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# Targeted IL-4Rα blockade ameliorates refractory allergic eosinophilic inflammation in a patient with dysregulated TGF-β signalling due to ERBIN deficiency

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Transforming growth factor beta (TGF-β) is a multifunctional cytokine that possesses immune stimulatory and inhibitory functions, influences T-lymphocyte differentiation, and promotes cell proliferation and wound healing.[1] TGF-β signaling activates the transcription factor SMAD3, which increases IL-4 receptor expression associated with type 2–skewed immune responses. (Figure 1). Dysregulated TGF-β signaling has been implicated in human syndromes with co-existent connective tissue abnormalities and atopy (e.g., Ehlers-Danlos syndrome, Loeys-Dietz syndrome).[2–4]

Protection against aberrant type 2 responses may be partially mediated by IL-6–driven STAT3 activation, which opposes Th2 skewing in T-lymphocytes. Patients with genetic defects leading to impaired IL-6 receptor or STAT3 signaling develop elevated IgE, atopy, and immunodeficiency.[5] Lyons *et al.* demonstrated that IL-6–induced STAT3

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activation inhibited TGF-β signaling by increasing the transcription of ERBB2-interacting protein (ERBIN), a protein scaffold that complexes with STAT3 to sequester cytoplasmic SMAD2/3 (Figure 1). Three family members with ERBIN deficiency (carrying a novel, disease-segregating *ERBB2IP* [c.1588G>T, p.D530Y] variant) had elevated IgE, atopy, and connective tissue abnormalities (e.g., hypermobility, aortic root dilation) associated with increased TGF-β signaling and activation of the type 2–skewing GATA-3/IL-4/IL-4Rα axis in naïve T and B lymphocytes.[6]

We present the clinical course of the 16-year-old male proband with ERBIN deficiency who presented with refractory eosinophilic gastrointestinal disease (EGID), uncontrolled eosinophilic respiratory disease, recurrent infections and hypogammaglobulinemia, peripheral eosinophilia, and elevated IgE. After failure of traditional therapies, we postulated that targeted treatment of the excessive IL-4R expression with IL-4R blockade would be an effective therapeutic strategy.

## Dupilumab-induced remission of refractory eosinophilic gastrointestinal disease (EGID)

The patient's past medical history revealed a progressive course of atopy and ineffectiveness and/or complications of standard therapies. The patient was diagnosed with eosinophilic esophagitis (an EGID, 6 yo), followed years later by eosinophilic gastritis (an EGID) and peripheral eosinophilia (9 yo). Multiple swallowed steroids (budesonide, fluticasone) initially induced histologic remission of his EGID. However, this regimen was complicated by esophageal candidiasis and iatrogenic adrenal insufficiency; necessary discontinuation of topical steroids led to EGID recurrence.

Given the persistent hypereosinophilia (blood eosinophils 1600–4450 cells/mcL for >6 months) and refractory gastrointestinal disease, mepolizumab (hypereosinophilic syndrome dosage: 300 mg every 4 weeks) was trialed. Prior to mepolizumab, tissue histology showed severe gastric eosinophilic inflammation with eosinophil degranulation and active eosinophilic esophagitis (Figure 2). After 5 months of mepolizumab, the blood absolute eosinophil count (AEC) and gastrointestinal tissue eosinophilia were markedly decreased (72% and 75% reduction, respectively); however, the gastrointestinal disease remained histologically active, and clinical symptoms failed to improve (Figure 2). Given the incomplete histologic response and poor clinical improvement, mepolizumab was discontinued, which caused an acute exacerbation of gastrointestinal symptoms, loss of asthma control, and worsening rhinitis symptoms. Severe eosinophilia (AEC 6850 cells/mcL) with elevated IL-5 (55 pg/mL; normal <1 pg/mL) and IL-4 (19 pg/mL; normal <8 pg/mL) levels in the peripheral blood developed.

Because IL-5–directed therapy was ineffective, we hypothesized that IL-4/13 blockade might be therapeutic and initiated dupilumab (300 mg, every 2 weeks). After 4 weeks of dupilumab, the patient reported improvement of his gastrointestinal symptoms, and his blood eosinophilia began downtrending. After 6 months of dupilumab, he reported nearly complete resolution of gastrointestinal symptoms and significant weight gain (6.4 kg/ 14 lbs; body mass index 50$^{th}$ percentile); AEC decreased to 970 cells/mcL, and peripheral blood

IL-5 levels normalized (<1 pg/mL). Esophageal and gastric biopsies demonstrated histologic remission of eosinophilic inflammation (Figure 2). Swallowed fluticasone was subsequently discontinued. The 12-month follow-up endoscopy for the course (dupilumab, crushed enteric budesonide) showed minimal esophageal eosinophilic inflammation (2 eosinophils/ high-power field) and no recurrence of gastric disease.

