead Box Protein P3 (FOXP3) among Allergic Asthma.
Methods: PubMed, Google Scholar, and Science Direct were scoured for information on FOXP3, polymorphism, and allergic asthma. The authors also reviewed the relevant literature, however only the most recent or comprehensive studies from December 2005 to January 2022 were included. Documents written in languages other than English have been disregarded because translation resources are inadequate. Unpublished articles, oral presentations, conference abstracts, and dissertations were not included because they were not considered to be part of major scientific projects.
Conclusion: The FOXP3 gene located on Xp11.23 has a great importance in immune hemostasis and prevention of a wide variety of diseases, including a number of allergy-related conditions. Therefore, it appears to prevent allergic disease, however, additional research is needed to determine how it affects asthma.
Keywords: Forkhead Box Protein P3, Allergic asthma.

INTRODUCTION

Asthma is a wide-ranging condition characterized by a history of wheezing, shortness of breath, chest tightness, and cough in addition to a history of variable expiratory air flow limitation [(1)]. The most prevalent form of asthma is allergic asthma, which is defined by the development of characteristic asthmatic symptoms following exposure to airborne allergens due to the IgE's sensitivity to these allergens. Inflammation of the airways of type 2 (T2) is the etiology of allergic asthma [(2)]. It is estimated that 300 million individuals around the world suffer from asthma. Using consistent methods, researchers have been able to determine that between 1 and 18% of the world's population suffers from asthma, with the condition affecting both young and old [(1)]. Adjusted prevalence estimates for asthma in the Middle East ranged from 4.4% to 7.6%, lower than those reported for Europe and North America [(3)].

The most common form of asthma, known as allergic asthma, typically manifests in early childhood and is associated with a personal or family history of other allergic disorders. Sputum analysis before treatment often demonstrates eosinophilic airway irritation in these patients. Patients with this subtype of asthma typically benefit from inhaled corticosteroids (ICS) (Figure 1) [(1)].

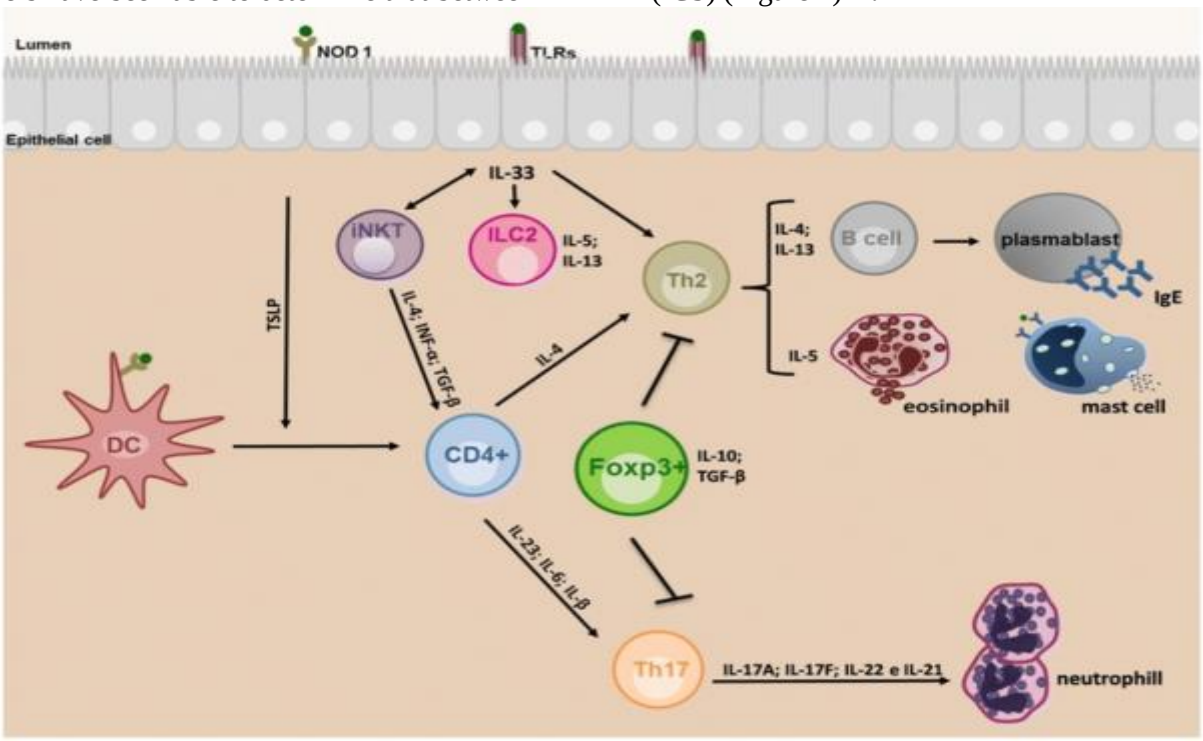

Figure (1): Pathophysiology of development of Asthma [(3)]

