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Review

Molecular mechanisms of allergic type 2 immunity in the pathogenesis of Crohn's disease: From epithelial alarmins to IgE signaling

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Abstract

Crohn's disease (CD) is a chronic inflammatory bowel disorder driven by complex interactions between genetic susceptibility, gut microbiota, and immune dysregulation, typically associated with Th1 and Th17 responses. However, emerging evidence highlights that type 2 allergic mechanisms also significantly contribute to CD pathogenesis. This review examines the cellular and molecular basis of allergic pathways in CD, focusing on IgE-mediated hypersensitivity, mast cell and eosinophil effector functions, and Th2 cytokines (IL-4, IL-5, IL-13). Key epithelial-derived alarmins—namely IL-33, TSLP, and IL-25—are discussed as critical upstream mediators linking mucosal barrier injury to type 2 immune activation in the CD gut. Elevated serum IgE, intestinal mast cell infiltration, and tissue eosinophilia have consistently been documented in CD patients. Mechanistically, FcεRI signaling on mast cells triggers degranulation and release of histamine, proteases, and pro-inflammatory cytokines such as TNF-α and IL-6, leading to increased epithelial permeability and visceral hypersensitivity. Moreover, crosstalk between Th2 and Th1/Th17 pathways further amplifies chronic intestinal inflammation. Understanding these allergic mechanisms opens novel therapeutic avenues, including anti-IgE (omalizumab), anti-IL-4/IL-13 (dupilumab), anti-IL-33 (itepekimab), anti-TSLP (tezepelumab), and mast cell stabilizers (ketotifen). This review integrates current molecular evidence on allergic reactions in CD and highlights their clinical and therapeutic relevance. Recognizing type 2 immune signatures in subsets of CD patients may enable more personalized treatment strategies.

Keywords: Crohn's disease, allergy, IgE, mast cells, Th2 immunity, inflammatory bowel disease

1. Introduction

Crohn's disease (CD) is a chronic, relapsing inflammatory condition of the gastrointestinal tract that arises from a complex interaction between genetic predisposition, environmental triggers, intestinal microbiota, and immune dysregulation. The disease can affect any segment of the gastrointestinal tract and is characterized by transmural inflammation leading to complications such as strictures, fistulas, and abscesses. The global incidence of CD continues to rise, particularly in industrialized and newly industrializing countries [1–3].

The pathogenesis of CD involves an inappropriate immune response to commensal microbiota in genetically susceptible individuals. Genome-wide association studies have identified numerous susceptibility genes, including those involved in innate immunity, autophagy, and epithelial barrier integrity, such as NOD2, ATG16L1, and IL23R [4–6]. These genetic alterations contribute to defective microbial handling and exaggerated immune activation, ultimately leading to chronic intestinal inflammation.

Current treatment strategies for CD aim to suppress inflammation and induce remission. These include corticosteroids, thiopurines, methotrexate, and biologic agents targeting tumor necrosis factor (TNF), integrins, and interleukin-12/23 pathways [7–9]. Although these therapies have improved clinical outcomes, a significant proportion of patients exhibit primary non-response or lose responsiveness over time [10,11]. Moreover, long-term immunosuppression is associated with an increased risk of infections and malignancies, highlighting the need for more selective therapeutic strategies.

Historically, CD has been conceptualized as a predominantly Th1- and Th17-driven disorder, with key cytokines such as interferon-γ (IFN-γ), tumor necrosis factor-α

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(TNF-α), interleukin-12 (IL-12), and interleukin-23 (IL-23) driving chronic mucosal inflammation. However, a growing body of evidence suggests that allergic mechanisms, characterized by type 2 immune responses, also play important roles in the development and perpetuation of CD. Elevated serum immunoglobulin E (IgE) levels, intestinal mast cell infiltration, eosinophilic inflammation, and Th2 cytokine expression have all been documented in CD patients, indicating that allergic pathways are not merely epiphenomena but active contributors to disease pathology [12,13].

The relationship between allergy and CD is further supported by epidemiological observations showing higher rates of allergic comorbidities, including atopic dermatitis, food allergies, and asthma, in patients with inflammatory bowel disease (IBD) compared with the general population [14,15]. These overlapping clinical features suggest shared immunological mechanisms. Understanding the contribution of allergic reactions to CD pathogenesis therefore represents a critical step toward developing more targeted and effective treatment approaches.

