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Neena Philips* and Mathew Samuel

School of Natural Sciences, Fairleigh Dickinson University, Teaneck, NJ 07666, USA

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***Corresponding author:** Neena Philips, Professor of Biology, Fairleigh Dickinson University, Teaneck, NJ 07666, USA, Tel: 201 692 6494; E-mail: nphilips@fdu.edu; neenaphilips@optonline.net

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Review Article

Inhibition of Interleukin-4 Signalling in the Treatment of Atopic Dermatitis and Allergic Asthma

Abstract

Atopic dermatitis and allergic asthma result from amplified immune response to environmental antigens, and allergic reactions from released IgE, histamine, leukotrienes and cytokines. Environmental antigens immune cells, of innate and adaptive immunity, to stimulate interleukin-4 (IL-4) mediated activation of T_h2 cells and subsequent isotype switching of B cells to produce IgE antibodies, responsible for the clinical manifestation of atopic diseases. The IL-4 receptor alpha chain (IL4Rα), which mediates IL-4 signaling, is common to IL-4 and IL-13 receptors, with IL-13 being an associated cytokine in the allergic response. US Food and Drug Administration recently approved dupilumab, which blocks IL4Rα for the treatment of moderate to severe atopic dermatitis. In controlled trials, dupilumab counteracted the allergic response and the clinical symptoms of dermatitis and asthma, and dupilumab was more effective than other available treatments. The primary safety concern of dupilumab is conjunctivitis and its long-term safety, which is unknown.

Introduction

Atopic dermatitis and allergic asthma (asthma) result from amplified immune response to environmental pollutants, irritants or toxins (antigens). A key player in the amplified immune response is interleukin (IL)-4 signaling through IL-4 receptor alpha (IL4Rα), which also mediates IL-13 signaling. Hence, the specific inhibition of IL4Rα by dupilumab, recently approved by US Food and Drug Administration (FDA) for atopic dermatitis, holds promise in the treatment of atopic dermatitis and asthma. We review the immune response to antigens and its counteraction by duplilumab.

Inflammation and Adaptive Immunity: Atopic Dermatitis and Asthma

Immune cells: Antigens are the predominant cause of skin and lung inflammation and adaptive immunity, and thereby atopic dermatitis and asthma. The skin and lung epithelium respond to infection or antigens through innate and adaptive immunity. The cells of the innate or non-specific immunity include macrophages, dendritic cells and granulocytes (neutrophils, eosinophils, basophils) [1,2]. The cells of the adaptive or specific immunity are the B lymphocytes, and the T lymphocytes [1,2]. The B cells produce antibodies or immunoglobulins against epitopes in antigens; and neutralize, opsonize or agglutinate antigens for removal by the innate immune cells [1,2]. There are 5 classes of antibodies, IgG (predominant), IgA, IgM, IgE, and IgD [1,2]. The IgE antibodies are responsible for the allergic response; present in negligible amounts in normal plasma but in high amounts in patients with atopic dermatitis or asthma [3]. The T lymphocytes consist of the cytotoxic T cells, which destroy antigen-infected cells, and the helper T cells, which activate the B cells [2]. The cytotoxic T cells (CD8) bind to antigen presenting cells (APC-macrophage, dendritic cell, B cells) displaying antigen on class I major histocompatibility complex (MHC), from having succumbed to the agent, and the helper T cells (CH4) bind to APC displaying antigen on class II MHC, from having been exposed to the agent [2]. The helper T cells consist of 2 predominant subsets: the T_h1 responsible for excessive inflammation and tissue injury, and the T_h2 that is responsible for the allergic reactions characteristic of atopic dermatitis and asthma [1-4].

Inflammatory Response: The exposure of skin or lung to antigens initially causes localized inflammatory response involving the innate immune cells and complement cascade, and later adaptive immunity [1]. The dendritic cells acquire the antigen, move to lymph nodes, and activate T cells, which in turn activate B cells [2]. The pathology of atopic dermatitis and asthma is from chronic inflammation and adaptive immunity due to the release of inflammatory mediators; especially cytokines that include the interleukins (IL), interferon (IFN), and tumor necrosis factor (TNF), and the lipid mediators such

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as prostaglandins and leukotrienes [1,2,4]. The source of the inflammatory mediators is largely the damaged tissue and the immune cells. TNF-α, IL-1, IL-6, and infection activate I-kB kinase that phosphorylates I-kBα which sequesters NF-kB transcription factor (p65/p50) in the cytoplasm, for proteasomal degradation [2]. The release of NF-kB, from I-kBα, exposes its nuclear localization signal (NLS) and allows NF-kB to translocate to the nucleus and transcriptionally activate specific genes that amplify the immune response [2]. The amplified immune response alters the structure of the extracellular matrix and thereby tissue integrity and function [4]. The mechanism to the inhibition of inflammation by hydrocortisone includes the inhibition of NF-kB [1].

Helper T cells/IgE production: The T_h1 cells, activated by Il-12, release IL-2 and IFN-γ, which mediate inflammation and tissue damage [1]. The T_h2 cells, activated by IL-4, release IL-4, 5, 6, 10, 13 to support allergic reaction through eosinophil activation and the activation of B cell to produce IgE, which is primarily responsible for dermatitis [1,3]. IgE binds to its high affinity receptors in mast cells and basophils to cause the local release of inflammatory mediators (histamine, leukotrienes, cytokines), and its low affinity receptors on B cells to augment secondary immune responses [3]. The release of IL-4 by T_h2 cells causes positive feedback stimulation of further IL-4 release from these cells [1].The mechanism of the activation of IgE production is the IL-4 signaling that allows for T_h2 differentiation and subsequently B cell isotype switching, through class switch recombination, to IgE expression [1,3]. IL-4, along with IL-13 and CD40 (TNF receptor superfamily member), direct the classic pathway of IgE class switching [3].

