Role of interleukin-4 and their antagonistic effect in asthma

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Abstract

Asthma is a chronic inflammatory disease of the lower airways, characterize by wheezing cough, chest tightness along with inflammation of airway and shortness of breath. Allergens like environmental substance are predispose asthmatics patients to allergy. Mast cells produced interleukin (IL)-4 which either activate signal transducer and activator of transcription 6 (STAT-6) pathway that involved in differentiation of naïve T-cells to TH2 or activation of TH2 cells indirectly. The aim of the current context is to present role of IL-4 in asthma and effect as antagonist. IL-4 results in increased mucus production and involve in IgE synthesis from B cells. IL4 facilitate chemotaxis and aid in displaying of VCAM-1 which attract eosinophil basophils monocytes T-lymphocytes to blood vessel. IL4 inhibit apoptosis either by preventing decrease in BCL-2 level or binding of FasL to Fas (cd32) receptor which result in acute allergic response. Elevated level of IL-4 has greatly adverse impact on asthmatic patients so by decreasing the level of IL-4 will greatly reduce asthma phenotype.

Introduction

Asthma is a chronic inflammatory disease whose treatment is only symptomatic, and it cannot eliminate completely.[1] Although asthma is chronic disease it has frequent exacerbations which can be fatal. Asthmatics are allergic to allergens like House dust, air pollutants, diesel smoke, tobacco smoke, mold and cockroach infestation.[2] Incidence of asthma is on the rise and is believed to be associated with increased urbanization and industrial development. Hygiene hypothesis is also believed to play some role.[3,4] Clinical symptoms of asthma include chest tightness, wheezing cough and shortness of breath.[2]

In adults asthma prevalence is high in females but in young children it is more prevalent in males, it may be related to females working in poorly ventilated kitchens where coal or raw wood is used to produce fire.[5] Dendritic cells are antigen presenting cells they present the antigen to TH2 cells these further produce cytokines such as IL-4 IL-5 IL-9 and IL-13.[2] The aim of this context is to provide the role of IL-4 in pathogenesis of asthma as well as their antagonistic effect.

Role of IL-4 in asthma

Gene responsible for production of IL-4 is found on chromosome 5q31.[3] IL-4 is produced by mast cells and Th2 cells along with other cytokines *i.e.* IL-5 IL-9 and IL-13(6). IL-4 plays important role in differentiation of TH0 type cells to TH2 type cells indirectly, in this way it acts as positive feedback and amplifies inflammatory response even further.[7,8]

Signal transducer and activator of transcription 6 (STAT-6) pathway is also involved in differentiation of naïve T-cells to TH2, and this pathway is activated by IL-4 binding to its receptor. IL-4R alpha is the receptor at which IL-4 binds and activates Janus kinase (JAK-3) present adjacent to IL-4R on a GammaC chain which phosphorylates the tail (cytoplasmic end) of IL-4R.[9]

Phosphorylation of IL-4R results in release of STAT-6 from receptor which forms a dimer and enters the nucleus and start transcription of genes which include CD 23, MHC class2 in B-cells and IL-4 IL-13 in T-cells along with exotoxin in fibroblasts. They amplify the inflammation causes mucus production[9] (Figures 1-4).

IL4 is involved in secretion of IgE from B-cells, in chemotaxis and it also helps in displaying of VCAM-1 on the endothelial surface.[10] These VCAM-1 helps in firm adhesion of eosinophils basophils monocytes T-lymphocytes to blood vessel which is followed by diapediasis from vessel into the tissue.[11]

IL-4 is believed to be responsible for the secretion of IL-8 and TNF- alpha, both agents increase the level of neutrophils in lung tissue. IL-8 is involved in chemotaxis of neutrophils which results in the production of O_2, matrix metalloproteinase-9 (MMP-9), leukotrienes-4 (LTB-4), and platelet activating factor (PAF). This results

