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Introduction to Mechanisms of Allergic Diseases

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CHAPTER OUTLINE

SUMMARY OF IMPORTANT CONCEPTS

- Allergic inflammation is a result of a complex interplay among structural tissue cells and inflammatory cells, including mast cells, basophils, lymphocytes, dendritic cells, eosinophils, and, sometimes, neutrophils.
- Cytokines are families of secreted proteins that mediate immune and inflammatory reactions at local or distant sites.
- The innate immune system first responds to early infectious and inflammatory signals, activating and instructing the adaptive immune system for antigen-specific T and B lymphocyte responses and the development of immunologic memory.
- Allergen recognition and uptake, allergic sensitization, inflammation, and disease originate in the innate immune system.
- Adaptive immune responses depend on activation of naive $CD4^+$ T cells and differentiation into effector cells. $CD4^+$ T

helper type 2 (Th2) cells are critical mediators of allergic inflammation.
- Production of IgE antibody is regulated mainly by Th2 cells. Activated Th2 cells trigger IgE production in B cells through a combination of signals, including secreted cytokine (interleukin [IL]-4 or IL-13) and cell surface (CD40L).
- Better understanding of the pathophysiology of allergic inflammation will enable us to identify novel therapeutic targets in the treatment of chronic allergic inflammation.

INTRODUCTION

The inflammatory process has several common characteristics shared by various different allergic diseases, including asthma, allergic rhinitis (AR) or rhinosinusitis, atopic dermatitis (AD) (eczema), and food allergy. Allergic inflammation is characterized by IgE-dependent activation of mucosal mast cells and an infiltration of eosinophils that is orchestrated by increased numbers of activated $CD4^+$ T helper type 2 (Th2) lymphocytes. In addition to these cells, various types of inflammatory cells produce multiple inflammatory mediators, including lipids, purines, cytokines, chemokines, and reactive oxygen species. Both innate and adaptive immune mechanisms and involvement of multiple cytokines and chemokines play roles.

INNATE IMMUNITY

Innate immunity is an essential part of the immune system and is the first line of defense against microorganisms and foreign bodies such as allergens. It acts by the action of a limited number of receptors specific to microbial components. As a result, both rapid immune response and activation of the adaptive immune system occurs. Starting from body surfaces, epithelial cells, dendritic cells (DCs), natural killer (NK) cells, innate lymphoid cells (ILCs), macrophages, mast cells, eosinophils, basophils, and neutrophils are main players for the innate immune response. Epithelial barrier and microbiome as well as physicochemical factors such as mucus, antimicrobial peptides (AMPs), ciliary movement, cough, and peristaltism all play a role in innate defense mechanisms.[1]

Microbial Pattern Recognition by the Innate Immune System

Microbial recognition by the innate immune system is mediated by germline-encoded receptors with genetically predetermined specificities for microbial constituents. Natural selection has formed and refined the repertoire of innate immune receptors to recognize highly conserved molecular structures that distinguish large groups of microorganisms from the host. These microbe-specific structures are called *pathogen-associated molecular patterns* (PAMPs), and the *pattern recognition receptors* (PRRs) of the innate immune system recognize these structures (Table 1.1).

Pattern Recognition Receptors

PRRs of the innate immune system can be divided into two groups: secreted receptors and transmembrane signal-transducing receptors (Table 1.1). *Secreted PRRs* typically have multiple effects in innate immunity and host defense, including direct microbial killing, serving as helper proteins for transmembrane receptors, opsonization for phagocytosis, and chemoattraction of innate and adaptive immune effector cells. AMPs are secreted PRRs that are microbicidal and rapidly acting. When secreted onto skin and mucous membranes, they create a microbicidal shield against microbial attachment and invasion.

Transmembrane PRRs are expressed on many innate immune cell types, including macrophages, DCs, monocytes, and B lymphocytes (Fig. 1.1). These PRRs are exemplified by the Toll-like receptors (TLRs) and their associated recognition, enhancing, and signal transduction proteins (Fig. 1.1). Innate immune response at the epithelial cell–related and DC-related processes are controlled by the activation of the epithelial PRR by PAMPS found in the microorganisms as well as the host-derived damage-associated molecular patterns (DAMPs). Airway epithelial cells and DCs express a wide range of TLRs, NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), AIM2-like receptors (ALRs), C-type lectin receptors (CLRs), protease-activated receptors (PARs), and others.[2,3]

Cellular Responses of Innate Immunity

Microbial detection by PRRs activates the cells that express or bind them. Those in frontline positions for detection are the first responders of the innate immune system, such as tissue macrophages, fibrocytes, epithelial cells, and mast cells.

Innate immune activation also leads to multifaceted antimicrobial responses by tissue infiltrating immune cells (e.g., neutrophils, NK cells, DCs, monocytes). These responses are potent antimicrobial effectors that usually are recruited by an innate immune intermediary to induce the full weight of their response, but they can respond directly to microbial stimuli through their own surface-expressed PRRs. On reaching the infected site, neutrophils phagocytose invading microorganisms that are opsonized by complement C3 fragments (e.g., C3b, iC3b) and immunoglobulin G (IgG).[4] Recruited and activated NK cells mediate antimicrobial activities by induction of apoptosis of cell targets and cytokine secretion that promote innate immune functions and contribute to adaptive immune responses.

DCs are transformed into active antigen-presenting cells (APCs) by stimulation of the TLR and they initiate and mediate adaptive immune responses. Additionally, DCs together with interferon (IFN)-γ can induce macrophage polarization, which is important for phagocytosis.[5] DCs in the blood can be divided into two groups as myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). mDCs selectively express TLR2–6 and TLR2–8 and respond to bacterial and viral infections by producing large amounts of interleukin (IL)-12. However, pDCs express TLR7 and TLR9 associated with the endosome and produce type 1 IFNs.[6] The newly described cell type native lymphoid cells have effector functions in homeostasis and inflammation. ILC1s and ILC3s are essential for defense against infection by viruses, intracellular bacteria, and parasites. However, ILC2s direct type 2 inflammation and mediate allergic inflammation, tissue repair, and anti-helminth innate immunity.[5]

TABLE 1.1 Innate Pattern Recognition Receptors in Humans

Pattern Recognition Receptors	PAMP Structures Recognized	Functions
Secreted		
Antimicrobial peptides		
α- and β-Defensins	Microbial membranes (negatively charged)	Opsonization, microbial cell lysis, immune cell chemoattractant
Cathelicidin (LL-37)		
Dermcidin		
RegIIIγ		
Collectins		
Mannose-binding lectin	Microbial mannan	Opsonization, complement activation, microbial cell lysis, chemoattraction, phagocytosis
Surfactant proteins A and D	Bacterial cell wall lipids; viral coat proteins	Opsonization, killing, phagocytosis, proinflammatory and antiinflammatory mediator release
Pentraxins		
C-reactive protein	Bacterial phospholipids (phosphorylcholine)	Opsonization, complement activation, microbial cell lysis, chemoattraction, phagocytosis
Secreted and membrane bound		
CD14	Endotoxin	TLR4 signaling
LPS binding protein	Endotoxin	TLR4 signaling
MD-2	Endotoxin	TLR4 co-receptor
Membrane bound		
Toll-like receptors	Microbial PAMPs	Immune cell activation
C-type lectin receptors		
Mannose receptor (CD206)	Microbial mannan	Cell activation, phagocytosis, proinflammatory mediator release
DECTIN-1	β-1,3-Glucan	Cell activation, phagocytosis, proinflammatory mediator release
DECTIN-2	Fungal mannose	Cell activation, phagocytosis, proinflammatory mediator release
DC-SIGN	Microbial mannose, fucose	Immunoregulation, IL-10 production
Siglecs	Sialic acid containing glycans	Cell inhibition, endocytosis
Cytosolic		
NOD-like receptors		
NOD-1	Peptidoglycans from gram-negative bacteria	Cell activation
NOD-2	Bacterial muramyl dipeptides	Cell activation
NLRP1	Anthrax lethal toxin	PAMP recognition in inflammasome
NLRP3 (cryopyrin)	Microbial RNA	PAMP recognition in inflammasome
NLRC4	Bacterial flagellin	PAMP recognition in inflammasome
RIG-I and MDA5	Viral double-stranded RNA	Type 1 IFN responses

DC-SIGN, Dendritic cell–specific intracellular adhesion molecule 3 (ICAM-3)–grabbing non-integrin; *DECTIN*, dendritic cell–specific receptor; *IFN*, interferon; *IL*, interleukin; *LPS*, lipopolysaccharide; *MD-2*, myeloid differentiation factor 2 (also called lymphocyte antigen 96 [LY98]); *MDA5*, melanoma differentiation-associated 5 (also called interferon induced with helicase domain 1 [IFIH1]); *NLR*, NOD-like receptor; *NOD*, nucleotide-binding oligomerization domain protein; *PAMP*, pathogen-associated molecular pattern; *RegIIIγ*, regenerating islet-derived 3 γ (REG3G); *RIG-I*, retinoic acid-inducible 1 (also called DDX58); *Siglecs*, sialic acid–binding immunoglobulin-like lectins; *TLR*, Toll-like receptor.

Innate Instruction of Adaptive Immune Responses

The immediate and infiltrative responses of innate immunity activate and instruct the adaptive immune system for antigen-specific T and B lymphocyte responses and the development of immunologic memory. Because the adaptive immune system essentially has a limitless antigen receptor repertoire, instruction is necessary to guide adaptive antimicrobial immune responses toward pathogens and not self-antigens or harmless environmental antigens. Microbial pattern recognition by innate immune cells controls the activation of adaptive immune responses by directing microbial antigens linked to TLRs and other PRRs through the cellular processes leading to antigen presentation and the expression of costimulatory molecules (e.g., CD80 with CD86). This two-step activation of the immune system, an innate immune response first and then an adaptive immune response, prevents unnecessary inflammatory responses and is highly effective.[7]

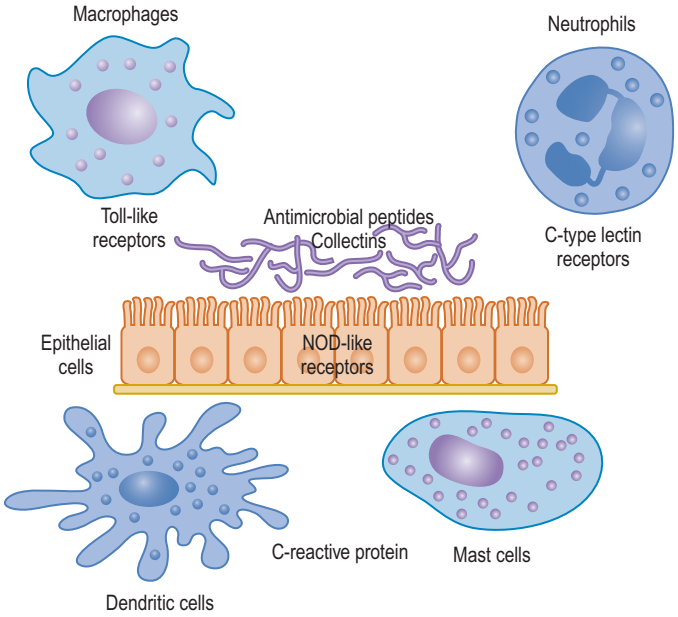

Fig. 1.1 Main categories of pattern recognition receptors and the innate immune cell types that express them. *NOD*, Nucleotide-binding oligomerization domain protein. (Adapted from Liu AH. Innate microbial sensors and their relevance to allergy. J Allergy Clin Immunol. 2008;122:846-858.)