## Dupilumab-induced remission of eosinophilic respiratory disease

Similar to the EGIDs (eosinophilic esophagitis, eosinophilic gastritis), asthma and chronic rhinitis progressively worsened during the patient's teenage years, with poor asthma symptom control, development of nasal polyps, and recurrent sinusitis. Treatment of his respiratory disease was complicated by iatrogenic adrenal insufficiency. The patient experienced weekly asthma symptoms and 2–3 exacerbations/year, requiring oral steroids while taking ICS plus long-acting β2-agonist (ICS-LABA) combination therapy and montelukast. Similarly, his allergic rhinitis remained poorly controlled, leading to recurrent sinusitis (5–6 episodes/year) and 4 surgical procedures to treat refractory sinusitis and nasal polyposis despite ongoing management (intranasal fluticasone, azelastine, and ipratropium; oral cetirizine; prophylactic azithromycin). With mepolizumab, there had been no significant improvements in upper or lower respiratory symptoms. Conversely, his asthma control significantly improved within 6–8 weeks of dupilumab therapy. After >17 months of dupilumab, he reported minimal asthma symptoms and had no oral steroid courses, the ICS-LABA dose was decreased, and montelukast discontinued (Figure 2). His FEV1 was normal prior to biologic therapy and did not change with dupilumab. He did report improved upper respiratory symptoms, with subsequent discontinuation of azithromycin and ipratropium, and no recurrence of nasal polyps nor sinus infections.

## Humoral immunity normalized with IL-4 blockade

Due to recurrent infections, the patient had serial immunologic evaluations. The patient developed intermittent hypogammaglobulinemia (IgG 385–791 mg/dL) of unclear etiology during adolescence in the context of robust vaccine responses and without gastrointestinal protein loss. He also demonstrated persistently elevated IgE (peak level 1460 IU/mL). Remarkably, his IgG titers increased during dupilumab therapy (IgG 941–1020 mg/dL), and IgE dramatically decreased to 90 IU/mL. We postulate that the hypogammaglobulinemia may have been, at least partially, due to the excessive type 2 response; however, a reduction in corticosteroid use could have also contributed to the observed IgG increase.

Damaging variants in ERBIN-encoding *ERBB2IP* manifest with connective tissue abnormalities and atopy associated with dysregulated TGF-β signaling and increased IL-4 receptor expression and type 2 immune responses. As ERBIN complexes with STAT3, there are reports of gastrointestinal disease improving with dupilumab therapy in patients with autosomal dominant hyper-IgE syndrome (AD-HIES) being treated with dupilumab for severe atopic dermatitis.[7,8] This case highlights that specifically blocking type 2 signaling via anti–IL-4Rα therapy (dupilumab) in a patient with ERBIN deficiency was an effective strategy to treat co-existent allergic inflammation and illustrates a potential strategy for treating other patients with dysregulated TGF-β signaling and comorbid atopy.

The impact of dupilumab on the patient's connective tissue disorder remains unclear; given that aberrant TGF-β signaling is thought to directly contribute to the underlying connective tissue abnormality independent of its effect on the IL-4/IL-4Rα axis, improvement is not anticipated. This case illustrates how clarity regarding a patient's underlying disease mechanism can effectively guide a targeted biologic therapy approach.[9]

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**Conflicts of Interest:**

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### Clinical Implications

ERBIN deficiency causes dysregulated TGF-β signaling driving aberrant IL-4–associated type 2 immunity. Anti–IL-4/IL-13 receptor immunotherapy effectively treated an ERBIN–deficient patient with refractory severe atopy including eosinophilic gastrointestinal disease and may benefit other patients with dysregulated TGF-β signaling–associated atopy.