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Age and sex presentation of asthma:

Asthma is more common in boys than in girls. Boys are nearly twice as likely as girls to have asthma before the age of 14. In adulthood, asthma is more common among women than males. The differences between the sexes tend to disappear as kids get older. Males are born with smaller lungs than girls, but grow into larger lungs as they mature, which is one example of how sex differences can arise [(1)].

Asthma phenotypes:

Allergic asthma: It typically begins in childhood and is associated with a history of allergic illnesses such as eczema, allergic rhinitis, or food or drug allergies. Allergic asthma is the most easily recognized phenotype of asthma. Sputum generated by these people is often examined pre-treatment demonstrates eosinophilic airway irritation. Patients with this subtype of asthma typically benefit from inhaled corticosteroids [(1, 2)].

Non-allergic asthma: There are cases of asthmatic patients whose allergies are not a contributing factor. Patients with non-allergic asthma frequently have a poorer short-term response to inhaled corticosteroid (ICS) treatment, despite the fact that their sputum may have a neutrophilic, eosinophilic, or paucigranulocytic cellular profile [(2)].

Adult-onset (late-onset) asthma: Asthma can strike for the first time in adulthood for some people, particularly women. Patients who are not allergic typically require higher dosages of ICS or show greater resistance to treatment. It is important to rule out occupational asthma, or asthma caused by exposures at work, when a patient presents with adult-onset asthma [(2)].

Asthma with persistent airflow limitation: Airway limitation might be permanent or temporary for some patients with persistent asthma. The reworking of the airway wall is responsible for this change.

Asthma and obesity: Even if their eosinophilic airway inflammation is low, some obese asthmatic patients still experience severe respiratory symptoms [(2)].

FOXP3 (Forkhead Box Protein P3):

Proteins belonging to the transcription factor family can bind DNA or RNA. The transcription process can be regulated by transcription factors binding to certain promoter or enhancer sequences in a DNA region. Selective activation or inhibition of transcription factor function is often the final step in intracellular signal transduction and is mediated by other cellular proteins [(4)].

The transcription factor family known as Forkhead Box (FOX) is necessary for cell division, survival, and differentiation, which are all tightly regulated by proteins. FOXP3 (Forkhead Box Protein P3) is a transcription factor that belongs to the Foxp3 protein family. Immunity cannot function without regulatory T cells [(5)]. It has direct effects on the maturation and function of conventional T-cells and is essential for maintaining immune system homeostasis [(6)].

The nature of the activity of the Foxp3 protein is determined by its interactions with other transcription factors in the cell. It can inhibit as well as promote transcription [(7)].

Phenotype of regulatory T cell:

The following markers are frequently used to identify the primary Treg subtypes: CD4 (T helper cells), CD25 (IL-2R), CD127 (IL-7R), and FOXP3-transcription factor (a nuclear Forkhead Box transcription factor). Natural (nTregs) and inducible (iTregs) Tregs can be separated based on neuropilin-1 expression (Nrp-1) [(8)]. In particular, nTregs (CD4+ CD25+ CD127low FOXP3+) are thymus-derived neuropilin-1+ T cells, whereas iTregs are categorized in iTreg (CD4+ CD25+ FOXP3+), Th3 (CD4+ CD25low FOXP3+) secreting IL-10 and TGF-β (transforming growth factor-β), and Tr1 (CD4+ CD25low FOXP3−) secreting IL-10 [(9)].

Structure of the Foxp3 Protein:

Genomic investigations have pinpointed the human FOXP3 gene's position on the X chromosome, specifically at Xp11.23 on the p arm [(10)], there are 12 exons in this gene [(11)].