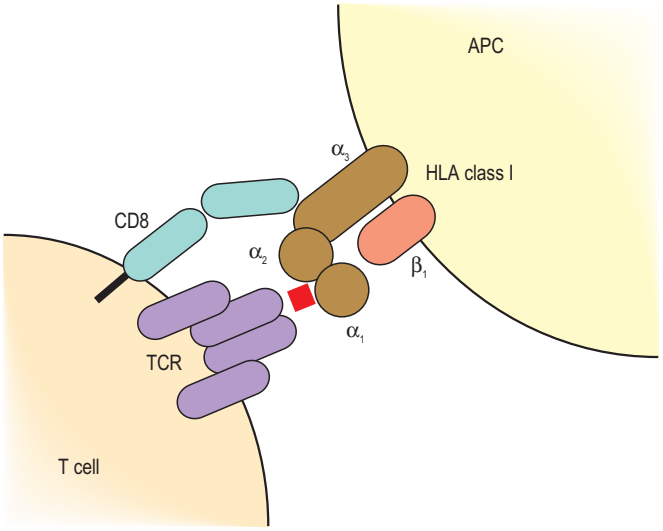

Fig. 1.2 Interaction of a human leukocyte antigen *(HLA)* class I molecule on an antigen-presenting cell *(APC)* with a $CD8^+$ T cell. The antigen receptor (i.e., T cell receptor *[TCR]*) complex *(purple)* recognizes a combination of an antigen peptide *(red)* and an HLA molecule (*brown* and *pink*). The CD8 molecule *(aqua blue)* in the T cells interacts with the α_3 domain of the HLA molecule. HLA class II molecules present antigen peptides to $CD4^+$ T cells in a similar manner, interacting with the TCR and the CD4 molecules.

Innate Immunity and Allergy

The innate immune system of the airways, gastrointestinal tract, and skin is continuously exposed to potential allergens. As with microbial antigens, allergens can engage innate PRRs, are processed through innate immune cells, and can lead to pathologic allergic/inflammatory immune responses. Although the circumstances leading to allergic immunity in humans are not clear, evidence suggests that allergic susceptibilities can originate in the innate immune system.[8]

ADAPTIVE IMMUNITY

Adaptive Immune Response in Allergic Disease

A remarkable property of the adaptive immune system is its memory. Immunologic memory is made possible by the clonal expansion of T and B lymphocytes in response to antigen (including allergen) stimulation. From the time the human immune system begins to differentiate in fetal life, lymphocytes possessing unique reactivity are created by the recombination of genes encoding antigen receptors expressed on the lymphocyte cell membrane. Through the expression of these receptors, T and B lymphocytes have the ability to bind to and become activated by a specific antigen, which may be natural or artificial. Interaction with antigen activates the lymphocytes and generates long-lived, antigen-specific memory T and B cell clones. When the same antigen enters the body, there is immediate recognition by these memory cells. Cellular and humoral responses to the antigen are produced more rapidly than in the first encounter, and more memory cells are generated. This process of expansion of clonal populations of uniquely reacting lymphocytes first explained the B cell origin of antibody diversity and applies to cellular (T cell) immune responses.

Main Components of the Adaptive Immune System

All cells of the immune system are derived from the pluripotent hematopoietic stem cell found in the bone marrow. This pluripotential stem cell gives rise to lymphoid stem cells and myeloid stem cells. The lymphoid progenitor cell differentiates into three types of cell, *T cell, B cell, and ILC and NK cell*, and contributes to the development of subsets of DCs. The myeloid stem cell gives rise to DCs, mast cells, basophils, neutrophils, eosinophils, monocytes, and macrophages, as well as megakaryocytes and erythrocytes. Differentiation of these committed stem cells depends on an array of cytokine and cell–cell interactions.

Features of the Adaptive Immune Response

APCs, which include DCs, monocytes, or macrophages, process and present antigen within an antigen-binding cleft of major histocompatibility complex (MHC) molecules. These events start at the APC cell surface with the capture and endocytosis of antigens, followed by a complex sequence of enzymatic activities leading to the association of antigenic peptides with MHC molecules and expression back to the cell surface. $CD4^+$ T cells recognize antigenic peptides when presented in the context of a class II MHC molecule (Fig. 1.2) together with the appropriate costimulatory signals and become activated in response to monocyte-derived IL-1 and other cytokines, including autocrine stimulation by IL-2.

Subsets of Th cells dictate the cytokine production involved in three types of immune responses. Th1 response, induced by IL-12 and IFN-γ, is responsible for T cell–mediated cytotoxicity. Th2 response, induced by IL-4, IL-5, and IL-13, is responsible for the development of IgE- and eosinophil-mediated allergic disease. Th17 response leads to a characteristic neutrophilic inflammation and is pathogenic in some experimental models of autoimmunity. Transforming growth factor-β (TGF-β), IL-23, and IL-6 are essential cytokines for developing the Th17 response, which is mediated by IL-17A, IL-17F, IL-21, and IL-22.

The defensive capacity of the immune system needs a mechanism to counterbalance this proinflammatory response and to minimize unnecessary tissue damage. Several processes ensure that the different immune effector cells are not activated against host tissues and innocuous substances and that they can downregulate a response after the threat is resolved. All of these processes underlie *immune tolerance*, which is classified as central when occurring in primary lymphoid organs, or as peripheral when occurring in other tissues. Together with central and peripheral tolerance processes, a subset of T cells characterized by high levels of CD25 expression (IL-2R α chain) have been identified as regulatory T (Treg) cells because they were found to suppress the function of other T cells when present in the same site (Fig. 1.3).[9]

Mechanisms of Diseases Involving Adaptive Immunity

Distinct mechanisms of immune-mediated diseases are IgE-mediated hypersensitivity, antibody-mediated cytotoxicity, immune complex reaction, delayed hypersensitivity response, antibody-mediated activation or inactivation of biologic function, cell-mediated cytotoxicity, and granulomatous reaction.

IMMUNOGLOBULIN STRUCTURE AND FUNCTION

B Lymphocytes and the Humoral Immune Response

Engagement of the B cell receptor (BCR) by antigen initiates receptor aggregation at the cell surface followed by recruitment to lipid rafts. Lipid rafts are specialized membrane microdomains that facilitate assembly and activation of downstream signaling molecules.[10] This step places the complex in proximity to the LYN tyrosine kinase, which phosphorylates tyrosine residues in the Igα/Igβ ITAM motifs and triggers recruitment of spleen tyrosine kinase (SYK) and Bruton tyrosine kinase (BTK). Activated SYK phosphorylates and recruits the B cell linker (BLNK) protein, which provides binding sites for phospholipase Cγ2 (PLCγ2), BTK, and VAV proteins, which are guanine nucleotide exchange factors. PLCγ2 generates the second messengers inositol triphosphate and diacylglycerol, which are necessary for calcium release from intracellular stores and protein kinase C activation. BCR signal transduction also leads to activation of the mitogen-activated protein kinase (MAPK) pathway. B cell activation is further aided by a co-receptor complex that amplifies signals delivered by the BCR. The members of this complex include CD19, the complement receptor type 2 (CR2 or CD21), and CD81. The CR2 enables the complement pathway to synergize with BCR signal transduction, which enhances B cell activation. Collectively, these signaling events lead to the activation of the transcription factors known as nuclear factor of activated T cells (NFAT), nuclear factor-κB (NF-κB), and activator protein 1 (AP-1). Activation of the BCR on naive and memory B cells results in their activation and migration to the draining lymph node or other lymphatic tissue. B cells can respond to three types of antigens, and the type of antigenic exposure dictates the quality of the ensuing response.

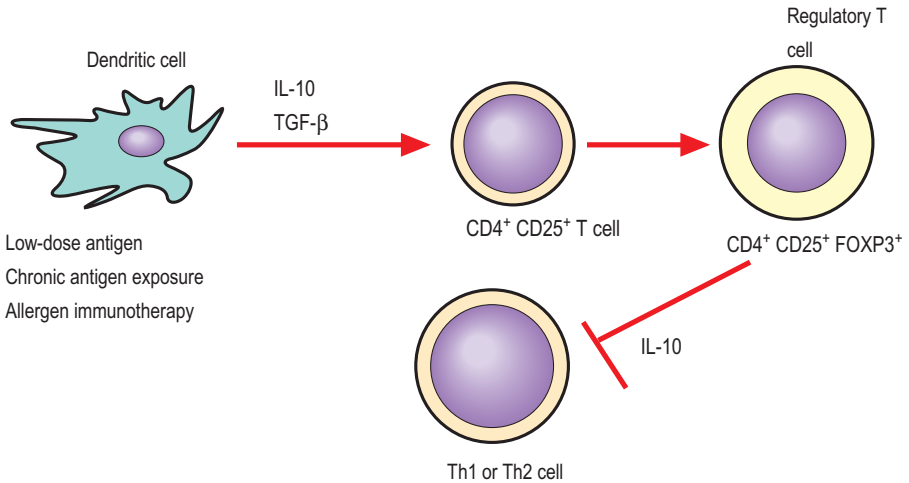

Fig. 1.3 Regulatory T cells are generated by the interaction of antigen-presenting cells and T cells, mediated by the cytokines interleukin-10 *(IL-10)* and transforming growth factor-β *(TGF-β)*. These cytokines are secreted when the antigen is presented under certain conditions, such as when administering allergen immunotherapy at very low concentration. Regulatory T cells secrete IL-10 and inhibit effector T cells that share similar antigen specificity.

Immunoglobulin Structure and Gene Rearrangement

Immunoglobulins are composed of two identical heavy chains and two identical light chains (Fig. 1.4A). Light chains lack transmembrane domains and are anchored to heavy chains by disulfide bonds. The two heavy chains are linked to each other by a distinct set of disulfide bonds. Each heavy chain or light chain has two major domains referred to as the *constant region* (C) and the *variable region* (V), with each domain responsible for a specialized function. They are denoted as C_L and V_L for the light chains and as CH and VH for the heavy chains.

Heavy-chain variable regions are encoded by one V gene, which encodes most V-region amino acids, as well as 1 of 23 diversity (D) and 1 of 6 joining (J) gene segments that are located 3′ of the V gene cluster. In contrast, light chain variable regions are encoded by only two types of genes: V genes and J genes. Whereas the J_κ genes are organized in a cluster 3′ to the V_κ gene cluster, J_λ genes are interspersed with λ constant-region genes.

Immunoglobulin diversity has four sources: multiple V(D)J genes in the germline, random assortment of heavy chains and light chains, junctional nucleotide variability introduced during pre-B cell immunoglobulin gene rearrangement, and somatic hypermutation of immunoglobulin variable regions after encounters with antigens.