Cytokine/IL-4 receptors: Cytokines, including IL-4 and IL-13, bind to specific cytokine receptors allowing for receptor dimerization and signal transduction [2]. The signal transduction includes activation of janus tyrosine kinase (JAK), phosphorylation of signal transducer of transcription (STAT) factor, STAT dimerization and exposure of its NLS for translocation to the nucleus, and binding to STAT to gene promoters, containing its binding site, to activate gene expression [2,3]. The IL4Rα is present in IL-4 and IL-13 receptors, allowing IL-4Rα to mediate effects of IL-4 and Il-13 [3]. The activation of IL-4Rα in stimulated B cells results in the activation of STAT-6 that binds to Iε promoter, for the expression of IgE, and subsequently the clinical manifestation of dermatitis or asthma [3].

Dupilumab: Atopic Dermatitis and Asthma

Dermatitis and Asthma: Atopic dermatitis or eczema is characterized by pruritus (itching), inflammation (redness), hyperplasia (skin thickening), and propensity for infection of skin [5]. The biomarkers of atopic dermatitis include thymus and activation regulated chemokine (TRAC), IgE, gene expression profile ("lesional transcriptome", in comparison with non lesional biopsy) and keratin-16, associated with epithelial proliferation [5]. Asthma is characterized by breathlessness and wheezing; and is associated with reduced forced expiratory volume (FEV), bronchial inflammation/ eosinophilic infiltration, and increased plasma IgE levels [6]. Atopic dermatitis and asthma result from activation of the T_h2 cells, and thereby several cytokines (IL-4, 5, 10, 13) and B cells, by IL-4 [1,3,5,6,7]. IL-4 and IL-13 are central to the pathogenesis of atopic diseases [7].

Dupilumab: Dupilumab is a human monoclonal antibody against the IL-4Rα, common to IL-4 and IL-13 receptors, that blocks signaling by Il-4 and IL-13 [5-10]. The pharmacokinetics for intravenous and subcutaneous administration of dupilumab is similar to other therapeutic monoclonal antibodies of IgG isotype and does not need dose adjustment for patient weight [11]. In 2017, FDA approved dupilumab (Dupixent®, 300mg, Sanofi and Regeneron Pharmaceuticals, Inc.) for the treatment of moderate to severe atopic dermatitis and granted its application Priority Review and Breakthrough Therapy designation, for demonstration of significant efficacy over available treatments [12,13]. The available treatments include topical corticosteroids or calcineurin inhibitor, phototherapy or systemic immunomodulators, such as cyclosporine [14]. This is the first biologic to be approved for the treatment of moderate to severe atopic dermatitis, in patients with ineffective routine control with topical therapies [14,15]. The Institute for Clinical and Economic Review (ICER), an independent non-profit group, graded dupilumab as B+ relative to topical treatments, for its overall health benefit; and C+ relative to cyclosporine, for comparable efficacy but uncertain long term safety [14]. However, the members of the Midwest Comparative Effectiveness Public Advisory Council (CEPAC) voted almost unanimously (10 yes, 1 no) that dupilumab has greater health benefit than cyclosporine [14]. Dupilumab has not yet been approved for asthma.

Dupilumab Clinical trials- Dermatitis and Asthma: In controlled trials for atopic dermatitis, dupilumab (including 300mg) showed efficacy through the inhibition of pruritus, TRAC, keratin-16, anxiety and depression, increased skin clearing (Eczema Area and Severity Index or Investigator Global Assessment Score), and improvement in "lesional transcriptome", suggesting improvement at the level of gene expression [5,8-10,14]. In trials for Asthma, dupilumab reduced asthma exacerbation, asthma symptoms and serum levels of TRAC and IgE, and increased FEV [6]. The adverse effects, with regard to safety, were nasopharyngitis, headache, and injection site soreness [5,6]. In addition, higher rates of conjunctivitis occurred in the groups that received dupilumab, in comparison with placebo [16].

Conclusion

Atopic dermatitis and allergic asthma are primarily from allergic response to environmental antigens. Dermatitis manifests as itching, discomfort, hyperplasia and infection of skin. Asthma manifests as wheezing, coughing, and shortness of breath. The pathophysiology of these atopic diseases is amplified immune response of inflammation and IL-4 signaling to differentiate T_h2 cells and amplify an allergic response, mediated by IgE production and release of histamine, leukotrienes, and cytokines. The signal transduction of IL-4 depends on cytokine receptors that dimerize and activate cytoplasmic JAKs and thereby STAT transcription factor to

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modulate the expression of genes that mediate the clinical symptoms. The mainstay treatment has been corticosteroids. FDA recently approved dupilumab (Dupixent®, Sanofi and Regeneron Pharmaceuticals, Inc.) as the first biologic for the treatment of moderate to severe dermatitis in patients with inadequate control with other available treatments. Dupilumab targets the IL4Rα receptor to block signaling from IL-4, as well as IL-13, and thereby counteracts the allergic response. Dupilumab is effective in counteracting the symptoms of dermatitis and asthma. However, it is expensive and its serious safety concerns include conjunctivitis and unknown long-term effects.

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