A protein with 431 amino acids, a molecular weight of 47.27 kDa, and an isoelectric point of 8.62 is encoded by the FOXP3 gene. Hydrophobic amino acids make up 47.33% of the FOXP3 protein's structure, while hydrophilic amino acids account for 52.67%. There are three other isoforms that have been shown to exist in human bodies (isoforms 2, 3, and 4). Proteins can vary in secondary structure, isoelectric point, and amino acid composition based on the length and number of their constituent of amino acids [(7)].

The structure is described as a "winged helix" because of the helix-turn-helix shape of its three-helices in its centre. DNA-binding Forkhead domains are 110 amino acids in length. Thus, the Forkhead family of transcription factors has a well-defined three-dimensional form and a specific way of recognizing DNA [(12)].

The four members of the FOXP family are simply designated as FOXP1–FOXP4. Stomach, brain, and lung FOXP1, FOXP2, and FOXP4 expression suggests an adult-maintained role in embryogenesis. FOXP1 and FOXP2 are activated in the immune system. Formation and co-expression of the FOXP1/FOXP3 heterodimer have been documented. FOXP3 is exclusively expressed in CD4+ CD25+ T cells, whereas FOXP1 is present in both CD4+ CD25+ and CD4+ CD25- T cells [(13)]. The human FOXP3 gene is found at Xp11.23 on the X-chromosome. FOXP3 is made up of four primary domains, and each domain's function contributes in a different way to the whole function of FOXP3 (Figure 2) [(14)].