Immunoglobulin Function

The five classes of antibody molecules are designated IgM, IgD, IgG, IgA, and IgE. The IgG and IgA classes have more than one member. There are four IgG (γ) sub-classes, designated as IgG1, IgG2, IgG3, and IgG4, and their constant regions exhibit 90% homology with each other. However, because each IgG sub-class constant region is encoded by a separate constant-region gene, the IgG sub-classes are closely related isotypes that exhibit a similar overall structure. The two sub-classes of IgA are similarly related to each other. There are two types of light chains: κ and λ. There are four λ sub-types but only one form of κ. The nine class and sub-classes of antibody molecules have significantly different expression levels, anatomic locations, and effector functions (Table 1.2). The five antibody classes also display characteristic structural features (Fig. 1.4B).

IMMUNOGLOBULINS AND HUMAN DISEASE

Human conditions of dysregulated immunoglobulin production include antibody deficiencies and overproduction of specific antibodies. The most serious of the three major categories of antibody deficiencies result in reduced B cell numbers and a severe decrease in all isotypes of serum immunoglobulin, as in agammaglobulinemia. This type of immunodeficiency underscores the importance of tyrosine kinases in early B cell BCR signal transduction. The second category includes selective deficiencies of IgA or IgG2 production and various genetic mutations that result in hypogammaglobulinemia, such as deficiencies in transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI). The third category includes a number of mutations that give rise to hyper-IgM syndromes, which result from the failure of B cells to undergo class-switch recombination. These disorders highlight the critical role that CD40–CD40L interaction plays in class-switch recombination, as revealed by the lack of IgG, IgA, and IgE antibodies in these patients.

There are also some other disorders characterized by abnormalities in immunoglobulins. IgG4-related disease is a chronic inflammatory condition characterized by tissue infiltration by lymphocytes and IgG4-secreting plasma cells, varying degrees of fibrosis (scarring), and generally rapid response to oral steroids. IgG4 serum levels increased in the acute period in two-thirds of the patients. IgA nephropathy, also known as Berger disease, is a kidney disease that occurs when IgA accumulates in the kidneys and causes inflammation that damages kidney tissues. Hyperimmunoglobulinemia E syndromes (HIESs) are a heterogeneous group of immune disorders characterized by recurrent "cold" staphylococcal infections (due to inadequate accumulation of neutrophils), unusual eczema-like skin rash, pneumatoceles, and severe lung infections resulting in very high serum IgE levels.

IMMUNE TOLERANCE

Introduction

The physiopathology of immune tolerance–related diseases, such as allergies, asthma, autoimmunity, organ transplantation, tumor, chronic infections, and abortions, is complex and is influenced by factors, such as genetic susceptibility, environmental factors and route, dose, or time of the antigen exposure. Many common biologic mechanisms prevent immune responsiveness to innocuous environmental allergens and to self-antigens. Although most autoreactive T cells undergo selection and clonal deletion in the thymus, a small fraction of cells escape into the periphery. Additional immunologic control mechanisms eliminate or inactivate potentially hazardous effector cells that emerge from the thymus and move into the periphery (Fig. 1.5). Allergens enter the body through the respiratory and alimentary tract or injured skin, and the result usually is induction of tolerance in healthy individuals.[11]

Central and Peripheral Tolerance Mechanisms

The processes that constitute immune tolerance normally ensure that immune effector cells are not activated against host tissues or innocuous agents. Immune tolerance is called *central* when the response occurs in primary lymphoid organs, such as thymus or *peripheral* when it occurs in peripheral lymph nodes, Peyer's patches, tonsils, or other tissues.

Central Tolerance

T cells experience the first step of tolerance during their maturation in the thymus. Prethymic T cells reach the subcapsular region of the thymus, where they proliferate. Maturing cells move deeper into the cortex and adhere to cortical epithelial cells. The T cell receptors (TCRs) on thymocytes are exposed to epithelial MHC molecules through these contacts. Negative

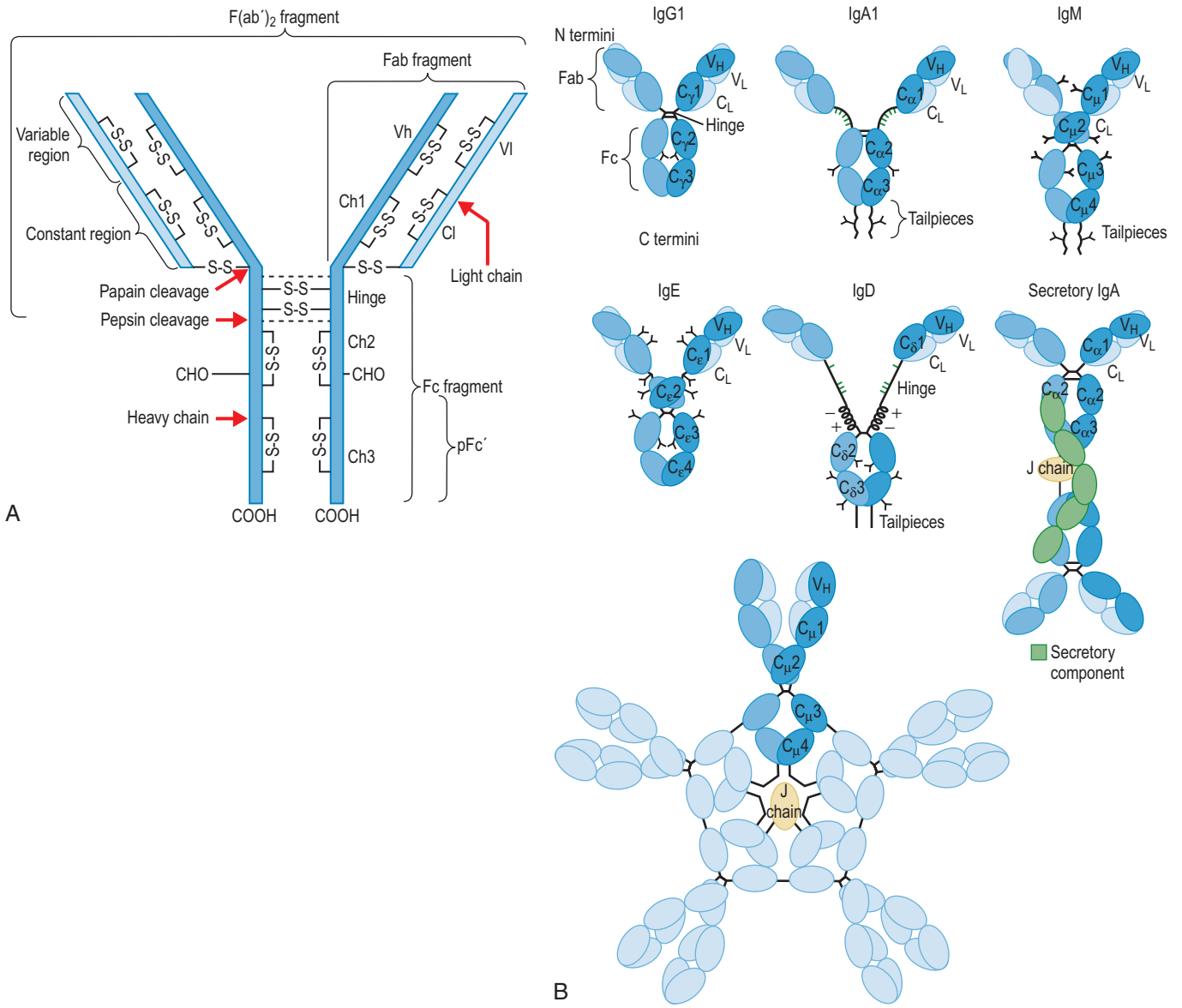

Fig. 1.4 Basic structure of immunoglobulin molecules. (A) In the monomeric structure of immunoglobulin molecules, disulfide bridges link the two heavy chains and the light chains with heavy chains. Enzymatic digestion with papain cleaves the immunoglobulin molecule into three fragments: two Fab fragments, each of which can bind a single antigen epitope, and the Fc fragment, which can bind to Fc receptors. Alternatively, pepsin digestion of immunoglobulins results in a single $F(ab')_2$ fragment, which remains capable of cross-linking and precipitating multivalent antigen. The Fc portion usually is digested into several smaller peptides by pepsin (pFc′). (B) Schematic structures of the five classes of antibodies. IgG1 and IgA1 are shown as examples of the basic structure of the IgG and IgA classes of antibodies. The other IgG sub-classes differ primarily in the nature and length of the hinge, and the IgA2 hinge region is very short compared with IgA1. Although membrane IgM and IgA exist as monomers, secreted IgA can exist as dimers, and secreted IgM as pentamers, when linked by an extra polypeptide called the J chain. Both multimeric forms of antibodies can be transported across mucosal surfaces by binding to the polymeric immunoglobulin receptor. Dimeric IgA coupled to the J chain and secretory component, a part of the polymeric immunoglobulin *(Ig)* receptor remaining after transport through epithelial cells, is shown as an example of secretory Ig. (From Delves PJ, Martin SJ, Burton DR, Roitt IM. Roitt's Essential Immunology. 12th ed. Oxford: Wiley-Blackwell; 2011:56, 62.)

selection occurs by deletion of self-reactive T cells. Autoantigens are presented by medullary thymic epithelial cells, interdigitating cells, and macrophages at the corticomedullary junction. Cells expressing CD4 or CD8 subsequently exit to the periphery. The autoimmune polyendocrine syndrome is a good example of central tolerance loss, which is caused by mutations in the AIRE gene. In this disease, self-antigens are not displayed in the thymus, and T cells escape from deletion and negative selection and enter the peripheral circulation. T cell infiltration of the tissues and autoantibody production results in tissue destruction.[12]

Cells that have escaped negative selection in the thymus are still subject to control in the periphery, because some self-reactive $CD4^+$ T cells that are not deleted by negative selection develop into central Treg cells. These central Treg cells circulate

TABLE 1.2 Selected Biologic Properties of Human Immunoglobulin Isotypes

Characteristics	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	IgD	IgE
Physical properties									
Molecular weight (kDa)	146	146	165	146	970[a]	160	160	170	190
Serum half-life (days)	29	27	7	16	5	6	6	–	2
Anatomic distribution									
Mean serum level (mg/mL)	5–12	2–6	0.5–1.0	0.2–1.0	0.5–1.5	0.5–2.0	0–0.2	0–0.4	0–0.002
Transport across placenta	+++	+	++	±	–	–	–	–	–
Transport across epithelium	–	–	–	–	+	+++[b]	+++[b]	–	–
Extravascular diffusion	+++	+++	+++	+++	±	++[c]	++[c]	+	+
Functional activity									
Antigen neutralization	++	++	++	++	++	++	++	–	–
Complement fixation	++	+	++	–	+++	+	+	–	–
ADCC	+	+	+	±	–	–	–	–	+
Immediate hypersensitivity	–	–	–	–	–	–	–	–	+++

ADCC, Antibody-dependent cellular cytotoxicity; –, no effect; ±, no effect or negligible degree; +, small degree; ++, moderate degree; +++, large degree.
[a]Pentameric IgM plus J chain.
[b]Dimer.
[c]Monomer.

in the periphery as mature T cells and inhibit immune or inflammatory responses against self-antigens.