This review aims to systematically summarize current evidence on the role of allergic reactions in CD, covering the etiology and pathogenesis of CD, the manifestations of various allergy types within the disease, the molecular mechanisms by which allergic pathways intersect with CD immunology, and the therapeutic strategies that specifically target allergy in the context of CD.

2. Etiology and Pathogenesis of Crohn's Disease

2.1. Genetic Predisposition

The genetic architecture of CD is complex, involving hundreds of susceptibility loci identified through genome-wide association studies (GWAS). The most well-characterized susceptibility gene is NOD2 (CARD15), encoding a cytoplasmic pattern recognition receptor that senses muramyl dipeptide from bacterial cell walls. Loss-of-function variants in NOD2 impair innate immune responses to intestinal bacteria and are among the strongest genetic risk factors for CD, particularly ileal disease [16]. Similarly, variants in ATG16L1 and IRGM, genes involved in the autophagy pathway, disrupt intracellular bacterial handling and contribute to Paneth cell dysfunction and abnormal microbial clearance [17].

The IL23R gene, encoding the receptor for interleukin-23, harbors protective and risk variants that modulate Th17 cell differentiation and intestinal inflammation [18]. Other important susceptibility loci include CARD9, which links innate immune sensing to adaptive immunity; FUT2, affecting susceptibility to gut microbial colonization; and HLA region variants, which influence antigen presentation and adaptive immune responses [19,20]. The cumulative effect of multiple low-penetrance variants, combined with environmental exposures, determines individual disease risk and phenotype.

2.2. Intestinal Barrier Dysfunction and Microbiome Dysbiosis

The intestinal epithelial barrier serves as the first line of defense against luminal antigens and microorganisms. In CD, barrier dysfunction arises from impaired tight junction assembly, reduced mucus layer thickness, and decreased expression of antimicrobial peptides such as defensins and lysozyme [21]. Paneth cell dysfunction, closely linked to NOD2 and ATG16L1 variants, results in defective secretion of α-defensins, compromising the control of intestinal microbial communities [22].

Intestinal microbiome dysbiosis is a consistent finding in CD and is characterized by reduced microbial diversity, depletion of beneficial commensal organisms such as Faecalibacterium prausnitzii, and expansion of potentially pathogenic bacteria including Escherichia coli adherent-invasive strains (AIEC) [23]. These alterations in microbial communities promote translocation of bacterial products across the epithelial barrier, triggering innate immune activation and sustaining chronic inflammation. The microbiome also profoundly influences mucosal immune education, with dysbiosis contributing to impaired tolerance mechanisms and heightened immune reactivity [24].

2.3. Immune Dysregulation: Th1/Th17 Pathways and Cytokine Networks

The mucosal immune response in CD is primarily characterized by a dysregulated Th1 and Th17 effector response. Th1 cells produce IFN-γ and TNF-α, which activate macrophages and promote granuloma formation, a histological hallmark of CD [25]. The IL-12/IL-23 axis plays a central role in this process: IL-12 drives naive T cell differentiation toward the Th1 phenotype, while IL-23 sustains Th17 cell expansion and stability. Th17 cells produce IL-17A, IL-17F, and IL-22, contributing to neutrophil recruitment, antimicrobial defense, and epithelial restitution, but also promoting tissue damage in the context of dysregulated inflammation [26].

Macrophages in the CD mucosa exhibit a pro-inflammatory M1-like phenotype, characterized by high production of TNF-α, IL-6, IL-1β, and reactive oxygen species. These cells orchestrate innate immune activation and contribute to tissue destruction. Regulatory T cells (Tregs), which normally suppress excessive immune responses, are functionally impaired in CD, allowing uncontrolled effector T cell activity [27]. Dendritic cells in the inflamed mucosa display altered maturation states and enhanced capacity to prime Th1 and Th17 responses, further perpetuating the inflammatory cycle. Collectively, these dysregulated cellular and cytokine networks drive the chronic, relapsing course of CD.

3. Manifestations of Various Types of Allergic Reactions in Crohn's Disease

3.1. Type I Hypersensitivity (IgE-Mediated Reactions)

Type I, or immediate hypersensitivity, is characterized by antigen-specific IgE production, mast cell sensitization, and rapid degranulation upon allergen re-exposure. In CD, elevated total and food-specific IgE levels have been reported in a subset of patients, suggesting activation of IgE-dependent pathways [28]. Studies have demonstrated increased frequencies of food-specific IgE sensitization to common dietary antigens such as cow's milk, wheat, and egg proteins in CD patients compared with healthy controls, raising the possibility that food allergen-driven IgE responses may contribute to mucosal inflammation [29].