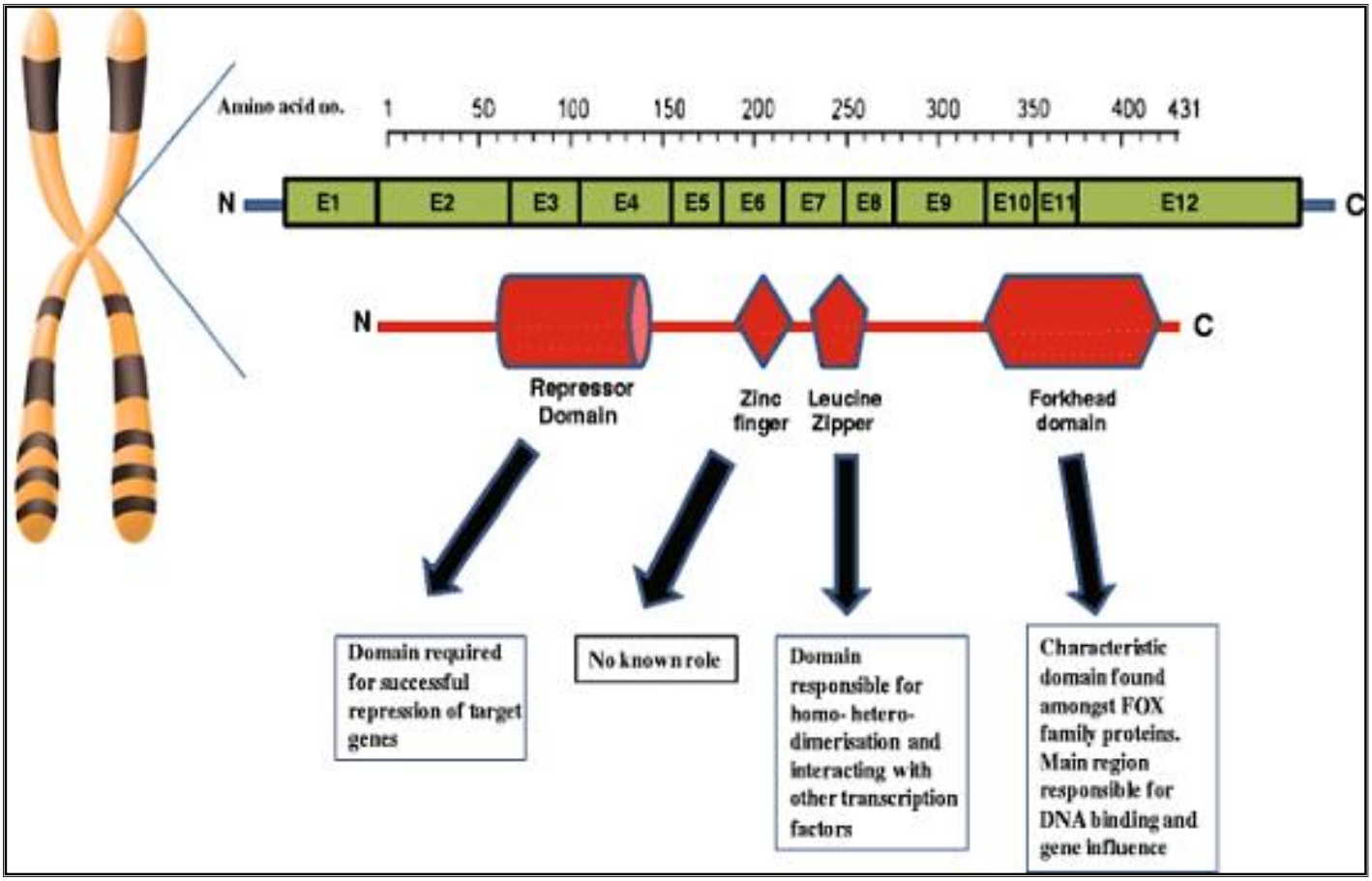

Figure (2): The human FOXP3 gene and protein's structure and functions.

Function of regulatory T cell and FOXP3 in human body:

Maintaining a healthy immune system and protecting against inflammatory diseases are both tasks for which Tregs are useful. Rheumatoid arthritis, Type 1 diabetes, multiple sclerosis, as well as asthma are just a few of the autoimmune, inflammatory, and allergy illnesses that have been related to compromised immune function [(9)].

It's crucial that TGF-β and IL-2 are necessary for the creation of both Treg lymphocyte populations (nTregs and iTreg) and perform similar tasks in the maintenance and survival of both. For nTregs to develop in the thymus in response to intrinsic antigens, the intrinsic antigens must have a high affinity with the MHC complexes [(15)]. To trigger the negative feedback process, T cells require CD28 co-stimulation to express CTLA-4, a protein that inhibits the cluster of differentiation 28 (CD28) signal [(16)].

Studies on gain-of-function have shown a connection between FOXP3 and Treg. In addition to FOXP3 expression, also antigen for cytotoxic T cells (CTLA-4), glucocorticoid-induced TNFR-related protein (GITR), and chemokine receptor 4 (CCR4) (CC chemokine receptor type 4) [(17)], and CD62L (L-selectin) are all expressed by natural nTreg cells [(18)].

Because nuclear FOXP3 inhibits the inflammatory response of Th2 cells triggered by allergen exposure, it has been proposed that genetic polymorphisms and epigenetic pathways that favour its expression can contribute to the development of asthma [(19)].

It is possible that FOXP3 regulates the production of molecules that mediate suppression since it can convert naive T cells into Treg cells that can suppress immunological responses in vivo and in vitro. To better comprehend Treg cells' suppressive capacity, it may be necessary to identify FOXP3 gene targets [(20)].

Reduced nuclear factor of activated T cells (NFAT) activity, as mediated by FOXP3, is essential for immune system regulation because it prevents activated protein1(AP-1) from binding to NFAT and activating the inflammatory pathway. The primary activities of FOXP3, which binds to NFAT in its promoter region, are to up-regulate CTL-4 and CD25 while simultaneously suppressing IL-2 and IL-4 production (Figure 3) [(21)].