Peripheral Tolerance

There are multiple mechanisms of peripheral immune tolerance (Fig. 1.5). These mechanisms prevent overactivation of immune system which cause intensive tissue inflammation. The fundamental strategy of immunotherapy for allergic diseases is to correct dysregulated immune responses by inducing peripheral allergen tolerance.

During inflammation, apoptosis of immune effector cells is induced by neighbor cells' death-inducing ligands. Immune effector cells can undergo apoptosis by expressing death receptors and ligands simultaneously. To keep tissue inflammation at low levels, effector T cells are directly tolerized by suppressive cytokines released by tissue cells. Treg cells suppress effector T cells. DCs induce tolerization of host T cells. In asthma, spatial separation of T cells and tissue cells, such as the presence of a basement membrane between the epithelium and immune cells, results in ignorance of effector mechanisms. Tissue cells in organs with immune privilege use many mechanisms to suppress or delete highly activated effector cells that could otherwise damage these tissues.

During an immune response, $CD4^+$ T cells normally receive signals activated through engagement of the TCR, which recognizes peptides of specific antigens presented on the surface of APCs by MHC class II molecules. Costimulatory receptors, such as CD28, CD2, and inducible costimulator (ICOS) recognize ligands, such as B7 proteins, CD80, CD86, lymphocyte function–associated antigen 3 (LFA-3), and ICOS ligand (ICOSL) expressed on the surface of APCs. These costimulatory receptors contribute to activation of the T cell. When T cells receive stimulus only through the TCR without any engagement of costimulatory receptors, they enter into a state of unresponsiveness. This state has been called *T cell anergy*. In addition to Treg cells, different subgroups of regulatory B cells (Breg) play important roles in peripheral tolerance to allergens as well as immune tolerance in autoimmunity, tumor and chronic infections.

Histamine Receptors in Peripheral Tolerance

One of the primary mediators released from mast cells is histamine and this acts through histamine receptors. Histamine receptor 2 (HR2) activation mediates early desensitization of basophils. The initial decrease in basophil activity is also associated with symptom scores in grass pollen immunotherapy. H2R suppresses allergen-associated FcεRI-mediated basophil activation. HR2 mainly plays a role in immune tolerance mechanisms. Its expression increases in Th2 cells and both suppress allergen-induced T cell responses and trigger the development of peripheral tolerance by increasing IL-10 production in beekeepers.[13–15] Histamine acts through HR2 and induces IL-10 production by DCs and Th2 cells; it increases the suppressive effect of TGF-β on T cells and decreases the production of Th2 cytokines, IL-4, and IL-13, which are central Th2-type cytokines.[14,16]

Immune Effector Cells and Molecules

Treg Cells and Regulatory B cells

Although various types of cell contribute to establishing immune tolerance, $CD4^+FOXP3^+$ Treg cells play a central role in immune control in the periphery. Additionally, in peanut allergy, demethylation of $FOXP3^+$ has been shown to be associated with tolerance development.[17] Two broad categories of Treg cells have been described: naturally occurring Treg cells and antigen-induced Treg cells that secrete inhibitory cytokines,

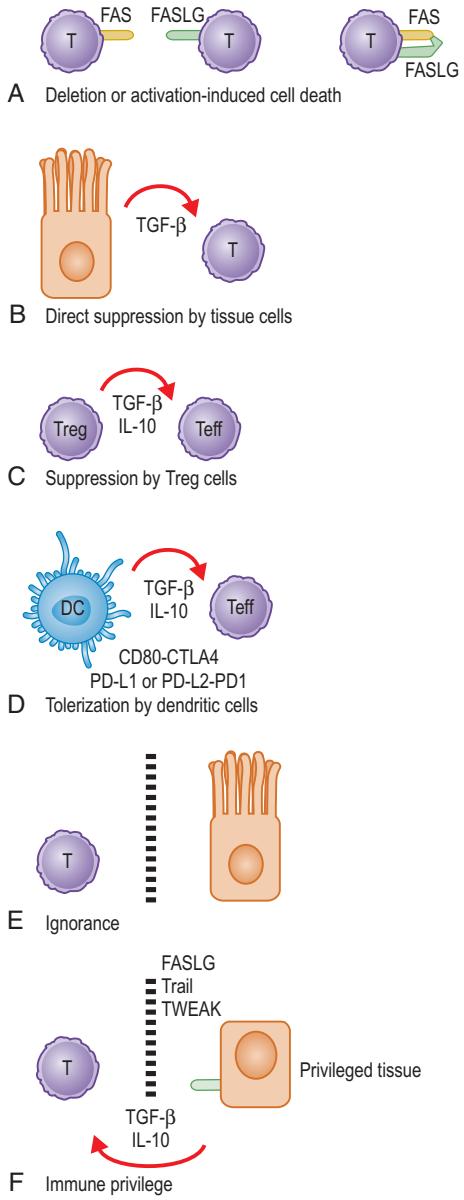

Fig. 1.5 Multiple mechanisms of immune tolerance. (A) Direct deletion of immune effector cell by expression of death-inducing ligands. (B) Direct tolerization of effector T cells by suppressive cytokines released by tissue cells. (C) Suppression of effector T cells by regulatory T cells. (D) Tolerization of host T cells by tolerizing dendritic cells. (E) Ignorance of effector mechanisms as a result of spatial separation of T cells and tissue cells, such as by basement membranes between the epithelium and immune cells in asthma. (F) Immune privilege refers to certain sites in the body that can tolerate the introduction of antigen without eliciting an inflammatory immune response. These sites include the eyes, the placenta and fetus, and the testicles. Tissue cells in these organs use many mechanisms to suppress or delete highly activated effector cells that can damage these tissues. *CTLA4*, Cytotoxic T lymphocyte–associated protein 4; *DC*, dendritic cell; *FAS*, member of the tumor necrosis factor receptor superfamily, member 6; *FASLG*, FAS ligand; *IL*, interleukin; *PD-L1*, programmed death-ligand 1; *PD-L2*, programmed death-ligand 2; *PD-1*, programmed cell death 1; *T*, T cell; *Teff*, effector T cell; *TGF-β*, transforming growth factor β; *Trail*, tumor necrosis factor (ligand) superfamily, member 10; *TWEAK*, tumor necrosis factor (ligand) superfamily, member 12; *Treg*, regulatory T cell.

such as IL-10 and TGF-β. In allergic disease, the balance between allergen-specific Treg cells and disease-promoting Th2 cells appears to determine whether an allergic or healthy immune response against allergen occurs. In healthy individuals, predominant Treg cells are specific for common environmental allergens, indicating a state of natural tolerance.

IL-10–secreting allergen-specific Breg cells have been defined in bee venom–tolerant beekeepers, and patients treated with venom immunotherapy (VIT). Breg cells are $CD73^{-}CD25^{+}CD71^{+}$ B cells, which are capable of suppressing allergen-specific $CD4^{+}$ T cells and produce allergen-specific IgG4 antibodies after allergy immunotherapy (AIT). Moreover, Breg cells produce IL-35 and TGF-β. IL-10–producing NK regulatory cells suppress allergen-stimulated T cell proliferation in patients during AIT, and these cells may take place in tolerance development as other regulatory cell types.[14,18]

T follicular helper cells (Tfh) are a newly defined cell type identified by $CXCR5^{+}$ surface receptor and function in B cell maturation and immunoglobulin class switching. A subgroup of Treg, defined as $CXCR5^{+}$ $FoxP3^{+}$ Treg cells, are called *follicular regulatory T (TFR)* cells. They act in the germinal centers of the lymph nodes and suppress T and B cell responses. TFR cells produce more IL-10 compared to TFH cells. There is plasticity between TFH and TFR cells, and this suggests that TFR cells may play essential roles in allergen-specific IgE production and suppression of Th2 responses during immune tolerance development.[13,19]

Transforming Growth Factor-β (TGF-β)

TGF-β is associated with the resolution of immune responses and the induction of Treg cell populations (Table 1.3). However, the effects of TGF-β in allergic disease are complex, with evidence of both disease inhibition and promotion. TGF-β can inhibit human Th2 responses in vitro. In a murine model, overexpression of TGF-β1 in OVA-specific $CD4^{+}$ T cells abolished airway hyperresponsiveness and airway inflammation induced by OVA-specific Th2 cells.

On the other hand, in a mouse model exhibiting properties of chronic asthma, blockade of TGF-β significantly reduced peribronchiolar extracellular matrix (ECM) deposition, airway smooth muscle (ASM) cell proliferation, and mucus production in the lung without affecting established airway inflammation or Th2 cytokine production. TGF-β1 may be involved in a negative feedback mechanism to control airway inflammation and repair of asthmatic airways, inducing remodeling and fibrosis to exaggerate disease development in humans.

Interleukin-10 (IL-10)

IL-10 plays a role in the control of allergy and asthma. IL-10 inhibits many effector cells and disease processes, and its levels are inversely correlated with disease incidence and severity. IL-10 is synthesized by a wide range of cell types, including B cells, monocytes, DCs, NK cells, and T cells. It inhibits proinflammatory cytokine production and Th1 and Th2 cell activation, which is likely attributable to the effects of IL-10 on APCs and its direct effects on T cell function (Table 1.3).

IL-10 levels inversely correlate with the incidence and severity of asthmatic disease in the lung. In addition, the levels of

TABLE 1.3 Functions of Interleukin-10 and Transforming Growth Factor-β

Cell Type	IL-10	TGF-β
Dendritic cells (DCs)	Inhibits DC maturation, reducing MHC class II and costimulatory ligand expression Inhibits proinflammatory cytokine secretion Inhibits APC function for induction of T cell proliferation and cytokine production (Th1 and Th2)	Promotes Langerhans cell development Inhibits dendritic cell maturation and antigen presentation Downregulates FcεRI expression on Langerhans cells
T cells	Suppresses allergen-specific Th1 and Th2 cells Blocks B7/CD28 costimulatory pathway on T cells	Promotes T cell survival Inhibits proliferation, differentiation, and effector function, including allergen-specific Th1 and Th2 cells Promotes the Th17 lineage
B cells and immunoglobulin (Ig) E	Enhances survival Promotes Ig production, including IgG4 Suppresses allergen-specific IgE	Inhibits proliferation Induces apoptosis of immature or naive B cells Inhibits most Ig class switching Switch factor for IgA Suppresses allergen-specific IgE
$CD25^+$ Tregs	Indirect effect on the generation	Upregulates FOXP3 Promotes generation in the periphery Potential effects on homeostasis
IL-10–secreting Tregs	Promotes induction of IL-10–secreting Tregs	Can promote IL-10 synthesis
Monocytes and macrophages	Inhibits proinflammatory cytokine production and antigen presentation	Inhibits scavenger and effector functions, including proinflammatory cytokine production and antigen presentation Promotes chemotaxis
Eosinophils	Inhibits survival and cytokine production	Chemoattractant
Mast cells	Inhibits mast cell activation, including cytokine production	Promotes chemotaxis Variable effects on other functions May inhibit expression of FcεR (receptor 1)
Neutrophils	Inhibits chemokine and proinflammatory cytokine production	Potent chemoattractant

APC, Antigen-presenting cell; *FcεR*, Fc fragment of IgE receptor; *FOXP3*, Forkhead box P3 protein; *IL*, interleukin; *MHC*, major histocompatibility complex; *TGF-β*, transforming growth factor-β; *Th*, T helper cell subset; *Treg*, regulatory T cell.