Mast cells, which are central effectors in IgE-mediated allergic reactions, are significantly expanded in the intestinal mucosa of CD patients. These cells express the high-affinity IgE receptor FcεRI and, upon crosslinking by IgE-antigen complexes, release histamine, prostaglandins, leukotrienes, and pro-inflammatory cytokines including

TNF-α and IL-6 [30]. This mast cell-derived mediator release contributes to increased intestinal permeability, smooth muscle contraction, visceral hypersensitivity, and recruitment of additional immune cells, thereby amplifying intestinal inflammation in CD [31,32].

The clinical relevance of IgE-mediated mechanisms in CD is further supported by observations that some patients experience symptomatic improvement on exclusion diets, and that food challenge studies can reproduce gastrointestinal symptoms in sensitized individuals. However, distinguishing IgE-mediated food allergy from non-immunological food intolerance in CD remains challenging and requires careful clinical and immunological characterization.

3.2. Type IV Hypersensitivity (Delayed-Type Reactions)

Type IV, or delayed-type hypersensitivity (DTH), is a T cell-mediated immune reaction that does not require antibody involvement and manifests 24–72 hours after antigen exposure. In CD, granulomatous inflammation represents a histological manifestation of DTH, driven by $CD4^+$ Th1 cells and activated macrophages responding to poorly degradable antigens [33]. Granuloma formation is a defining histological feature of CD and reflects persistent antigen-driven T cell activation and macrophage accumulation.

Patterns reminiscent of contact hypersensitivity have been observed in CD patients, with reports of nickel, cobalt, and dietary antigen sensitivities that correlate with disease activity [34]. Furthermore, DTH-like responses to microbial antigens, including anti-Saccharomyces cerevisiae antibodies (ASCA) and antibodies against bacterial flagellins, are well-established serological markers in CD and reflect aberrant T cell-dependent immune reactivity to intestinal microbiota. The interplay between DTH mechanisms and the classical Th1 response in CD underscores the complexity of T cell-mediated pathways in this disease.

3.3. Extraintestinal Allergic Manifestations in Crohn's Disease

CD is associated with a broad spectrum of extraintestinal manifestations, including cutaneous, articular, hepatobiliary, and ocular involvement. Among these, skin manifestations such as erythema nodosum and pyoderma gangrenosum may reflect systemic immune dysregulation with features overlapping allergic and autoinflammatory pathways [35]. Atopic dermatitis has been reported at higher frequencies in IBD patients than in the general population, suggesting shared type 2 immune mechanisms and potentially common epithelial barrier vulnerabilities.

Respiratory involvement in IBD patients, including increased rates of asthma and eosinophilic bronchitis, has been documented in population-based studies [36]. These associations may be explained by systemic activation of Th2-skewed immune responses, common genetic predispositions affecting epithelial barriers across mucosal surfaces, and shared regulatory defects. The gut-lung axis, mediated in part by systemic cytokine networks and shared mucosal immunity, may provide a mechanistic link between intestinal and respiratory allergic manifestations in CD [37]. Recognizing these extraintestinal allergic features in CD patients is important for comprehensive clinical management and for understanding the systemic nature of immune dysregulation in this disease.

4. The Role of Allergy in the General Pathogenesis of Crohn's Disease

4.1. Th2 Cytokine Involvement and Crosstalk with Th1/Th17 Pathways

Although CD was originally characterized as a predominantly Th1-mediated disease, subsequent research has revealed a more complex cytokine milieu in the inflamed intestinal mucosa. Th2 cytokines, particularly IL-4, IL-13, and IL-5, have been detected in the intestinal tissue of CD patients, albeit at variable levels [38]. IL-4 promotes IgE class switching, mast cell survival, and alternatively activated (M2) macrophage polarization, while IL-13 drives goblet cell hyperplasia, mucus overproduction, and smooth muscle hyperreactivity—features that contribute to altered intestinal motility and permeability in CD [39].

The crosstalk between Th2 and Th1/Th17 pathways in CD is bidirectional and context-dependent. IL-4 and IL-13 can suppress Th1 differentiation by downregulating IL-12 receptor expression, but may conversely amplify inflammatory responses by activating mast cells and eosinophils. Conversely, IFN-γ and TNF-α can enhance the expression of NKG2D ligands and stress molecules on epithelial cells, creating a permissive environment for type 2 effector cell activation [40]. Group 2 innate lymphoid cells (ILC2s), which produce large amounts of IL-4, IL-5, and IL-13 without requiring antigen-specific stimulation, have been identified in the intestinal mucosa and may bridge innate and adaptive type 2 immune responses in CD [41].