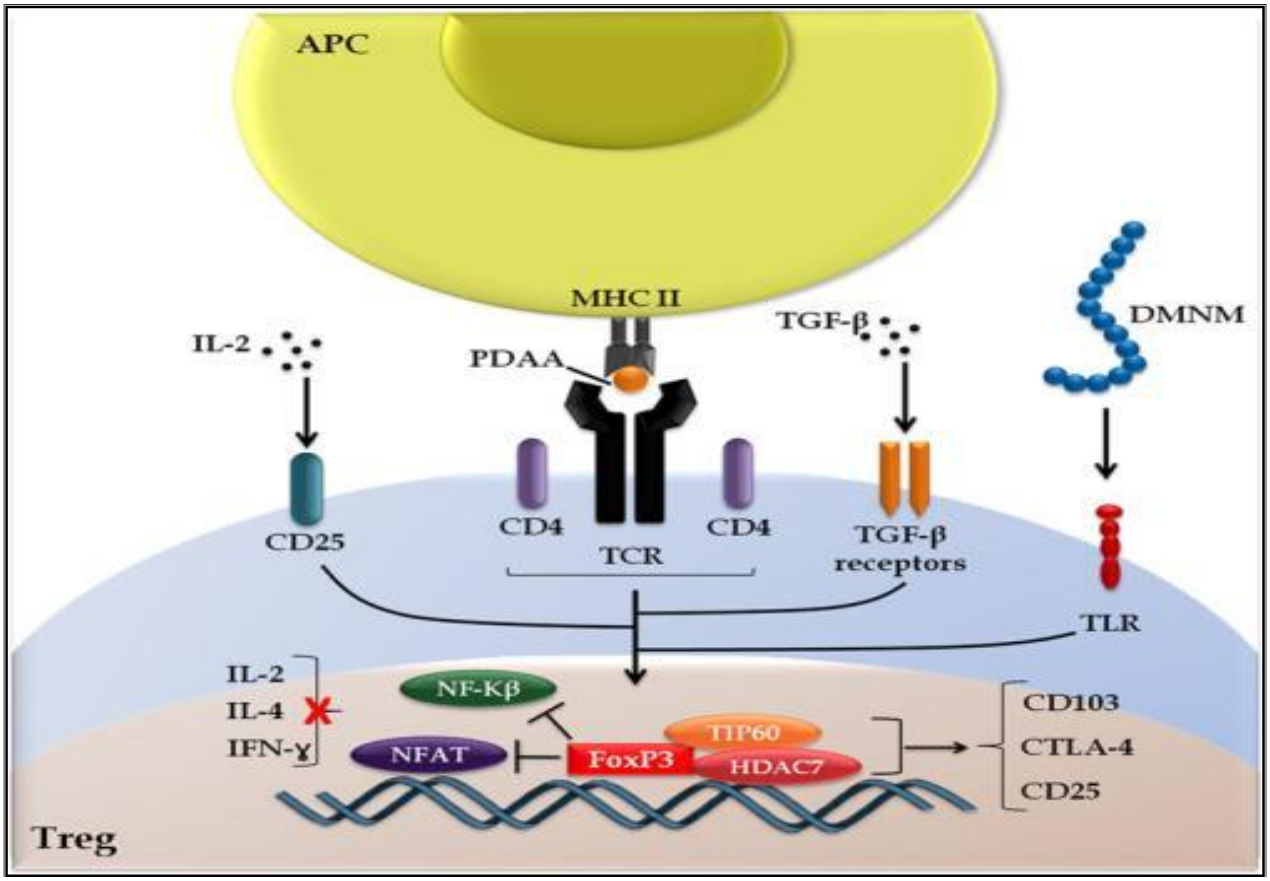

Figure (3): Forkhead box protein 3 signaling (FOXP3).

After autoantigen-derived peptides are presented by antigen-presenting cells (APC), T cell receptor (TCR) interaction with major histocompatibility complex class II (TCR-MHC II) activates FOXP3 (PDAA). Intestinal microbiota-derived metabolites (DMNM), interleukin (IL-2), and transforming growth factor (TGF) are all examples of alternative stimuli. Although NF-kappa B and NF-kappa T do not interact with the activating cytokine cell response genes (IL-2, IL-4, and interferon-), FOXP3 does through its interactions with chromatin remodeling factors (TIP60 and HDAC7). FOXP3 has a dual role in transcriptional activation and repression, as it also increases the expression of genes (CD103, CTLA-4, and CD25) associated with the activation of regulatory T cells (Tregs) [(22)].

Role of regulatory T cell and FOXP3 in asthma:

Reactive airway disease and bronchial tissue remodeling have both been linked to defective Treg function. However the role of Tregs in the etiopathogenesis of severe asthma is still unknown. Researchers have found that a lack of regulatory responses plays a role in the immunopathogenesis of severe chronic asthma [(23)].

Protecting against mucosal damage through the maintenance of immunotolerance is a key function of both FOXP3+ natural Tregs and peripherally produced Tregs [(24)].

Several preclinical and clinical studies of asthma have reported the presence of diverse Treg subsets, including natural Tregs, induced Tregs, and CD8+ Treg cells. All of which play immunosuppressive roles against the ongoing cellular and tissue dysfunctions. The need for Treg-cell based immunotherapies has increased dramatically as a result [(25)].

Depletion of FOXP3+ Tregs increases lung allergic responses, while reconstitution decreases them, and in certain examinations of airway hyperresponsiveness. Although, Tregs' function in asthma remains controversial, numerous studies have shown their therapeutic efficacy [(26)]. Instead, it has been shown that depleting Tregs before sensitization is enough to amplify lung inflammation hyperresponsiveness [(27)].