IL-10 inversely correlate with skin-prick test reactivity to allergens. Beekeepers, who undergo multiple bee stings and are naturally tolerant to bee venom allergen, have a high IL-10 response. IL-10 and IL-10–producing Treg and Breg cells play essential roles in immune tolerance to allergens. In addition, the roles of Treg and Breg cells and IL-10 have been shown in many autoimmune, organ transplantation, tumor tolerance conditions.[20]

Cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) are negative regulators of T cell function. Inhibition of these targets leads to increased activation of the immune system. While CTLA-4 is thought to regulate T cell proliferation early during an immune response, particularly in lymph nodes, PD-1 is thought to suppress T cells later, especially in peripheral tissues. In other words, CTLA-4 acts early on tolerance induction and PD-1 acts late to maintain long-term tolerance.[21]

TABLE 1.4 Sources of Interleukins IL-4 and IL-13

Cell Source	IL-4	IL-13
T helper lymphocytes		
Naive T cells	No	No
T follicular helper (Tfh) cells	Yes	No
Th2 cells	Yes	Yes
Natural killer (NK) T cells	Yes	Yes
Basophils	Yes	Yes
Eosinophils	Yes	Yes
Mast cells	Yes	Yes
Type 2 innate lymphoid cells (ILC2)	Yes	Yes

CYTOKINES AND CHEMOKINES IN ALLERGIC INFLAMMATION

Cytokines in Allergic Inflammation

Interleukin-4 (IL-4)

In addition to T helper lymphocytes, IL-4 is derived from basophils, NK T cells, ILC2 mast cells, and eosinophils (Table 1.4). IL-4 induces immunoglobulin isotype switch from IgM to IgE. IL-4 has important influences on T lymphocyte growth, differentiation, and survival. As discussed later, IL-4 establishes the differentiation of naive Th0 lymphocytes into the Th2 phenotype.

Another important activity of IL-4 is its ability to induce expression of vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells. This enhances adhesiveness of endothelium for T cells, eosinophils, basophils, and monocytes, but not

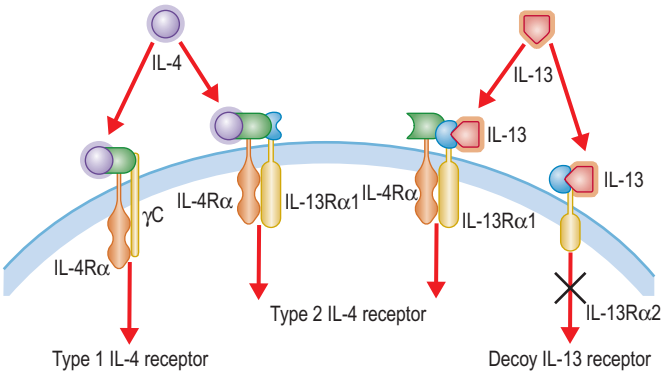

Fig. 1.6 IL-4 and IL-13 receptors. Type 1 IL-4 receptors are heterodimers of IL-4Rα interacting with the shared γC chain and bind only IL-4. Their unique expression on most T helper cells and mast cells renders these cells only responsive to IL-4. Type 2 receptors can bind both IL-4 and IL-13. They are more widely expressed and consist of heterodimers of IL-4Rα and IL-13Rα1. In addition, IL-13 can bind to the IL-13Rα2, which lacks a cytoplasmic domain and thereby functions as a decoy receptor. *IL*, Interleukin.

neutrophils, as a characteristic of allergic reactions. IL-4 receptors are present on mast cells, where they function to stimulate IgE receptor expression, along with the expression of the enzyme leukotriene C_4 (LTC_4) synthase. Functional IL-4 receptors are heterodimers consisting of the IL-4Rα chain interacting with either the shared γ chain or the IL-13Rα1 chain (Fig. 1.6). This shared use of the IL-4Rα chain by IL-4 and IL-13 and the activation by this chain of the signaling protein STAT6 serve to explain many of the common biologic activities of these two cytokines.

Interleukin-5 (IL-5)

IL-5 is the most important eosinophilopoietin and also can induce basophil differentiation. In addition to stimulating eosinophil production, IL-5 is chemotactic for eosinophils and activates mature eosinophils, inducing secretion and enhancing their cytotoxicity. IL-5 promotes accumulation of eosinophils through its ability to upregulate responses to chemokines and $\alpha_d\beta_2$ integrins on eosinophils, thereby promoting their adherence to VCAM-1–expressing endothelial cells. IL-5 prolongs eosinophil survival by blocking apoptosis.

Interleukin-9 (IL-9)

The primary source of IL-9 is the T helper lymphocyte population, including Th2 cells, with additional amounts coming from mast cells ILC2 and eosinophils. IL-9 contributes to mast cell–mediated allergic responses through its ability to stimulate production of mast cell proteases, inflammatory cytokines, and chemokines. Additionally, IL-9 primes mast cells to respond to allergens by increasing their expression of FcεRIα. IL-9 synergizes with IL-4 to enhance production of IgE and memory B cell differentiation. The same synergy leads to enhanced IL-5 production resulting in greater numbers and maturation of immature eosinophil precursors. IL-9 acts on airway epithelial cells by inducing T cell and eosinophil chemotactic factors, such as CCL11 (eotaxin), CCL2 (MCP-1), CCL3 (MIP-1α), and CCL7 (MCP-3).

Interleukin-13 (IL-13)

IL-13 is homologous to IL-4 and shares many of its biologic activities on mononuclear phagocytic cells, endothelial cells, epithelial cells, and B cells. Thus IL-13 induces IgE isotype switch and VCAM-1 expression. Biologic activities of IL-4 and IL-13 are additionally distinguished by their distinct cellular sources (Table 1.4). IL-13, acting through this hormonal mechanism, causes mucus hypersecretion and nonspecific airway hyperreactivity (AHR), and its expression results in the characteristic airway metaplasia of asthma, with the replacement of epithelial cells with goblet cells. The importance of IL-13 in presentations of asthma associated with a robust IL-13 signature is supported by the efficacy of IL-13–targeting therapies in this endotype.

Interleukin-25 (IL-25)

IL-25 is a member of the IL-17 family (IL-17E), but because of its unique spectrum of activities, it has been given this distinct nomenclature. Binding of IL-25 occurs via a heterodimer complex composed of IL-17RB and IL-17RA.[22] It is mainly derived from epithelial cells. The production of IL-25 by injured epithelial cells is an important innate immune signal driving Th2 immune deviation in the subsequent adaptive immune response. IL-25 stimulates release of IL-4, IL-5, and IL-13 from Th2 lymphocytes but, of note, also drives IL-5 and IL-13 secretion from type 2 innate lymphoid cells (ILC2).

Interleukin-33 (IL-33)

IL-33 is a member of the IL-1 superfamily (in which it is designated IL-1F11) that signals through an IL-1 receptor–related protein (originally termed ST2) and its co-receptor IL-1RAcP.[23]

IL-33 is primarily expressed by bronchial epithelial cells, with additional sources including fibroblasts and smooth muscle cells and it is also inducible in lung and dermal fibroblasts, keratinocytes, activated DCs, and macrophages. IL-33 receptors are expressed on T cells (specifically, Th2-like cells), macrophages, hematopoietic stem cells, eosinophils, basophils, mast cells, ILC2, and fibroblasts. As discussed, IL-33 enhances cytokine secretion by Th2 cells and, like IL-25, induces IL-5 and IL-13 secretion by ILC2.

It is possible to avoid food allergy development and to suppress ongoing food allergy by blocking the IL-25, IL-33, and TSLP.[24] Moreover, presence of IL-33 in the airways together with an inhaled allergen which is tolerogenic previously causes the breakdown of the tolerance.[25]

Interleukin-35 (IL-35)

IL-35 is an antiinflammatory cytokine included in the IL-12 superfamily. IL-35 is predominantly secreted by Treg and Breg cells. It consists of two chains, IL-12α chain p35 and IL-27α chain EBV-induced gene3 (Ebi3). IL-35 is involved in the development of tolerance and the production of regulatory cells that express IL-35. Bregs secrete IL-35, which has an autocrine role, to further expand Breg cells to produce more IL-35 and IL-10.[26,27] In addition to its biological function in immune cells, IL-35 is required for the maximum suppressive activity of Treg cells. IL-35 mediates the differentiation of a new subset of inducible Treg cells known as iTR35.[28] While IL-35 can

inhibit the proliferation of Th1 and Th17 cells by blocking cell division, it can also hinder Th2 development through GATA3 and IL-4 suppression.[29] In addition to these effects, IL-35 mediates the transformation of Th2 cells into Treg cells, which can be reversed in the presence of IFN-γ.[30] Despite the limited number of studies in humans, it is clear that IL-35 has essential roles in the development of immune tolerance.[31]

Thymic Stromal Lymphopoietin (TSLP)

TSLP is another important contributor to Th2 immune deviation.[32] TSLP is expressed by epithelial cells of the skin, gut, and lung and primes resident DCs in such a way as to promote Th2 cytokine production by their subsequently engaged effector T cells. High levels of TSLP are found in the keratinocytes of patients with AD and in the lungs of asthmatic patients. The TSLP receptor is a heterodimer composed of a unique TSLP-specific receptor and the IL-7Rα chain (CD127). TSLP receptors are expressed primarily by DCs, but their expression by mast cells Th2 cells and ILC2 also promotes secretion of Th2 signature cytokines.

The role of IL-25, IL-33, and TSLP in promoting a Th2-associated milieu is summarized in Fig. 1.7. In this model, injured epithelium has a central role in driving allergic inflammation through its ability to produce these cytokines. TSLP acts primarily on DCs to drive them to induce a Th2-like process. In addition, both IL-25 and IL-33 act directly on mast cells to drive their repertoire of Th2-associated cytokines. More important, IL-25, TSLP, and IL-33 act on ILC2 to increase their selective production of IL-5 and IL-13. These actions on ILC2 and mast cells can occur independent of ongoing allergen exposure, suggesting a mechanism for allergen-independent perpetuation of allergic inflammation.

Chemokines in Allergic Diseases

Asthma

Asthma is a chronic inflammatory lung disease characterized by airway inflammation, mucus hypersecretion, and bronchial hyperresponsiveness. The cellular inflammatory infiltrate in asthma is composed of eosinophils, lymphocytes, mast cells, and to a varying extent, basophils and neutrophils.