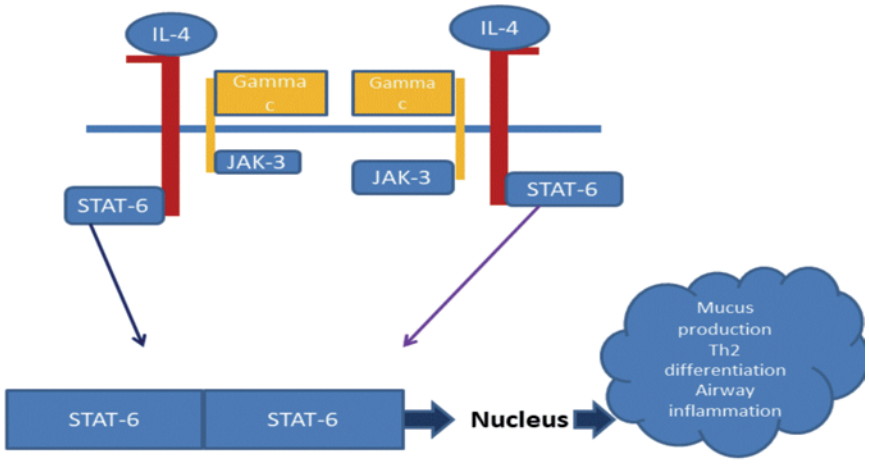

Figure 1. Interleukin (IL)-4 enhancing inflammation through signal transducer and activator of transcription 6 (STAT-6) pathway.

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in accumulation of eosinophils within and near the airway.[12]

IL-4 is also believed to increase obstruction of airway by increased secretion of mucus.[10] Indirectly IL-4 maintains the acute allergic response by inhibiting apoptosis of T-lymphocytes and eosinophils.[10] Eosinophil presence is associated with persistence of asthma.

There are two mechanisms with which IL-4 prevents apoptosis one is to prevent decrease in the level of proapoptotic protein BCL-2.[13,14] 2nd is to prevent binding of ligand FasL to Fas (cd32) receptor expressed on T-lymphocyte surface. Some studies have suggested a mutation in the Fas receptor which makes them resistant to apoptosis.[10]

IL-4 levels are found in serum, BALF and mucus secretion in asthmatic patients. IL-4 when nebulized to mild asthmatics resulted in them developing severe asthma.[13,15]

IL-4 and IL-13 are normally found to be in lower conc. within the body. They are expressed in higher conc. when body deviates from the homeostatic conc.[16] IL-4 initiates inflammation by initially bonding with IL-4α receptors, it leads to a conformational change leading to bonding with IL-13Rα1 chain. IL-13 bonding results in weak tyrosine phosphorylation. This degree pattern This helps in maturation of macrophages. IL-4 using STAT-6 pathway is associated in inflammation of asthma, whereas IL-13 is mostly associated with the expression of ulcerative colitis. IL-13 performs in a manner similar IL-4 and amplifies asthmatic inflammation.[17] Structure of IL-4 and IL-13 receptors are much similar. IL-13R consists of IL-13Ra1 or a2 chain that binds to IL-13 and IL-4Ra chain.[17] For signal processing both cytokines use STAT-6 dependent domains, which is common to both cytokine receptors. Cell response is similar with either IL-4 or IL-13.[18] IL-4 has played a prominent role in initial development of Th2 during initial sensitization, while IL-13 has been released and expresses more important role during secondary antigen exposure.[19]

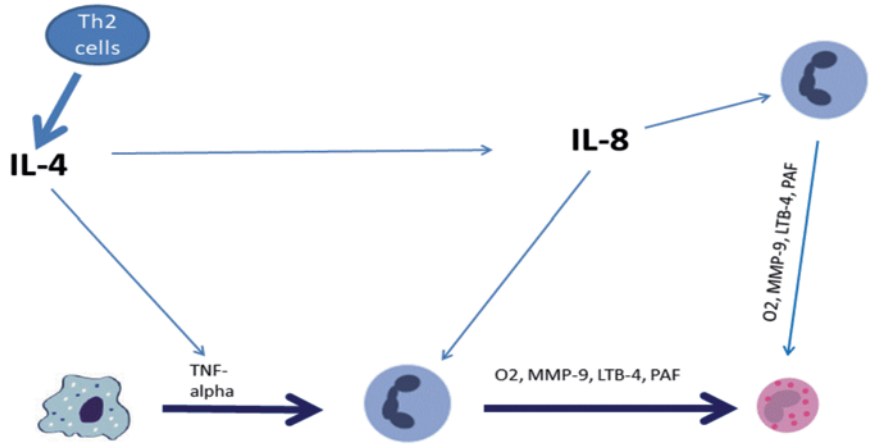

Figure 2. Recruitment of neutrophils under the umbrella of interleukin (IL)-4.

