Analyzing Eosinophilic Esophagitis and Allergic Disorder Pathways and Potential Drug Solutions

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Abstract

Eosinophilic esophagitis (EoE) is a disorder that affects the esophagus and is caused by an accumulation of eosinophils in the esophageal lining. The disorder affects individuals of all ages, and its symptoms include inflammation, esophagus narrowing, difficulty swallowing, nausea, and chest pain. EoE is a T-helper type 2 (Th2) mediated disorder whose pathogenesis is not completely understood. The disorder is caused by adverse immune responses to a variety of foods, and the Th2 pathway and epithelial barrier dysfunction pathway play a crucial role in developing an EoE response. In this report, I analyze these pathways and potential drug solutions for patients with EoE and similar allergic conditions. I found proteins involved in both pathways that were either significantly upregulated or downregulated in patients with EoE. I then conducted further research and used FINDSITE to gather more information about potential drug options such as monoclonal antibodies, and drugs containing molecules alpha-L-fucose and beta-D-glucose.

Introduction

Eosinophilic esophagitis (EoE) is a chronic disorder of the esophagus caused by an accumulation of eosinophils in the esophageal lining. EoE affects patients from birth to adulthood with symptoms including inflammation, esophagus narrowing, difficulty swallowing, nausea, and chest pain. Initially viewed as a manifestation of gastroesophageal reflux disease (GERD), EoE has grown significantly in the past three decades, affecting 4 in every 10,000 people worldwide with increased prevalence for men in Western countries. Diagnosis of EoE

typically involves endoscopy with biopsy, and treatment options include dietary therapy, such as food trialing and elemental-formula diets, proton pump inhibitors, and topical corticosteroids.

Th2 Response Pathway

EoE is caused by adverse immune responses to a variety of foods. Studies have identified several genetic variations associated with an increased risk of EoE, including variations in genes involved in the immune response and the regulation of eosinophil development and function. EoE is a T-helper type 2 (Th2) mediated disorder whose pathogenesis is not completely understood. However, it is thought that Interleukin (IL) 4 is responsible for initiating the Th2 response through the differentiation of naive T helper cells into Th2-type cells. The EoE response starts when antigenic proteins such as casein in milk, or ovalbumin in eggs, produce cytokines such as interleukin (IL) 5 and IL-13. IL-5 is a key cytokine that regulates the survival, activation, and trafficking of eosinophils to the esophagus while IL-13 triggers esophageal epithelial cells to produce proteins such as eotaxin 3, which recruits eosinophils from peripheral blood into the tissue. The CCR3 receptor receives signals from Th2 cells, and its expression is increased in the esophagus, correlating positively with Eotaxin 3 frequency and eosinophil number. Recruited eosinophils express antigen-4 and P-selectin glycoprotein ligand-1, which bind to vascular cell adhesion molecule-1 and P-selectin, respectively, and migrate into the tissue. Eosinophils in EoE patients have increased expression of proteins such as eotaxin and interleukins 4, 5, and 13.