4.2. Mast Cells and Eosinophils as Effector Cells in Crohn's Disease

Mast cells and eosinophils are pivotal effector cells in type 2 immune responses and both exhibit expanded numbers and enhanced activation states in CD intestinal tissue. Intestinal mast cells in CD produce not only classical allergic mediators such as histamine and prostaglandin D2, but also pro-inflammatory cytokines including TNF-α, IL-6, and protease-activated receptor (PAR)-activating enzymes that disrupt epithelial tight junctions and enhance barrier permeability [42]. Mast cell-derived proteases, including tryptase and chymase, activate PAR-2 on epithelial cells, promoting visceral hypersensitivity and contributing to functional bowel symptoms in CD patients even during mucosal healing.

Eosinophil infiltration of the intestinal mucosa, while more characteristic of eosinophilic gastrointestinal disorders, is also documented in CD. Activated eosinophils release major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin, which damage epithelial cells, trigger mast cell degranulation, and promote fibrosis through TGF-β secretion [43]. IL-5, produced by Th2 cells and ILC2s, drives eosinophil differentiation and survival, linking adaptive type 2 immunity to eosinophilic tissue inflammation. The eotaxin/CCL11 axis facilitates intestinal eosinophil recruitment and has been found upregulated in CD mucosa [44,45].

4.3. IgE Receptor Signaling and Its Downstream Effects on Intestinal Inflammation

The high-affinity IgE receptor FcεRI is expressed on mast cells and basophils, and its activation by IgE-antigen

complexes triggers a cascade of downstream signaling events including activation of Syk, Btk, and phospholipase C-γ, leading to calcium mobilization and degranulation [46]. In addition to immediate mediator release, FcεRI signaling promotes synthesis and secretion of late-phase mediators such as prostaglandins, leukotrienes, and cytokines over several hours, sustaining mucosal inflammation. In the intestinal context, these mediators alter epithelial permeability, stimulate enteric neurons, and recruit effector immune cells, collectively exacerbating mucosal injury in CD [47].

Recent data suggest that IgE-independent FcεRI activation, through IgE-immune complexes or direct pattern recognition receptor co-stimulation, may also contribute to mast cell activation in CD. Furthermore, the low-affinity IgE receptor FcεRII (CD23) expressed on B cells and macrophages regulates IgE production and immune complex-mediated antigen presentation, providing additional mechanisms by which IgE-related pathways modulate intestinal immunity in CD [48].

4.4. Epithelial Alarmins: TSLP, IL-33, and IL-25 as Bridges Between Allergy and Crohn's Disease

Epithelial alarmins—TSLP (thymic stromal lymphopoietin), IL-33, and IL-25 (IL-17E)—are cytokines released by stressed or damaged epithelial cells that serve as upstream activators of type 2 immune responses. TSLP promotes dendritic cell maturation toward a Th2-polarizing phenotype and directly activates mast cells, ILC2s, and basophils [49]. In CD, TSLP expression is elevated in the inflamed intestinal epithelium and correlates with disease activity, suggesting a role in perpetuating type 2 immune activation at the mucosal surface.

IL-33, acting through its receptor ST2, activates ILC2s, mast cells, basophils, and Th2 cells, amplifying IL-4, IL-5, and IL-13 production [50]. IL-33 is released as an alarmin during epithelial damage, necrosis, or mechanical stress, making it a critical sensor linking epithelial injury to allergic immune activation. Elevated IL-33 and soluble ST2 levels have been reported in CD patients and correlate with inflammatory activity and treatment response [51]. IL-25 (IL-17E) selectively activates ILC2s and promotes Th2 differentiation, providing an additional epithelial-derived signal that sustains allergic responses in the intestinal mucosa [52]. Together, these alarmins form an epithelial-immune axis that connects mucosal barrier dysfunction to type 2 immune activation in CD, offering multiple mechanistic targets for therapeutic intervention.

5. Potential Therapeutic Approaches Targeting Allergy in Crohn's Disease

Recognition of the contribution of allergic mechanisms to CD pathogenesis creates new opportunities for therapeutic intervention beyond classical anti-inflammatory and immunosuppressive strategies. Several biologic agents originally developed for atopic conditions are now being explored in the context of CD, with promising early results [53].

