International Journal of Medical and Pharmaceutical Sciences
Open access peer-reviewed Journal
Volume 2, Issue 7, Page 484-487.
https://doi.org/10.5281/zenodo.21274289

Review Article

Immunoglobulin E (IgE): From Discovery and Structure to Molecular Regulation, Genetics, and Therapeutic Targets in Allergic and Autoimmune Diseases

Dinesh P.*, N. Nandhakumar, P. Krishnakumar, S. Parthiban, M. Madhumithra, A. Manoj, S. Nandhini, G. Rathinavel

K. S. Rangasamy College of Pharmacy

Immunoglobulin E (IgE) represents the fifth identified class of human immunoglobulins and plays a central, pivotal role in the pathogenesis of type I hypersensitivity reactions, allergic asthma, and related atopic disorders. First identified in the late 1960s through pioneering research on reaginic antibodies and myeloma protein ND, IgE is characterized by unique structural features, including its high-affinity interaction with its cognate receptor FcεRI. This review paper synthesizes key historical milestones, physical and chemical properties, complex molecular regulation mechanisms governing isotype switching (driven primarily by interleukin-4 and interleukin-13), and the genetic control of serum IgE concentrations. Furthermore, we explore modern clinical insights regarding the dual nature of IgE in mediating protective immunity versus driving autoallergy and systemic autoimmunity. Finally, we evaluate the therapeutic revolution introduced by anti-IgE targeted monoclonal antibodies, such as omalizumab, which block receptor-binding pathways and provide a foundation for precision medicine in severe allergic diseases.

Keywords: Immunoglobulin E (IgE), Reaginic Antibodies, Isotype Switching, Interleukin-4, Omalizumab, Autoallergy, Genetic Heritability.

INTRODUCTION

Introduction and Historical Context

The designation "reagin" was historically assigned to spontaneously produced skin-sensitizing antibodies found within allergic human sera. The pioneering discovery of this immune component dates back to 1921 when Prausnitz and Küstner demonstrated immediate hypersensitivity passive transfer. In their classic experiment, Prausnitz injected serum from his allergic patient, Küstner, into his own forearm, subsequently eliciting an erythema-wheal reaction upon challenge with the specific fish antigen. This definitive passive transfer mechanism established that atopic individuals possess circulating serum factors responsible for immediate allergy manifestations. For over four decades following this fundamental observation, the exact molecular nature of reaginic antibodies remained elusive despite strenuous efforts using diverse serum fractionation methodologies. The breakthrough arrived in 1966-1967 when Kimishige Ishizaka and Teruko Ishizaka successfully isolated and characterized human reaginic antibodies, demonstrating that reaginic activity could not be attributed to known immunoglobulin classes (IgG, IgA, IgM, or IgD). Instead, it belonged to a novel, distinct class designated as Immunoglobulin E (IgE). Concurrently, Hans Bennich and S. Gunnar O. Johansson in Sweden identified a unique atypical myeloma protein (termed Myeloma Protein ND) that shared structural, physicochemical, and antigenic properties with the newly discovered IgE molecule. In 1968, the World Health Organization (WHO) International Reference Centre for Immunoglobulins officially declared IgE as the fifth class of human immunoglobulins, igniting a modern era of molecular allergology and immunology.

2. Structural and Physicochemical Properties of IgE

Structurally, IgE is distinct from other immunoglobulins due to its higher molecular weight (approximately 190,000 Daltons) and its unique heavy chain composition. While standard IgG molecules possess three constant domains (CH1, CH2, CH3), the IgE heavy chain—referred to as the epsilon (ε) chain—contains an extra constant domain, giving it four constant domains (Cε1, Cε2, Cε3, and Cε4). This additional domain replaces the hinge region found in IgG, contributing to its structural rigidity and unique receptor binding configurations.

IgE exhibits a carbohydrate content of roughly 12%, making it highly glycosylated compared to IgG. It possesses a sedimentation coefficient of approximately 8S and is exceptionally heat-labile; exposure to a temperature of 56°C for 4 to 24 hours completely destroys its capacity to passively sensitize human skin tissues, a property that historically differentiated it from heat-stable IgG antibodies. Enzymatic digestion of IgE using papain yields two monovalent Fab fragments and one Fc fragment, whereas pepsin digestion produces a bivalent F(ab')2 fragment and leaves the Cε3 and Cε4 domains intact. The critical biological functions of IgE, including its ability to bind with extremely high affinity (Ka ≈ 10^10 M^-1) to the high-affinity receptor FcεRI expressed on mast cells and basophils, are strictly mediated by the structural motifs contained within the Cε3 and Cε4 domains.