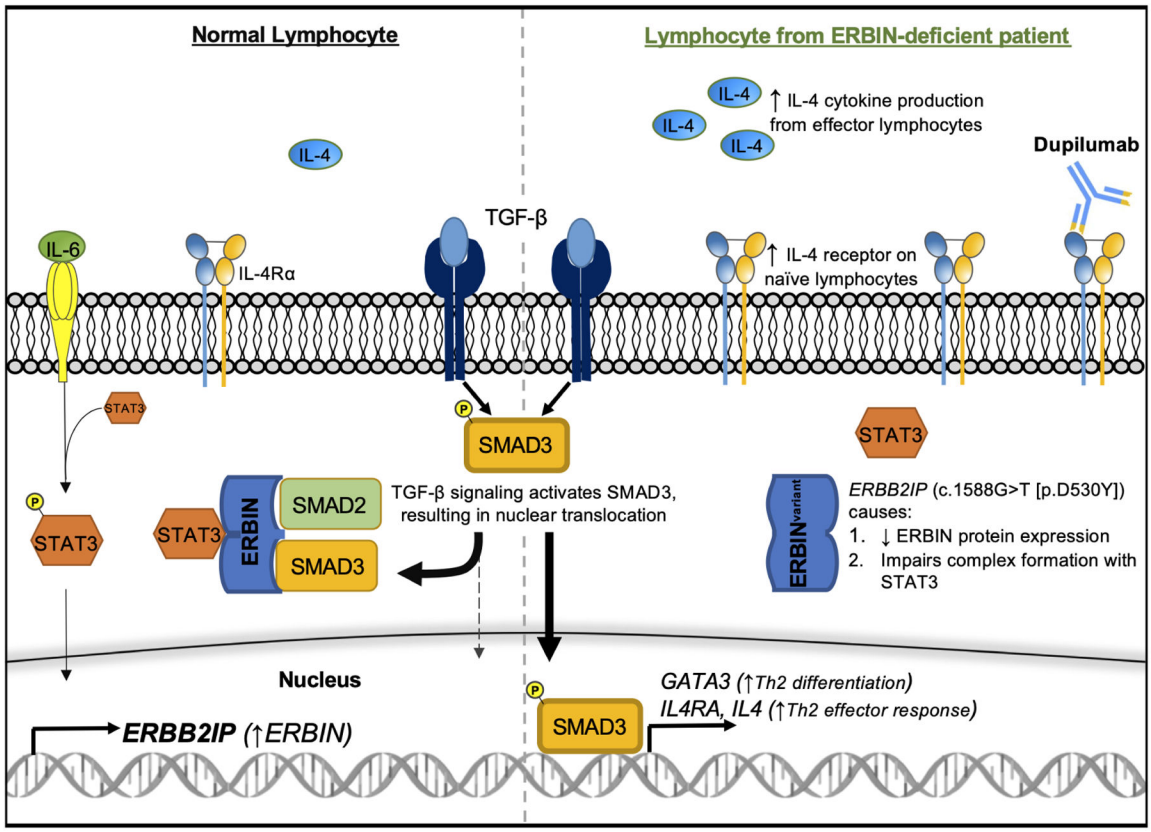



**Figure 1. TGF-β signaling and ERBIN regulation.**

TGF-β activates SMAD3, which translocates into the nucleus to promote Th2 skewing of lymphocyte responses. The STAT3-ERBIN complex negatively regulates TGF-β signaling by sequestering cytoplasmic SMAD3. The *ERBB2IP* variant (c.1588G>T [p.D530Y]) impairs STAT3-ERBIN-SMAD2/3 complex formation, increasing TGF-β signaling through SMAD3. Dupilumab targets IL-4Rα and can block IL-4–mediated effects of dysregulated TGF-β signaling. P, phosphorylation