5.1. Anti-IL-4/IL-13 therapy

Dupilumab, a fully human monoclonal antibody targeting the IL-4 receptor α subunit (IL-4Rα) and blocking both IL-4 and IL-13 signaling, has demonstrated efficacy in atopic dermatitis, asthma, and eosinophilic esophagitis. Preclinical and early clinical data suggest that IL-4/IL-13 blockade may reduce intestinal permeability, decrease

Table 1. Summary of key allergic pathways and their roles in Crohn's disease pathogenesis.

Pathway/Mediator	Cell Type	Effect in Crohn's Disease	Therapeutic Potential
IgE/FcεRI signaling	Mast cells, basophils	Mucosal permeability increase, pro-inflammatory mediator release, tissue edema	Anti-IgE therapy (omalizumab)
IL-4/IL-13 (Th2 cytokines)	Th2 lymphocytes, ILC2s	Goblet cell hyperplasia, mucus overproduction, epithelial barrier disruption	Dupilumab (anti-IL-4Rα)
IL-5/eosinophil axis	Eosinophils, Th2 cells	Tissue eosinophilia, granule protein-mediated epithelial damage, fibrosis	Anti-IL-5 (mepolizumab)
IL-33/ST2 signaling	ILC2s, mast cells, Th2	Alarmin-driven type 2 inflammation, amplification of mast cell responses	Anti-IL-33 (itepekimab)
TSLP pathway	Dendritic cells, ILC2s	Dendritic cell maturation, Th2 polarization, mucosal sensitization	Anti-TSLP (tezepelumab)
IL-25/IL-17RB axis	ILC2s, goblet cells	ILC2 activation, eosinophil recruitment, mucosal inflammation	IL-25 receptor blockade (experimental)
Histamine (H1/H2 receptors)	Mast cells, basophils	Vasodilation, smooth muscle contraction, visceral hypersensitivity	Antihistamines, ketotifen
Complement activation	Multiple immune cells	Amplification of mucosal inflammation, membrane attack complex formation	Complement inhibitors (investigational)

mast cell activation, and attenuate type 2-driven mucosal inflammation in IBD, including CD [54]. Given the overlapping immunological features between atopic diseases and CD, dupilumab represents a candidate agent for evaluation in CD patients with evidence of elevated Th2 activity [55].

5.2. Anti-IgE therapy

Omalizumab, an anti-IgE monoclonal antibody that sequesters free IgE and downregulates FcεRI expression, has been approved for allergic asthma and chronic spontaneous urticaria. Case series and small cohort studies have reported clinical benefit of omalizumab in IBD patients with concomitant allergic conditions, and pilot data suggest that IgE blockade may reduce mast cell activation and improve mucosal barrier function in CD [56,57]. Larger controlled trials are needed to establish the efficacy and safety of anti-IgE therapy specifically in CD.

5.3.Mast cell stabilizers and antihistamines

Ketotifen, a mast cell stabilizer with antihistamine properties, has been evaluated in small studies of CD and IBD patients with functional symptoms. Results indicate reductions in abdominal pain, diarrhea, and mast cell counts in intestinal biopsies, supporting the role of mast cells in symptom generation in CD [58]. Cromolyn sodium, another mast cell stabilizer, has shown benefit in patients with suspected food hypersensitivity contributing to IBD symptoms [59]. While these agents are unlikely to serve as primary disease-modifying therapies, they may have a role in managing functional symptoms and mast cell-driven mucosal inflammation in selected CD patients.

5.4. Anti-IL-33 and anti-TSLP biologics

Itepekimab (anti-IL-33) and tezepelumab (anti-TSLP) are biologic agents that target epithelial alarmins and have demonstrated efficacy in eosinophilic esophagitis and asthma. Given the documented elevation of IL-33 and TSLP in CD mucosa, these agents are being explored as potential therapeutic options in IBD [60,61]. Targeting upstream alarmins may provide broader immunomodulatory effects by simultaneously dampening mast cell, ILC2, and Th2 cell activation.

5.5. Dietary interventions and elimination diets

Identification and elimination of specific food triggers may reduce antigen-driven IgE activation and mucosal inflammation in CD patients with food sensitivities. The specific carbohydrate diet, exclusive enteral nutrition, and elimination diets targeting common allergenic foods have demonstrated clinical benefit in some CD patients [62]. These dietary strategies may act in part by reducing mast cell activation, restoring microbiome diversity, and decreasing epithelial alarmin release [63].