Epithelial Barrier Dysfunction Pathway

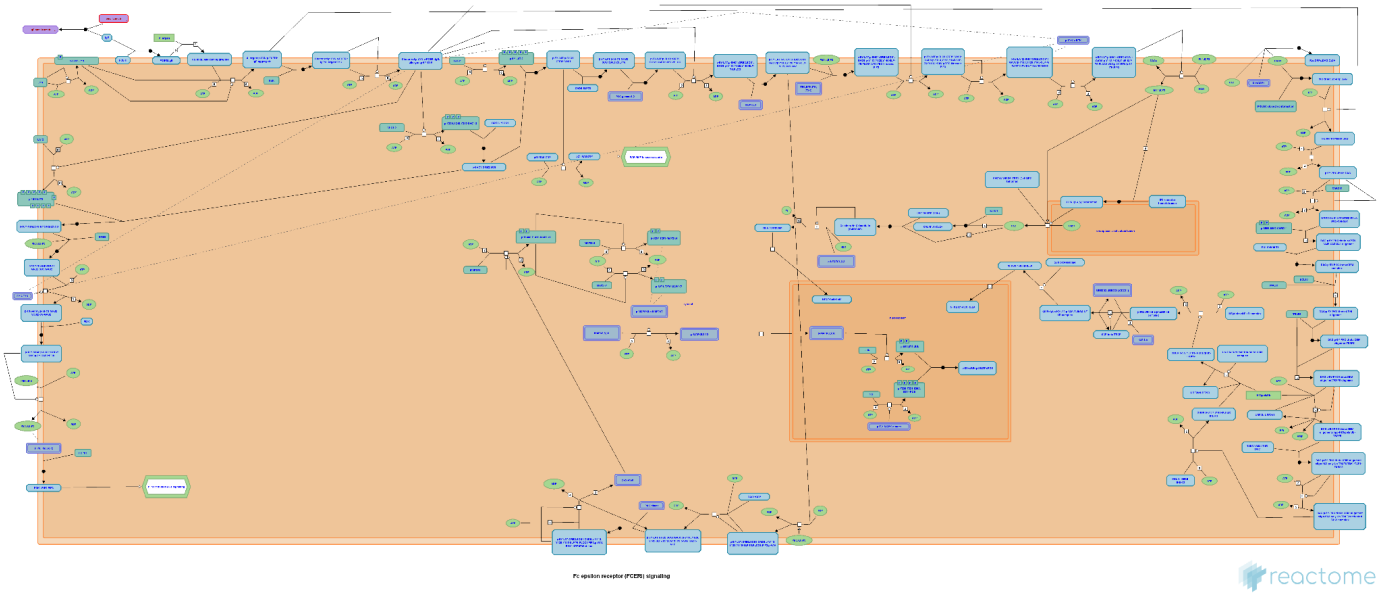
Alongside the Th2 pathway, the epithelial barrier dysfunction pathway is another pathway that plays a crucial role in developing an EoE response. Epithelial barrier dysfunction is a significant factor in a variety of IgE allergic conditions, including EoE, and most EoE patients

have IgE-involved comorbid allergic conditions. It refers to the loss of integrity of the protective barrier that lines the esophagus, which allows eosinophils to penetrate the tissues underneath. After allergen exposure, mast cells in the esophagus are activated by crosslinking of IgE receptors on their surface. This leads to the activation of a signaling pathway that involves the tyrosine kinase Syk and the adaptor protein LAT. Activating these proteins leads to the release of mediators such as histamine, tryptase, and leukotrienes, which contribute to the symptoms of EoE. The release of mediators from mast cells and proteins from eosinophils cause alterations in the disrupt tight junctions, desmosomes, adherens junctions, and other barrier proteins. This leads to increased permeability of the epithelial layer and exposure of the underlying tissue to allergens, triggering the Th2 immune response.

Target: FCER1 Receptor and FCER1A Gene

A specific upstream receptor involved in mast cell activation in EoE is the FCER1 receptor. This upstream receptor binds to IgE, and the signaling proteins Syk and LAT. In EoE, there may be genetic variations that affect the expression or function of FCER1 or IgE, leading to an increased sensitivity to allergens and a heightened immune response. For example, a recent study identified a variant in the FCER1A gene that is associated with an increased risk of EoE. This variant may alter the expression or function of FCER1A, leading to increased activation of eosinophils and other immune cells in response to allergens. FCER1A is a cell surface receptor protein and a component of the FCER1 receptor complex. FCER1 is the receptor itself that mediates allergic responses when activated by IgE antibodies bound to FCER1A. FCER1A is found on the surface of mast cells and basophils that triggers an immune response when cross-linked by IgE molecules bound to allergens. Currently, one study shows the use of