Airway exposure to proteases from common allergens, such as mites and molds, disrupts airway epithelial integrity and induces epithelial TSLP production (Fig. 1.8). TSLP expands the number of basophils, prolongs eosinophil survival, and increases eosinophil production of CCL2, CXCL1, and CXCL8. Two other epithelial cytokines, IL-25 and IL-33, also are produced on allergen exposure or epithelial damage. IL-25 and IL-33 upregulate the production of TSLP by epithelial cells and mast cells; induce mast cell release of IL-4, IL-5, IL-13, CCL1, and CXCL8; promote eosinophil survival; and enhance eosinophil production of CCL2 and CCL3. Activated basophils release IL-4, IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), and CCL3 as well as histamine and leukotriene C_4 (LTC_4), which causes vasodilation and increases vascular permeability. Activated eosinophils generate IL-3, IL-4, IL-5, tumor necrosis factor-α (TNF-α), LTC_4, platelet-activating factor (PAF), CCL3, CCL5, and CCL11. In addition to tryptase and chymase, activated mast cells are also a significant source of histamine, lipid mediators (LTB_4, PGD_2), cytokines (IL-3, IL-5, IL-13, IL-6, IL-10, TNF-α, GM-CSF), and chemokines (CCL1, CCL2, CCL3, CCL5, CCL17, CCL22, CXCL8).

Activation and differentiation of naive T cells into Th2 cells are marked by downregulation of L-selectin and CCR7 and appearance of CCR4, CCR8, CRTh2, and the BLT1 receptor

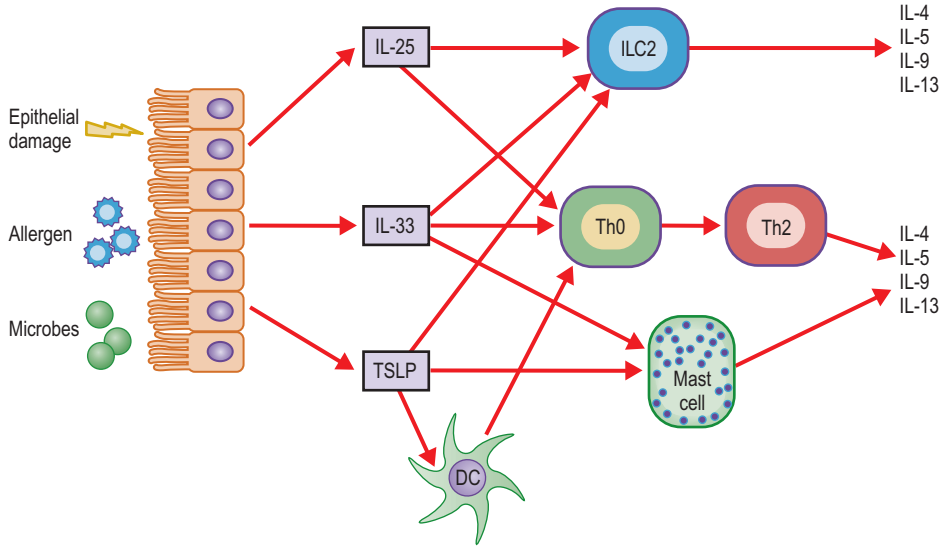

Fig. 1.7 Epithelium-derived cytokines in Th2 differentiation and allergic inflammation. The interleukins IL-25 and IL-33 and thymic stromal lymphopoietin *(TSLP)* are produced by injured epithelium and play critical roles in driving expression of Th2 cytokines. TSLP acts on dendritic cells to direct them to promote the differentiation of naive T cells into Th2 cells. By contrast, IL-25 and IL-33 act directly on the naive T cells to promote Th2 immune deviation. In addition, these three cytokines can generate a Th2 cytokine milieu independent of the adaptive immune system. TSLP and IL-33 directly induce the full repertoire of Th2 cytokine secretion from mast cells. Similarly, IL-25, TSLP, and IL-33 act on type 2 innate lymphoid cells (ILC2) to drive their more restricted secretion of IL-5 and IL-13. *DC*, Dendritic cell; *IL*, interleukin; *Th*, T helper.

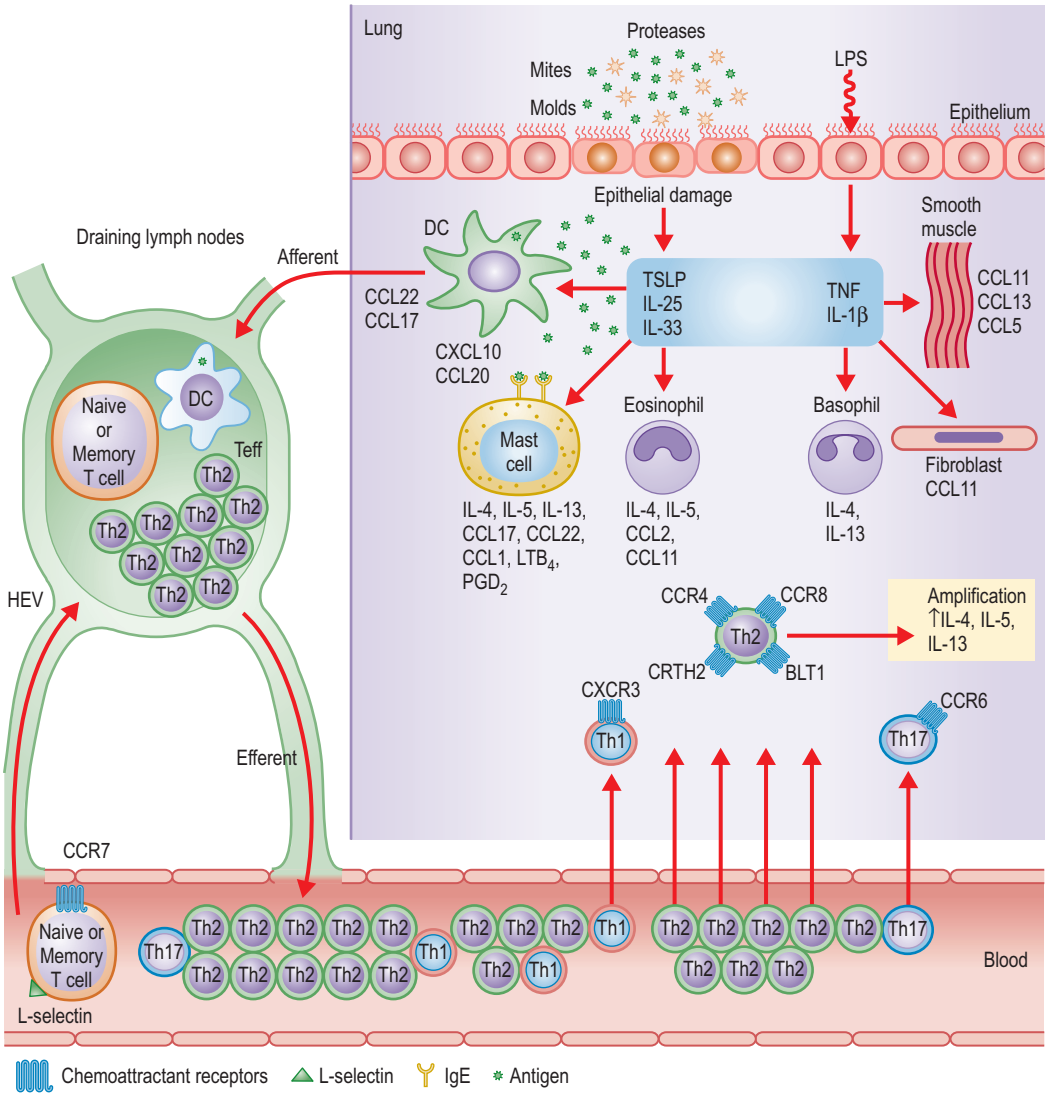

Fig. 1.8 Chemokines and asthma. Asthma is characterized by the infiltration of lung tissue with T helper type 2 *(Th2)* cells producing IL-4, IL-5, and IL-13. Allergen proteases disrupt airway epithelial integrity and induce thymic stromal lymphopoietin *(TSLP)*, IL-25, and IL-33, while epithelial toll-like receptor activation leads to IL-1β and tumor necrosis factor *(TNF)* production. These cytokines upregulate CC chemokine and Th2 cytokine production and release by smooth muscle cells, fibroblasts, mast cells, eosinophils, and basophils. Activated antigen-presenting cells travel to the draining lymph nodes and promote the generation of Th2 cells, which enter the lung and release more Th2 cytokines, thus amplifying the allergic response in the lung. *CCL*, C–C chemokine ligand; *CCR*, C–C chemokine receptor; *DC*, dendritic cell; *HEV*, high endothelial venules; *IgE*, immunoglobulin E; *IL*, interleukin; *LPS*, lipopolysaccharide.

for leukotriene B_4 (LTB_4). These receptors enable Th2 cells to move down the concentration gradient in response to CCL17, CCL22, CCL1, prostaglandin D_2 (PGD_2), and LTB_4, mediators released by DCs and activated mast cells. IL-4 and IL-13 induce lung-residing macrophages, DCs, epithelial cells, and endothelial cells to produce CCL11, CCL24, CCL26, CCL1, CCL17, and CCL22, thus amplifying the allergic inflammatory response by attracting more eosinophils and Th2 cells.

Atopic Dermatitis

AD is a pruritic chronic inflammatory disease of the skin in which $CD4^+$ memory T lymphocytes, DC subsets, eosinophils, and mast cells infiltrate the perivascular, subepidermal, and intraepidermal areas. A number of chemokines are aberrantly expressed in the skin of patients with AD and help recruit the inflammatory infiltrate in this disorder. These include CCR2 and CCR3 ligands (CCL13, CCL11, and CCL26) for eosinophil and mast cell recruitment, CCR4 and CCR8 ligands (CCL22 and CCL1) for Th2 cell recruitment, CCR10 ligand (CCL27) for T cell entry into the epidermis, and CCL18.

The pathophysiology of AD begins with intense pruritus and the mechanical injury that results from chronic scratching (Fig. 1.9). Mechanical trauma can directly activate mast cells, which release histamine, neuropeptides, proteases, kinins, and cytokines, many of which further exacerbate pruritus. Furthermore, TSLP levels increase acutely in the skin after mechanical trauma. TSLP induces DC activation and DC production of CCL17 and CCL22.