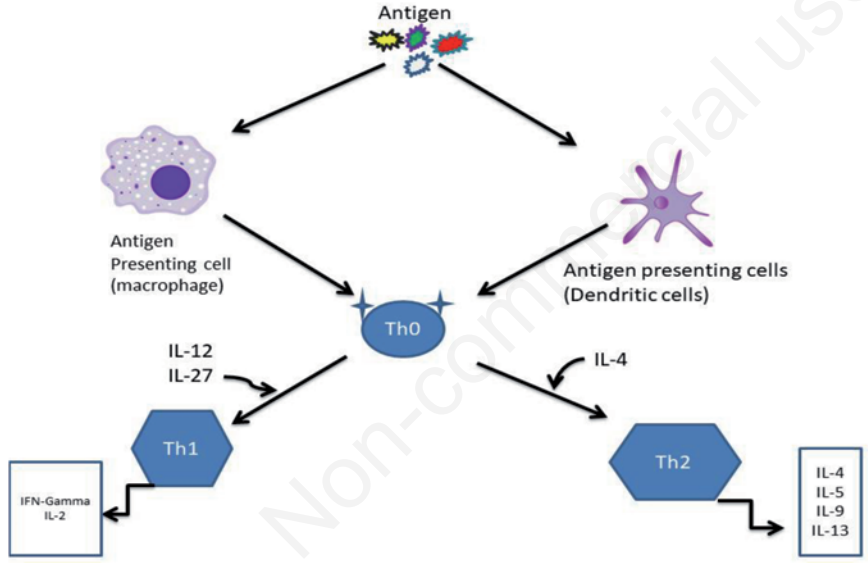

Figure 3. Pathway for activation Th2 cell response and positive feedback caused by interleukin (IL)-4.

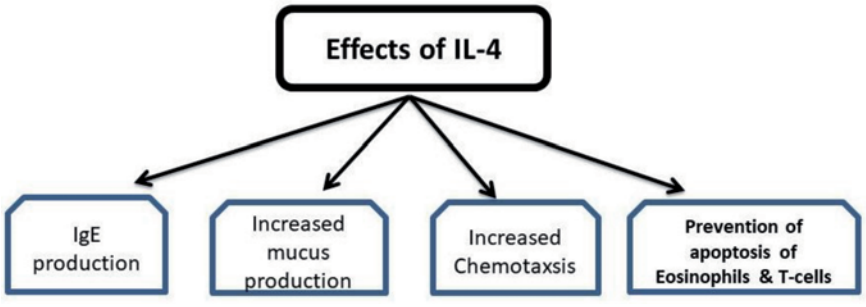

Figure 4. Effects of increased interleukin (IL)-4 production.

Effect of IL-4 antagonists

All this evidence points to us that if we decrease the level of IL-4 in asthmatic patients it will result in improvement.

However, IL-4 antagonist therapy has shown mixed results. It does improve FEV1 and there are few exacerbations compared to placebo after corticosteroid withdrawal.[20] IL4 antagonist only reduced eosinophils in tissue by 55% and bone marrow eosinophil by 52% after continued treatment for 20 week period. Corticosteroid at the same time diminish eosinophils within a tissue. There is also suggestion that IL-4 is not the only cytokine with asthmatic effect but combination of others which also play important role in pathophysiology of asthma.[6]

Selective targeting of IL-4 by nebulizing IL-4R has resulted in improved FEV1 and improved response to methacholine challenge.[10,20]

Another IL-4 antagonist pitrakinra which is administered through inhalational route is found to decrease level of nitric oxide through forced expiration, this indicates decreased in inflammation level.[9,21]

Selective STAT-6 inhibitors like YM-341619 hydrochloride are found to prevent differentiation of T-cells into TH2 cells in the spleen of mice. They also found to decrease level of plasma IgE both of which point that it has some degree of anti-inflammatory property.[9]

IL-4 is involved in parasitic infections so IL-4 inhibition can lead to increased incidence of parasitic infections, but asthma is rarely endemic in areas where parasitic infections can occur. IL-4 is also involved in placenta and forms immune privilege inhibiting it can cause some reproductive concerns.[10,22] The current study suffers with some notable limitations that were not carried out in accordance another study.[23]

Conclusions

IL-4 is an important cytokine which along with other cytokines plays an essential role in the pathogenesis of asthma. IL-4 antagonists do give beneficial response, but they are in early phase studies and have shown some degree of adverse effects. As asthma prevalence is on the rise especially in developing countries it is of utmost importance to find definitive and permanent cure as soon as possible. IL-4 can be that pathway which can lead us to asthma permanent management protocol but for that more clinical research needs to be conducted on this pathway.

Limitations of the study

Study is primarily a review study conducted through various articles data collected through Google scholar. It must also be kept in mind that inflammatory process does not occur with one or two cytokines involvement. It is a combination of cascade of processes occurring with the human body. Primarily inflammatory process is a protective response of body which unintentionally causes a lot of damage and there are mechanisms designed to keep it in check. But unfortunately, we have only tried to explain IL-4 role in these inflammatory procedures.

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