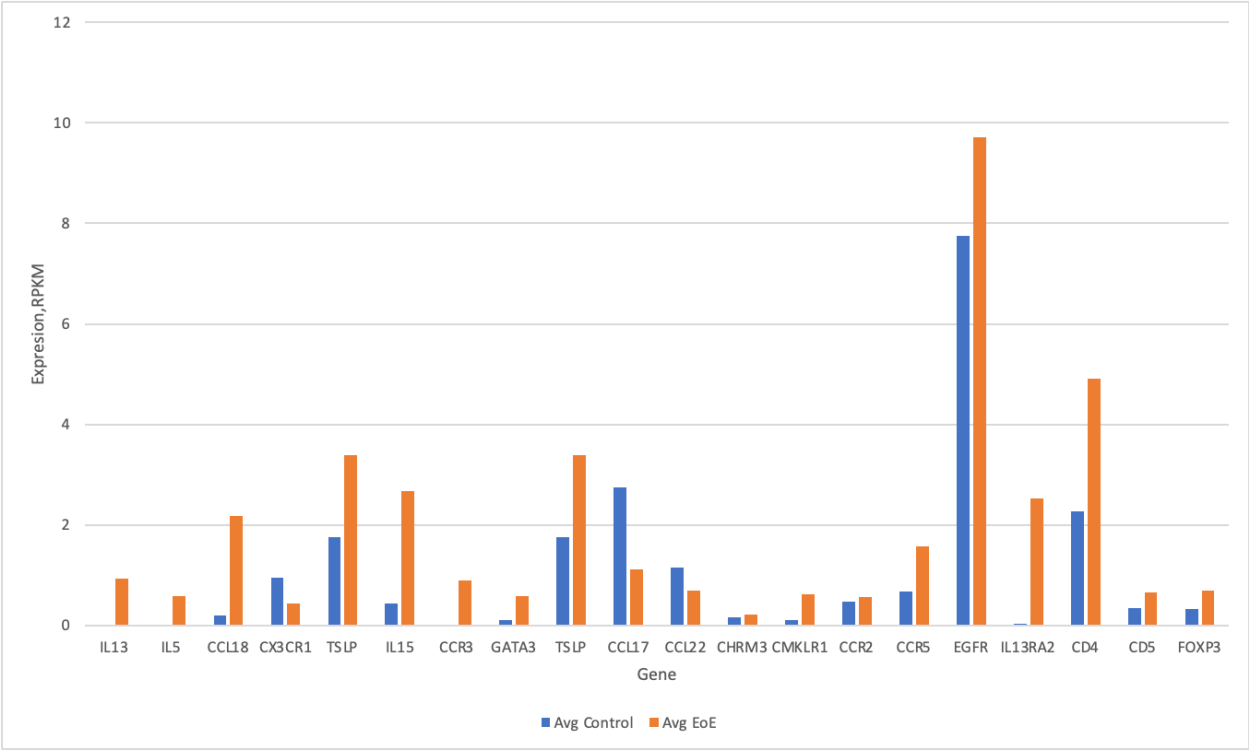
monoclonal antibodies to bind to this receptor and prevent a downstream response. Further information on this study and other drugs will be discussed later.



FCER1 Receptor Signaling Pathway via Reactome

Methods

The goal of this research project was to analyze the genetics of EoE while finding potential repurposed drug options for patients with EoE and similar allergic conditions. The first part of my research phase was finding proteins involved in the Th2 pathway that were either significantly upregulated or downregulated in patients with EoE. I used patient RNA Sequencing data from EGIDExpress to identify these genes and gather more information about each one. In the graph below, upregulated genes and their expressions (RPKM) were plotted for healthy controls and EoE patients. As expected, many interleukins and proteins discussed in the Th2 pathway section of the introduction were upregulated.



Gene and Expression data for healthy controls and EoE patients for a set of researched upregulated genes.

While this data was beneficial for confirming the mechanisms of the Th2 pathway, the goal of this project was to investigate a gene that could prevent the downstream reaction cascade, and I had to look at another pathway to do this. After doing research using previous studies and LeMeDISCO, I found the epithelial barrier dysfunction pathway, the FCER1 receptor, and the corresponding FCER1A protein. As mentioned earlier, cross-linkage with this receptor caused the downstream immune response, so I focused on finding molecules using FINDSITE that could prevent this pathway from starting in the first place.