The trafficking of memory T cells into the skin requires cutaneous lymphocyte antigen (CLA), which interacts with E-selectin on inflamed endothelium, and initiates rolling. The

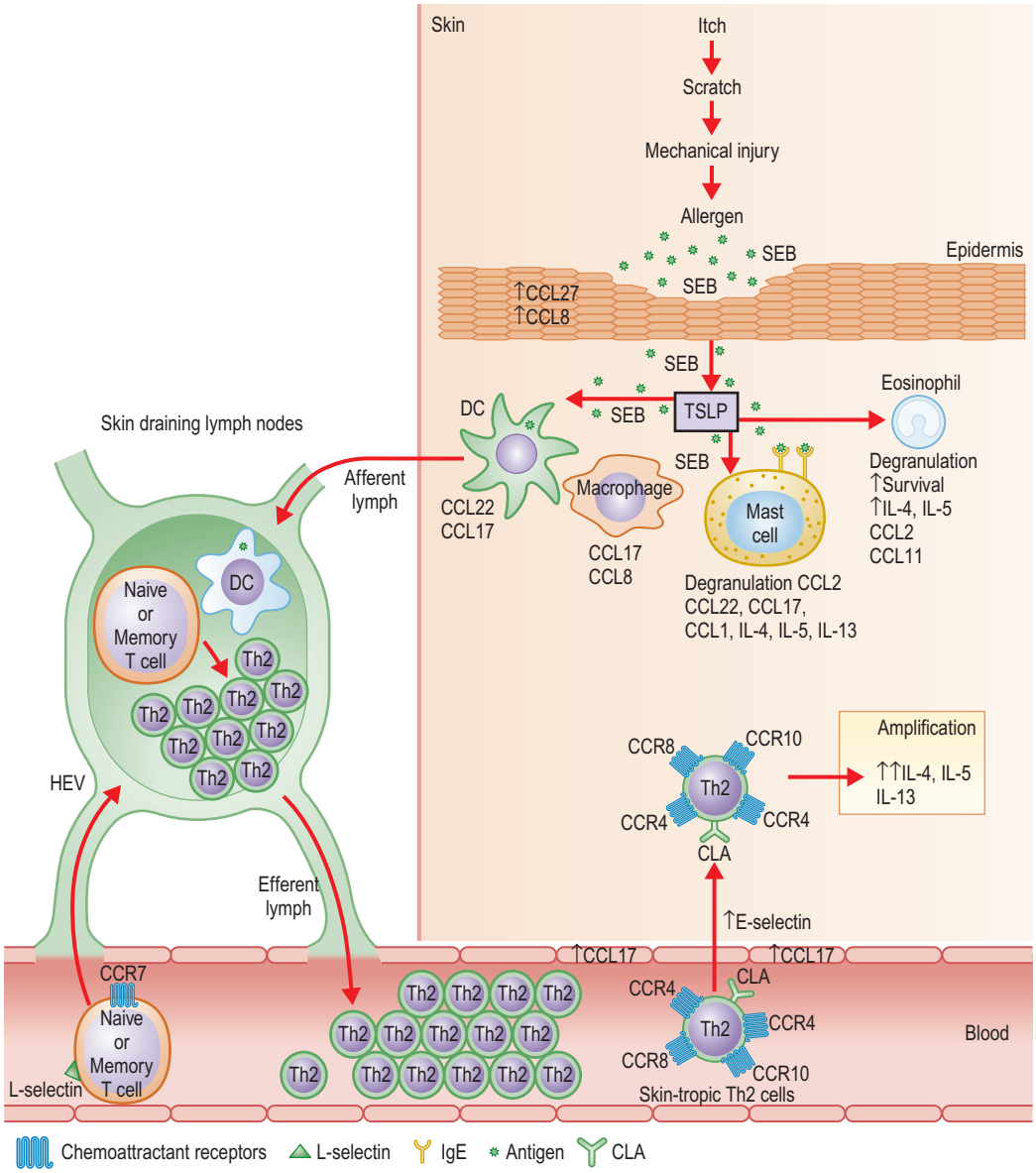

Fig. 1.9 Chemokines and atopic dermatitis. Atopic dermatitis begins with intense pruritus, chronic scratching, and mechanical injury to the skin. Mechanical trauma leads to mast cell release of Th2 cytokines and CC chemokines and upregulates local TSLP production, while loss of normal barrier function increases exposure to allergens and SEB. TSLP-activated dendritic cells travel to the draining lymph nodes and promote Th2 cell differentiation. Th2 cells enter the skin and release Th2 cytokines, thus amplifying the allergic response in the skin. *CCL*, C–C chemokine ligand; *CCR*, C–C chemokine receptor; *CLA*, cutaneous lymphocyte antigen; *DC*, dendritic cell; *IgE*, immunoglobulin E; *IL*, interleukin; *SEB*, staphylococcal enterotoxin B; *Th2*, T helper type 2; *TSLP*, thymic stromal lymphopoietin.

trafficking molecules most highly expressed by T cells isolated from healthy skin are CLA, CCR4, CCR6 (>80%–90%), and, to a lesser extent, CCR8 (50%). Whereas the ligands for CCR6 and CCR8 are upregulated in inflammation, skin endothelial cells and keratinocytes constitutively express CCL17 (one of the ligands for CCR4) and CCL27 (only known ligand for CCR10), respectively.

Eczema lesions as the hallmark of AD and allergic contact dermatitis lesions are induced by keratinocyte apoptosis, related to IFN-γ, Fas-Fas–ligand interaction, TNF-α, TNF-related weak inducer of apoptosis (TWEAK), and IL-32.[33,34]

BIOLOGY OF IMMUNE CELLS

T Lymphocytes

Two classes of α/β T lymphocytes that bear the co-receptors CD4 or CD8 are involved in adaptive immune responses. $CD4^+$ T cells are traditionally called Th cells because they activate and direct other immune cells. There are also populations of $CD4^+$ Treg cells that modulate immune responses. $CD4^+$ T cells recognize antigen presented by class II MHC molecules on APCs, including DCs, B cells, and macrophages. Exogenous protein antigens are taken up by APCs and processed into peptides in endocytic

vesicles, which are presented on the cell surface bound to class II MHC molecules. The $CD8^+$ cytotoxic T cells (CTLs) recognize antigen presented on MHC class I molecules. Class I MHC molecules are present on the surface of all nucleated cells. Their cytotoxic functions are carried out by release of preformed effector molecules and by interactions of cell surface molecules.

Antigen-activated $CD4^+$ T cells have the potential to differentiate into effector cells, each with distinct functional properties conferred by the pattern of cytokines they secrete (Fig. 1.10).[35] Th1 cells are a subset of $CD4^+$ T cells that secrete IFN-γ, whereas Th2 cells produce IL-4, IL-5, IL-9, IL-10, and IL-13. Th17 cells produce IL-17A, IL-17F, and IL-22. Treg cells produce IL-10 and TGF-β1, are naturally occurring and induced, suppress T cell differentiation and APC activation, and are not considered effector cells. Th1 cells stimulate strong cell-mediated immune responses, particularly against intracellular pathogens. Th2 cells are elicited in immune responses that require a strong humoral component and in antiparasitic responses. Th17 serve critical host defense functions at mucosal surfaces.

Cytokines are the primary factors that influence the $CD4^+$ Th cell generation and are considered the third signal in $CD4^+$ T cell differentiation.[20] IFN-γ and IL-12 stimulate the induction of Th1 cells. IL-4 drives Th2 cell generation by direct action on $CD4^+$ T cells. IL-13 is involved in the induction of Th2 cells by an unknown mechanism, although not through direct effects on

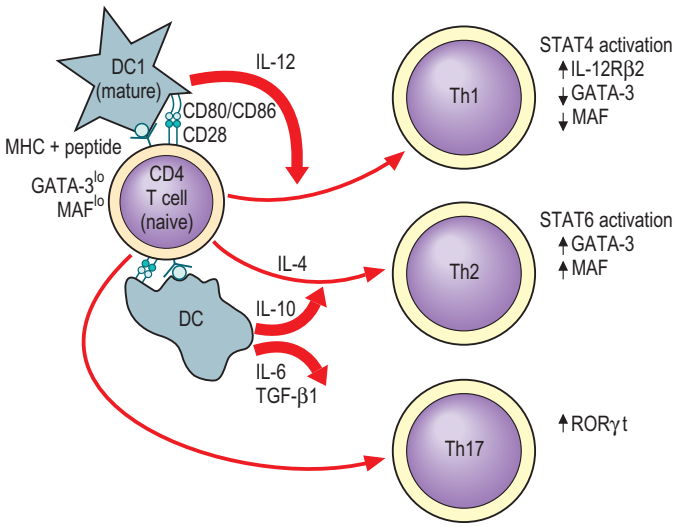

Fig. 1.10 Generation of helper T cell types 1, 2, and 17 (*Th1*, *Th2*, and *Th17*) from a naive $CD4^+$ T cell. A naive $CD4^+$ T cell does not secrete cytokines and has low expression levels of transcription factors GATA-3 and MAF. Differentiation along the Th1, Th2, or Th17 pathway is triggered by stimulation by antigen presented to the T cell receptor in the context of the major histocompatibility complex *(MHC)* by the appropriate antigen-presenting cell (APC) and a second signal imparted by ligation of costimulatory molecules CD80/CD86 and CD28. Dendritic cells *(DCs)* represent the key APCs for naive T cells. Those that produce interleukin-10 *(IL-10)* favor Th2 differentiation, and those that produce interleukin-12 *(IL-12)* stimulate Th1 differentiation. Th17 cells can be generated in the presence of interleukin-6 *(IL-6)* and transforming growth factor-β1 *(TGF-β1)*, presumably produced by DCs.

$CD4^+$ T cells. IL-6, IL-1β, TGF-β1, and in some situations, IL-23 promote Th17 development.

In the secondary lymphoid tissue, a naive T cell differentiates into an effector cell. Compared with naive T cells, effector cells do not require costimulation to be activated, allowing these cells to respond to antigen with hair-trigger rapidity to produce high levels of cytokines and chemokines, which then direct the immune response. Most activated effector $CD4^+$ T cells die subsequent to an immune response through the process of activation-induced cell death, but a subset of $CD4^+$ T cells will persist as memory cells for the life of the host. $CD4^+$ memory T cells persist in lymphoid organs as central memory cells and in nonlymphoid tissues as effector memory cells. The effector memory T cells respond rapidly to repeat exposures to antigen, whereas central memory T cells are slower to be mobilized.

B Lymphocytes

The humoral immune response is generated by B cells. Mature B cells express immunoglobulin on its cell surface, which constitutes the antigen-specific BCR. BCR is a molecular complex made up of antigen-binding or variable (V) regions. This region of the protein varies among immunoglobulins, allowing each antibody to bind to any foreign structure that the individual may encounter. To generate this diverse immunoglobulin repertoire, during development in the bone marrow, B cells undergo somatic deoxyribonucleic acid (DNA) recombination of the variability (V), diversity (D), and joining (J) regions of the immunoglobulin heavy and light chains. The invariant or constant region of the antibody is specialized for different effector functions in the immune system after antibody is secreted. There are five main constant-region forms: IgM, IgD, IgG, IgE, and IgA. The BCR in the membrane-bound form recognizes and binds antigen and transmits activation signals into the cell.

Naive B cells recirculate through peripheral lymphoid tissues until it binds specific antigen through surface immunoglobulin and is activated (i.e., signal 1). Most antibody responses, including antibody responses to protein antigens, require antigen-specific T cell help. Antigen bound to surface immunoglobulin is internalized, processed, complexed with MHC class II molecules, and displayed on the cell surface. Previously primed $CD4^+$ T cells that recognize the peptide-MHC class II complex on the B cell provide the second signal for activation. The cytokines secreted by $CD4^+$ Th cells during B cell activation regulate which immunoglobulin heavy-chain constant regions will be selected during class-switch recombination to best serve the functions of the specific immune response. Th2 responses to allergens stimulate B cell activation and result in elevated levels of allergen-specific IgE.