3. Molecular Mechanisms of IgE Regulation and Isotype Switching

The regulation of IgE synthesis is an extraordinarily tight, multi-step molecular procedure. Under physiological conditions, IgE is the least abundant immunoglobulin class in human serum, with baseline concentrations frequently being 10,000-fold lower than those of IgG. B lymphocyte production of IgE requires an ordered genomic rearrangement process known as Class Switch Recombination (CSR). The immunoglobulin heavy chain locus on human chromosome 14 contains an array of constant region genes arranged in tandem, with the epsilon (Cε) gene positioned downstream of the mu (Cμ), delta (Cδ), and gamma (Cγ) genes.

Isotype switching to IgE requires two essential signals delivered by helper T cells (specifically Th2 cells) and cooperating cytokines. The primary signal is mediated by the cytokines Interleukin-4 (IL-4) or Interleukin-13 (IL-13). Binding of IL-4 or IL-13 to their respective receptor complexes on B cells triggers a signal transduction cascade involving the Janus Kinase / Signal Transducer and Activator of Transcription (JAK/STAT6) pathway. This pathway initiates the transcription of germline ε transcripts (Iε-Cε), rendering the locus physically accessible to the recombination machinery. The secondary signal requires direct cell-to-cell contact, mediated by the interaction between the CD40 ligand (CD154) expressed on activated T cells and the CD40 receptor constitutively expressed on B cells. This contact induces expression of Activation-Induced Cytidine Deaminase (AID) and standard recombination activation genes (RAG-1 and RAG-2), which catalyze loops and double-stranded DNA breaks within the switch (S) regions. Specifically, the recombination aligns the Sμ region with the Sε region, creating an Sμ/Sε junction and deleting the intervening genomic fragments. This permanently shifts the B-cell clone to produce antigen-specific IgE antibodies.

4. Genetic Control of Serum IgE Concentrations

Serum concentrations of total IgE (tIgE) are subject to profound genetic control, operating independently or in concert with specific allergen sensitization (sIgE). Classic heritability trials using twin cohorts and large family pedigrees have demonstrated a strong genetic foundation for baseline IgE production. Early pioneering models estimated total IgE heritability to be between 0.40 and 0.60 in adults, and up to 0.79 in pediatric populations. Segregation analyses have frequently pointed to a major regulatory locus displaying mendelian inheritance patterns where low IgE levels act as a dominant trait and high IgE levels exhibit a recessive phenotype.

Linkage analyses and genome-wide association studies have identified several key chromosomal regions associated with elevated IgE phenotypes. Foremost among these is chromosome 5q31.1, a dense cytokine cluster containing the genes for IL-3, IL-4, IL-5, IL-13, and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF). Polymorphisms within the IL-13 gene, particularly a cluster of tightly linked variants, show robust statistical associations with total serum IgE concentrations across diverse racial and geographic populations. Additionally, linkage markers on chromosome 14q, located near the immunoglobulin heavy chain variable and constant loci, play an integrative role in modulating the baseline propensity of the immune system to undergo isotype switching toward the IgE lineage.

5. Pathophysiological Roles in Health and Disease

5.1 Allergic Reactions and Type I Hypersensitivity

The primary classical mechanism of IgE-mediated disease is Type I immediate hypersensitivity. Upon primary exposure to an environmental allergen (e.g., pollen, dust mite, or animal dander), susceptible individuals generate allergen-specific IgE. These antibodies rapidly bind to high-affinity FcεRI receptors on the surfaces of tissue-resident mast cells and circulating basophils. Upon subsequent re-exposure, the multivalent allergen cross-links adjacent receptor-bound IgE molecules, triggering intracellular signaling cascades that culminate in immediate degranulation. This release introduces preformed mediators such as histamine, proteoglycans, and neutral proteases, alongside newly synthesized lipid mediators (leukotrienes and prostaglandins) and cytokines into the local tissue environment. Clinically, these mediators induce smooth muscle contraction, vasodilation, and tissue inflammation, characteristic of allergic asthma, allergic rhinitis, and systemic anaphylaxis.