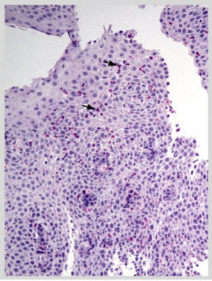
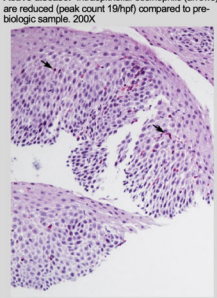
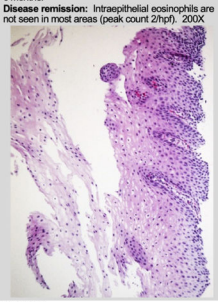
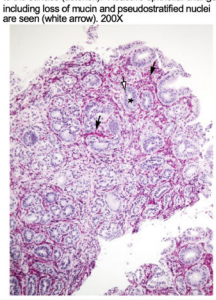
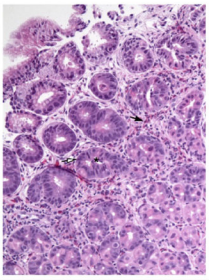
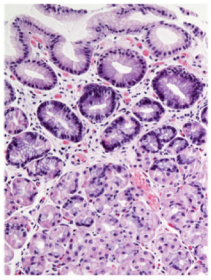
| | Pre-biologic Therapy | Mepolizumab (Treatment: 5 months) | Dupilumab (Treatment: 17 months) |
|---|---|---|---|
| **Eosinophilic gastrointestinal disease** | | | |
| **Symptoms** | Dysphagia, abdominal pain, early satiety, vomiting weekly, diarrhea<br>BMI ~ 30th percentile | Dysphagia, abdominal pain, early satiety, vomiting 1-2 times per month | Improvement in dysphagia, abdominal pain, and early satiety; no vomiting<br>14 lb weight gain, BMI increased to 50th percentile |
| **Treatment** | Fluticasone 660 mcg twice daily<br>Budesonide 3 mg daily<br>Fluconazole 100 mg daily | Fluticasone 660 mcg twice daily<br>Budesonide 3 mg daily<br>Fluconazole 100 mg daily | Budesonide 3 mg daily |
| **Endoscopy** | Diffuse edema, antral nodularity, and white plaques in lower esophagus on swallowed steroids. Course complicated by eosphageal candidiasis. | Normal appearance of esophageal lining with diffuse nodularity of stomach antrum | *6 months:* Patchy furrowing of esophagus and patchy nodularity of stomach |
| **Tissue Biopsy** | | | |
| ***Esophagus (Distal)*** | **Active disease:** Numerous intraepithelial eosinophils (arrows) (peak count 67/hpf). 200X  | **Active disease:** Intraepithelial eosinophils (arrows) are reduced (peak count 19/hpf) compared to pre-biologic sample. 200X  | *6 months:* **Disease remission:** Intraepithelial eosinophils are not seen in most areas (peak count 2/hpf). 200X  |
| ***Stomach (Body/Antrum)*** | **Active disease:** Sheets of eosinophils in the lamina propria (black arrows) (peak count 184/hpf). Glandular distortion is present in some areas in which glands appear parallel and not perpendicular to the surface (asterisk). Reactive epithelial changes including loss of mucin and pseudostratified nuclei are seen (white arrow). 200X  | **Active disease:** Eosinophils are increased in the lamina propria (black arrow) but appear reduced compared to pre-biologic sample (peak count 47/hpf). Glandular alterations (asterisk, white arrow) are less prevalent. 200X  | *6 months:* **Disease remission:** Eosinophils are not seen in this area and most areas of the biopsy are devoid of eosinophils (peak count 4/hpf). Glandular architecture and epithelium appear normal. 200X  |
| **Eosinophilic asthma** | | | |
| **Symptoms** | Dyspnea 3-6 times a week<br>Rescue inhaler (albuterol) 2-3 times per week<br>2-3 courses of oral steroids per year | Dyspnea 3-6 times a week<br>Rescue inhaler (albuterol) 2-3 times per week<br>1 course of oral steroids | Dyspnea ≤1 time per week<br>Rescue inhaler (albuterol) ≤1 per week<br>No courses of oral steroid courses |
| **ACT (Well-controlled ≥20)** | 18-21 | 18 | 21 |
| **Treatment** | Fluticasone/salmeterol 100-50 mcg/inhalation 1 puff twice daily<br>Montelukast 10 mg daily<br>Albuterol as needed | Fluticasone/salmeterol 100-50 mcg/inhhalation 1 puff twice daily<br>Montelukast 10 mg daily<br>Albuterol as needed | Fluticasone/salmeterol 100-50 mcg/inhhalation 1 puff **daily**<br>Albuterol as needed |
| **Allergic rhinitis with nasal polyps and recurrent sinusitis** | | | |
| **Symptoms** | Chronic congestion and postnasal drip<br>1-2 sinus infections per year | Chronic congestion and postnasal drip<br>No sinus infections | Improved congestion and postnasal drip<br>No sinus infections |
| **Treatment** | Cetirizine 10 mg daily<br>Azithromycin 500 mg Monday, Wednesday, Friday<br>Fluticasone 2 sprays each nostril daily<br>Azelastine 1-2 sprays each nostril twice daily<br>Ipratropium 2 sprays each nostril twice daily | Cetirizine 10 mg daily<br>Azithromycin 500 mg Monday, Wednesday, Friday<br>Fluticasone 2 sprays each nostril daily<br>Azelastine 1-2 sprays each nostril twice daily<br>Ipratropium 2 sprays each nostril twice daily | Cetirizine 10 mg daily<br>Fluticasone 2 sprays each nostril **as needed seasonally**<br>Azelastine 1-2 sprays each nostril **as needed** |
| **Laboratory results** | | | |
| **AEC (normal range: 0-500 cells/mcL)** | 470-4450 cells/mcL | 1150 --> 140 cells/mcL (Pre --> Post-Mepolizumab) | 6850 --> 940 cells/mcL (Pre --> Post-Dupilumab) |
| **IgG (normal range: 680-1351 mg/dL)** | 592 mg/dL | 762 mg/dL | 1020 mg/dL |
| **IgE (normal range: 0-120 IU/mL)** | 1045 IU/mL | Not measured | 1460 --> 90 IU/mL (Pre --> Post-Dupilumab) |

**Figure 2. Patient characteristics by treatment stage.**

ACT = Asthma Control Test is a subjective scoring system filled out by the patient, 20–25 suggests controlled asthma, 16–19 suggests partially controlled asthma, and less than 16 suggests poorly controlled asthma; AEC = Absolute Eosinophil Count; IgG = Immunoglobulin G; IgE = Immunoglobulin E; BMI = Body Mass Index; hpf = High powered field