5.6. JAK inhibitors

Janus kinase (JAK) inhibitors, including upadacitinib and tofacitinib, broadly inhibit cytokine signaling through the JAK-STAT pathway, affecting both Th1/Th17 and Th2 responses. In addition to their established effects on TNF-α, IL-6, and IL-12/23 signaling, JAK inhibitors suppress IL-4 and IL-13 signaling through STAT6, and may reduce ILC2 activation and mast cell cytokine production [64]. Upadacitinib has demonstrated significant efficacy in CD in phase III trials and its broad immunomodulatory profile, encompassing allergy-related pathways, may contribute to its clinical benefit [65].

6. Discussion

The evidence reviewed here demonstrates that allergic mechanisms are not peripheral or incidental features of CD but constitute a pathogenically relevant component of the disease's complex immunological landscape. The presence of elevated IgE, intestinal mast cell expansion, eosinophilic infiltration, Th2 cytokine expression, and alarmin upregulation across diverse CD patient cohorts indicates that type 2 immune activation is a consistent, if variably expressed, feature of this disease [27,38].

A key conceptual challenge in this field is reconciling the classical Th1/Th17 paradigm of CD with the mounting evidence for type 2 immune involvement. Current understanding supports a model in which multiple immune axes operate simultaneously and interact dynamically in the CD mucosa. The relative contribution of Th1/Th17 versus type 2 pathways may vary between patients based on genetic background, environmental exposures, disease location, and disease phase [53]. This immunological heterogeneity underscores the need for biomarkers capable of stratifying patients according to their dominant immune phenotype, thereby enabling more targeted therapeutic selection.

The identification of epithelial alarmins—particularly TSLP, IL-33, and IL-25—as upstream integrators of both barrier dysfunction and type 2 immune activation is a conceptually important advance, as it provides a mechanistic link between the epithelial injury characteristic of CD and the allergic immune responses observed in the mucosa [60]. Targeting these alarmins may therefore address a fundamental upstream driver of allergic pathology in CD rather than individual downstream effectors.

Several limitations of current evidence must be acknowledged. The majority of studies examining allergic mechanisms in CD are observational or performed in small patient cohorts, limiting causal inference. Moreover, the distinction between cause and effect—whether allergic mechanisms drive CD or whether CD-associated inflammation promotes allergic responses—remains incompletely resolved. Future prospective studies with integrated immunophenotyping and clinical outcome data will be essential to clarify these relationships and identify patients most likely to benefit from allergy-targeted therapies [64].

7. Conclusions

The accumulated evidence supports a significant and multifaceted role for allergic reactions in the pathogenesis of Crohn's disease. First, type 2 immune mechanisms, including IgE-mediated activation, mast cell hyperplasia, eosinophilic infiltration, and Th2 cytokine production, are consistently documented features of CD that contribute to epithelial barrier disruption, mucosal permeability, and inflammatory amplification. Second, epithelial alarmins—TSLP, IL-33, and IL-25—link mucosal stress and barrier dysfunction to type 2 immune activation, representing critical upstream molecular connections between allergic and classical CD pathways.

Third, the interplay between Th2 and Th1/Th17 immune responses in CD is dynamic and bidirectional, suggesting that effective disease management may require targeting multiple immune axes simultaneously rather

than focusing exclusively on Th1/Th17-directed therapies. Fourth, emerging therapeutic strategies targeting IgE, IL-4/IL-13, IL-33, TSLP, and mast cell activation offer promising avenues for patients with allergy-predominant CD immune profiles who may not respond adequately to conventional biologics.

Finally, the development of biomarkers capable of identifying patients with dominant type 2 immune phenotypes will be essential for implementing personalized treatment strategies in CD. Future clinical trials specifically designed to evaluate allergy-targeted therapies in molecularly defined CD patient subgroups, combined with mechanistic studies elucidating the interactions between allergic and classical inflammatory pathways, will be critical for translating these insights into clinical practice.

Conflict of Interests
The author has no conflicts of interest.

Ethics approval and consent to participate
No human or animals were used in the present research.

Informed Consent
The authors declare that no patients were used in this study.

Availability of data and material
Not applicable.

Authors' contributions
All authors had equal roles in study design, work, statistical analysis and manuscript writing.

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