5.2 IgE-Mediated Autoimmunity (Autoallergy)

While historically categorized exclusively as a driver of exogenous allergic diseases, recent evidence has uncovered a pathological role for IgE in mediating autoimmune diseases, a paradigm termed "autoallergy." In these scenarios, B-cell clones undergo isotype switching to produce IgE autoantibodies directed against self-antigens. Conditions such as Systemic Lupus Erythematosus (SLE), Bullous Pemphigoid (BP), and Chronic Spontaneous Urticaria (CSU) exhibit prominent IgE-mediated autoimmune mechanisms. For instance, in SLE, patients often harbor IgE autoantibodies specific to double-stranded DNA (dsDNA) or Smith antigen. These IgE-autoantigen complexes activate basophils or plasmacytoid dendritic cells, significantly amplifying the production of type I interferons and accelerating tissue injury. In Bullous Pemphigoid, IgE antibodies target the hemidesmosomal proteins BP180 and BP230, driving mast cell activation and subsequent subepidermal blistering, highlighting IgE's broad impact beyond traditional allergy.

6. Clinical Insights and Therapeutic Targeting: Anti-IgE Therapy

Given its central positioning within the allergic inflammatory cascade, neutralizing IgE has emerged as a major therapeutic strategy. Omalizumab (commercially known as Xolair) represents the first-in-class recombinant humanized monoclonal antibody designed to specifically target human IgE. The therapeutic mechanism of omalizumab relies on its precise binding to the Cε3 domain of circulating IgE, at the exact site where IgE interacts with its high-affinity (FcεRI) and low-affinity (FcεRII/CD23) receptors. By capturing free, unbound IgE in the circulation, omalizumab effectively reduces the concentration of free serum IgE by greater than 95%. Crucially, omalizumab cannot bind to IgE that is already anchored to receptors on mast cells or basophils, thereby preventing the danger of cross-linking receptors and accidentally inducing anaphylaxis. The massive reduction in circulating free IgE causes a profound down-regulation of FcεRI expression on mast cells, basophils, and dendritic cells, rendering them significantly less responsive to allergen challenge. Extensive clinical trials in pediatric and adult patients with moderate-to-severe allergic asthma have demonstrated that anti-IgE therapy markedly reduces asthma exacerbations, decreases emergency room visits, and allows a significant down-titration of inhaled corticosteroids, cementing IgE's status as a highly validated therapeutic target.

CONCLUSION AND FUTURE DIRECTIONS

Over a century since the initial description of the Prausnitz-Küstner reaction, research into

Immunoglobulin E has evolved from identifying mysterious "reaginic" properties to mapping complex genomic and cellular landscapes. IgE represents a highly potent immunological molecule whose regulation, while strict, can become perturbed due to genetic susceptibility or environmental cues, leading to severe atopic or autoimmune pathologies. The clinical success of anti-IgE targeting with omalizumab validates this pathway and opens the door for next-generation biologics with enhanced affinity or multi-specific targeting capabilities. Future research must continue to unravel the precise triggers of autoallergic IgE synthesis and explore the potential role of IgE in protective mucosal barriers, ensuring the delivery of optimal, personalized immunotherapies.

REFERENCES

1. Ishizaka, K., and Ishizaka, T. Human reaginic antibodies and immunoglobulin E. The Journal of Allergy and Clinical Immunology.
2. Bennich, H., and Johansson, S. G. O. Structure and Function of Human Immunoglobulin E. Advances in Immunology, Academic Press.
3. Bacharier, L. B., Jabara, H., and Geha, R. S. Molecular Mechanisms of Immunoglobulin E Regulation. International Archives of Allergy and Immunology.
4. Gerrard, J. W., Rao, D. C., and Morton, N. E. A Genetic Study of Immunoglobulin E. American Journal of Human Genetics.
5. Amarasekera, M. Immunoglobulin E in health and disease. Asia Pacific Allergy.
6. Maurer, M., Altrichter, S., Schmetzer, O., Scheffel, J., Church, M. K., and Metz, M. Immunoglobulin E-Mediated Autoimmunity. Frontiers in Immunology.
7. Owen, C. E. Immunoglobulin E: Role in asthma and allergic disease: Lessons from the clinic. Pharmacology & Therapeutics.

Cite: Dinesh P.*, N. Nandhakumar, P. Krishnakumar, S. Parthiban, M. Madhumithra, A. Manoj, S. Nandhini, G. Rathinavel, Immunoglobulin E (IgE): From Discovery and Structure to Molecular Regulation, Genetics, and Therapeutic Targets in Allergic and Autoimmune Diseases, Int. J. Med. Pharm. Sci., 2026, 2 (7), 484-487. https://doi.org/10.5281/zenodo.21274289