Results

After using the amino acid sequence for the FCER1A to do a FINDSITE search, I found a variety of compounds for further investigation. In this section, I will give an overview of these molecules alongside two other drugs that have relevance for patients with EoE and other IgE-related allergic conditions. After doing a ligand screening for the FCER1A protein. I found

two related molecules that could be used for potential drug repurposing. Alpha-L-fucose and beta-D-glucose ranked first in the ligand screen match with an mTC score of 0.969. Alpha-L-fucose is associated in humans with blood cells and immune system recognition while beta-D-glucose is involved in cell signaling and immune recognition. In one study in Uganda, it was discovered that reactivity to specific cross-reactive carbohydrate determinants (CCD) moieties, including core beta-D-glucose and alpha-L-fucose, was positively associated with sensitization to extracts, rural environment, and Schistosoma mansoni infection but not with skin reactivity to extracts or sensitization to their major allergenic components. However, reactivity to a subset of alpha-L-fucose-carrying N-glycans was inversely associated with asthma, suggesting a potential protective effect of certain environmental exposures against asthma.

Dupilumab

Dupixent (dupilumab) is a biologic that blocks the IL-4 and IL-13 signaling pathways, which are involved in immune response, inflammation, and tissue remodeling. Dupixent specifically targets the IL-4 receptor alpha subunit to prevent the release of proinflammatory cytokines, chemokines, and immunoglobulin E. Multiple studies have shown that Dupixent can reduce IL-4, IL-13, and eotaxin-3 expression, which has led to its use in treating conditions such as asthma, eczema, and eosinophilic esophagitis. However, there is also a risk of immunosuppression and off-target effects on other parts of the immune system with other minor side effects including body aches, chills, and coughing. Despite this, trials have shown that Dupixent demonstrates efficacy in blocking the Th2 pathway and reducing biomarker expression, making it a promising treatment option for various allergic conditions.

Omalizumab and Monoclonal Antibodies:

A recent study discussed the use of monoclonal antibodies (mAbs) to target IgE. There has been immense difficulty in identifying therapeutic agents that could block its effects without triggering the cross-linking of IgE bound to its high-affinity receptor (FCER1). Omalizumab is an anti-IgE monoclonal antibody, which has been effective in reducing IgE responses without causing an anaphylactic reaction. Omalizumab has been used to treat severe allergic asthma in adults and children over the age of 12 years. It binds to the FCER1 receptor to prevent the epithelial barrier dysfunction pathway from starting. However, it does have side effects including blood vessel inflammation (rare), fever, rash, and muscle aches. QGE031 is another monoclonal antibody that is creating further opportunities for anti-IgE therapy. It is more potent and would be used for severe cases of asthma, atopic dermatitis, and food allergy conditions.

Conclusion

As EoE and IgE allergy disorders continue to impact millions of people worldwide, more investigation into solutions that impact an upstream area of the pathways is necessary. In the future, setting up an experiment could be beneficial to figuring out the impact of these drugs. To start, one could run computer simulations to understand the impact of these molecules, and to see if they are actually benefitting a patient. To validate this, animal models could then be used to see if the molecules are beneficial or harmful to the patient. In previous studies, animal models with EoE were treated with drugs such as biologics where some drugs reversed inflammation in the esophagal area. Another study showcased the significance of mouse models for Eosinophilic disorders such as EoE as it can mimic the human EoE pathegenesis. To continue this experiment, it could then be beneficial to gather a group of patients aged 12 and above with EoE and asthma (common comorbidity) to trial drugs such as dupilumab, omalizumab, stronger monoclonal antibodies, and compounds containing alpha-L-fucose and beta-D-glucose. This way we can see

the impact of each drug on various stages of the Th2 and epithelial barrier dysfunction pathways. Additionally, while there has been significant research on the FCER1 receptor in other IgE conditions, it would be interesting to see more exploration of its applications in EoE. In conclusion, investigating the impact of various drugs on the Th2 and epithelial barrier dysfunction pathways, as well as further exploring the applications of the FCER1 receptor in EoE, could provide valuable insights for continuing the development of treatments for various allergic disorders.

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