It has been established that Tregs transferred by adoption are sufficient for attenuating inflammation before tissue inflammation and microvascular healing begin [(28)]. These studies demonstrate the importance of antigen-specific FOXP3+ Tregs in reducing allergic inflammatory responses and hyperreactivity, further suppressing existing inflammation, and preventing airway remodeling when administered after disease onset [(29)]. Tregs have been used therapeutically in the reduction of asthma inflammation and the generation of desirable immunosuppression in both clinical and experimental settings (Figure 4) [(30)].

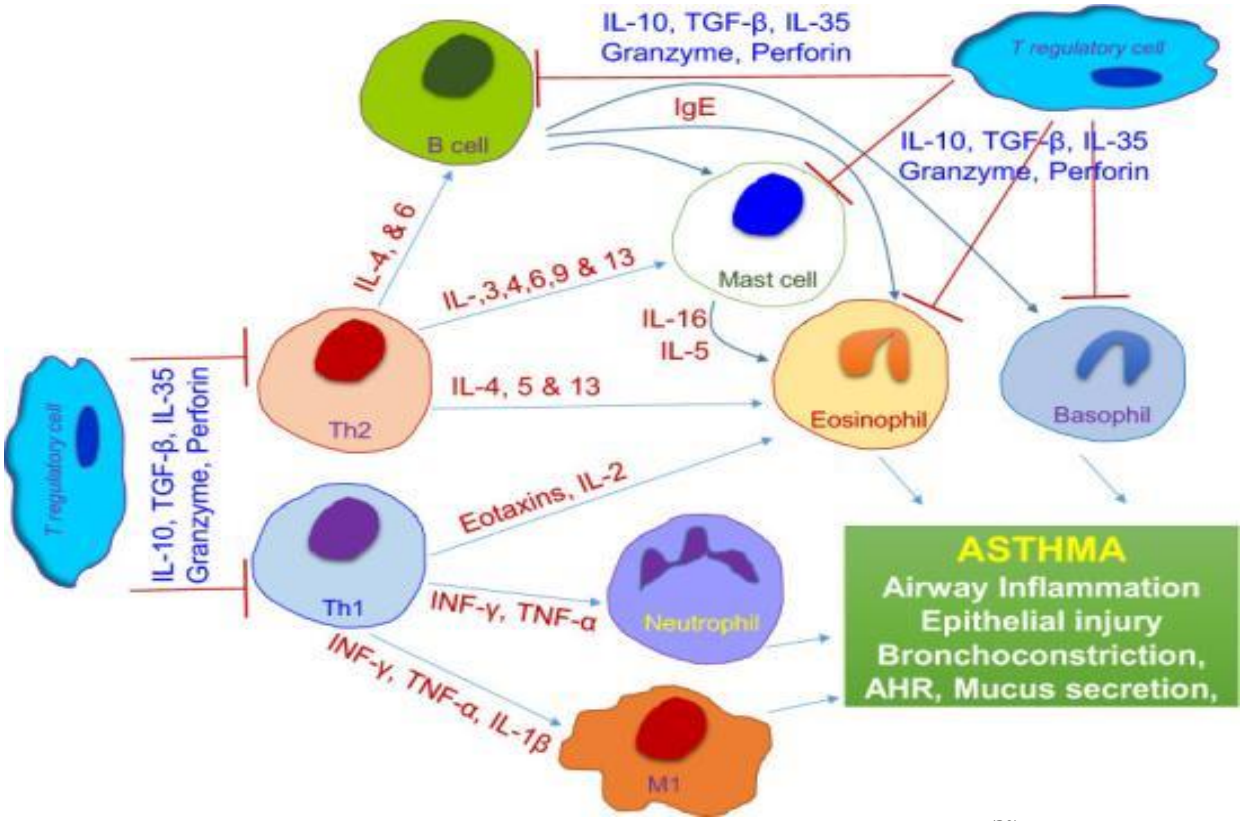

Figure (4): Asthma inflammation and immune system activation [30].

CONCLUSION

Although the FOXP3 has been linked to a variety of allergy illnesses, its role in the development of asthma remains poorly understood. Epigenetic alterations in the FOXP3 locus of Treg cells have been linked to asthma phenotypes, according to several lines of evidence.

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