Innate Lymphoid Cells

Populations of lymphoid cells that lack rearranged antigen receptors, which were called ILCs, have been recently identified. These ILC populations can be divided into three groups, based on shared phenotypic and functional properties like T cells. Type 1 ILC (ILC1) constitutively express T-bet and are able to produce IFN-γ upon activation. Type 2 ILC (ILC2) constitutively express GATA-3 and in response to IL-25, IL-33, and

TSLP stimulation produce IL-5 and IL-13. Type 3 ILC (ILC3) constitutively express ROR-γ and in response to IL-1β and IL-23 produce IL-17, IL-22, and IFN-γ.[36]

ILC type 2 seems to be important in allergic responses. The ILC2/ILC1 ratio is high in patients with perennial AR sensitized to house dust mite; however, it turns to normal levels following a successful AIT. In the presence of retinoic acid, ILC2 cells transformed into regulatory ILCs (ILCregs) which produce IL-10. These cells can suppress Th2 cell and ILC2 activation. DCs that have the capability of retinoic acid production also induce peripheral Treg cell differentiation. Putting these together, one may suggest that ILCregs may participate in tolerance induction in the mechanisms of AIT.[13,19] ILC2s take place in many functions during the inflammatory process in asthma and AD (Fig. 1.11)

Another type of ILC, ILC type 3, may have essential roles in immune tolerance induction. CD40L-expressing ILC3s locate in close contact with B cells in tonsils. Both cells work interdependently, as ILC3s induce IL-15 production in B cells and IL-15 which is a potent growth factor for ILC3s increases CD40L expression on ILC3s. $CD40L^+$ ILC3s induce IL-10–secreting Breg cells through the CD40L and BAFF-receptor–dependent pathway. ILC3-induced Breg cells are characterized by $CD27^-IgD^+IgM^+CD24^{high}CD38^{high}CD1d^+$ immature transitional (itBreg) phenotype. This interaction is important for the maintenance of immune tolerance against innocuous antigens and is inadequate in allergic diseases. In tonsils, generation of functional allergen-specific Treg cells takes place. ILC3s, Breg cells, and Treg cells localize side by side in the interfollicular regions of palatine tonsils. $CD40L^+$ ILC3s may be essential in the maintenance of immune tolerance in tonsils through induction of functional itBreg cells. These cells can contribute to immune tolerance induction and suppression of T cell responses both by a cell-to-cell contact through programmed cell death-ligand 1 and by secretion of IL-10.[13]

Dendritic Cells

DCs are the most important APCs found throughout the body and are mainly recognized for their exceptional potential to generate a primary immune response and sensitization to allergens. DCs determine the T cell polarization process that produces Th1 cells (generating mainly IFN-γ), Th2 cells (generating mainly IL-4, IL-5, and IL-13), Th17 cells (generating mainly IL-17), and Treg cells (generating mainly IL-10 and TGF-β). These cells are also recognized for their ability to produce ongoing effector responses that are crucial in maintaining allergic inflammation. In humans, circulating DCs can be broadly divided into two groups: (1) mDCs and (2) pDCs. Both subsets express a different repertoire of TLRs and display a diverse cytokine signature after microbial stimulation. mDCs selectively express TLR2–6 and TLR8 and respond to bacterial and viral infections by producing large amounts of IL-12. In contrast, pDCs constitutively express the endosome-associated TLR7 and TLR9, and they are the main producers of type 1 IFNs in humans.[6]

Mast Cells

Mast cells are present throughout connective tissues and mucosal surfaces and are especially prominent at the interface with the external environment, such as the skin, respiratory tract, conjunctiva, and gastrointestinal tract. Mast cells contribute to the maintenance of tissue homeostasis, with important roles in

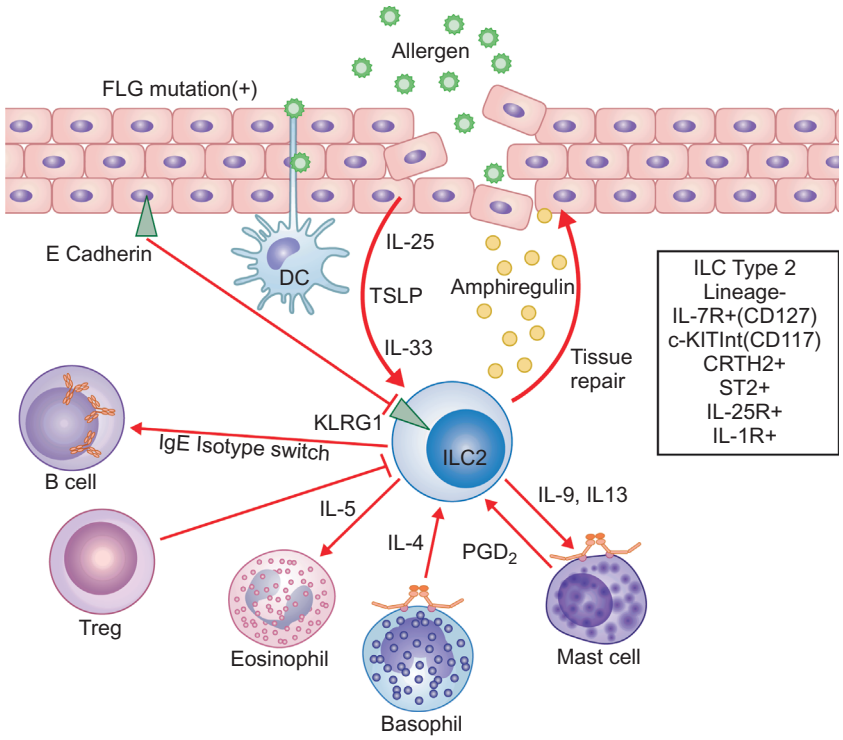

Fig. 1.11 The role of ILC2 during the inflammatory process in asthma and atopic dermatitis. *DC*, Dendritic cell; *IgE*, immunoglobulin E; *IL*, interleukin; *ILC*, innate lymphoid cell; *PGD_2*, prostaglandin D_2; *Treg*, regulatory T.

wound repair, revascularization, and protective responses to bacterial infection and envenomation. Their "misguided" activation by allergens contributes to the development of allergic symptoms.

The best-studied mechanism of mast cell activation, and the one considered most relevant to allergic disease, is activation mediated through the high-affinity IgE receptor FcεRI. IgE-dependent signaling in vivo is initiated when multivalent allergen binds to allergen-specific IgE bound to the FcεRIα chain. IgE-dependent activation of the mast cell induces granule swelling, crystal dissolution, and granule fusion. This sequence is followed by exocytosis with release of mediators into the extracellular space—a process termed *anaphylactic degranulation*. In addition to the stored granule-derived mediators, newly formed metabolites of arachidonic acid also are released from mast cells after IgE-dependent activation (Table 1.5).

Basophils

Basophil granulocytes develop in the bone marrow and are released into the circulation as mature end-stage cells representing less than 1% of blood leukocytes. Basophils play a critical role in allergic disease by infiltrating sites of allergic inflammation and releasing mediators and cytokines that perpetuate type I (immediate) hypersensitivity reactions. Degranulation events resulting in the release of these mediators are preceded by the interaction of allergen with specific IgE molecules bound to the high-affinity IgE receptors on the surface of these cells. This IgE-dependent activation also leads to the production of immunomodulatory cytokines. In particular, basophils are a significant source of IL-4 and IL-13, two Th2 cytokines, whose expression is characteristic of allergic lesions and which are now considered critical components in the pathogenesis of allergic disease.

TABLE 1.5 Classical Preformed and Newly Generated Human Mast Cell Autacoid Mediators and Proteases With Examples of Their Biologic Effects

Mediator	Activity
Histamine (stored)	Bronchoconstriction; tissue edema; ↑vascular permeability; ↑ mucus secretion; ↑ fibroblast proliferation; ↑ collagen synthesis; ↑ endothelial cell proliferation, dendritic cell differentiation and activation
Heparin (stored)	Anticoagulant; mediator storage matrix; sequesters growth factors; fibroblast activation; endothelial cell migration
Tryptase (stored)	Degrades respiratory allergens and cross-linked IgE; generates C3a and bradykinin; degrades neuropeptides; TGF-β activation; increases basal heart rate and ASM contractility; ↑ fibroblast proliferation and collagen synthesis; epithelial ICAM-1 expression and CXCL8 release; potentiation of mast cell histamine release; neutrophil recruitment
Chymase (stored)	↑ mucus secretion; ECM degradation, type I procollagen processing; converts angiotensin I to angiotensin II; ↓ T cell adhesion to airway smooth muscle; activates IL-1β, degrades IL-4, releases membrane-bound SCF
PGD_2 (synthesized)	Bronchoconstriction; tissue edema; ↑ mucus secretion; dendritic cell activation; chemotaxis of eosinophils, Th2 cells, and basophils via the CRTH2 (CD294) receptor
LTC_4/LTD_4 (synthesized)	Bronchoconstriction; tissue edema; ↑ mucus secretion; enhances IL-13–dependent airway smooth muscle proliferation; dendritic cell maturation and recruitment; eosinophil IL-4 secretion; mast cell IL-5, IL-8, and TNF-α secretion; tissue fibrosis

ASM, Airway smooth muscle; *CRTH2*, chemoattractant receptor of Th2 cells; *ECM*, extracellular matrix; *ICAM-1*, intercellular adhesion molecule 1; *IgE*, immunoglobulin E; *IL*, interleukin; *LTC_4*, leukotriene C_4; *LTD_4*, leukotriene D_4; *PGD_2*, prostaglandin D_2; *SCF*, stem cell factor; *TGF-β*, transforming growth factor-β; *TNF-α*, tumor necrosis factor-α.

Eosinophils

Eosinophils are bone marrow–derived granulocytes that play an important pathophysiologic role in a wide range of conditions, including asthma and related allergic diseases and parasitic helminth infections. Eosinophils are unique among circulating leukocytes in their prodigious capacity to produce a variety of mediators, including granule proteins, cytokines, lipids, oxidative products, and enzymes (Table 1.6). Eosinophils express receptors recognizing the Fc portion of various immunoglobulins (FcR). Beads coated with IgA or secretory IgA (sIgA) induce degranulation of eosinophils, and eosinophils from allergic individuals display enhanced FcαR expression. However, most reports suggest that ligation of FcεRI does not result in measurable eosinophil degranulation. Exposure of eosinophils ex vivo to various cytokines mimics in vivo primed eosinophils. IL-5 activates LTC_4 and O2− generation, phagocytosis, and helminthotoxic activity, as well as Ig-induced degranulation. Both TSLP and IL-33 activate eosinophil effector functions, such as adhesion to matrix proteins, cytokine production, and degranulation.

TABLE 1.6 Eosinophil Mediators

Granule proteins
Major basic protein (MBP)
MBP homolog (MBP2)
Eosinophil cationic protein (ECP)
Eosinophil-derived neurotoxin (EDN)
Eosinophil peroxidase (EPX)
Charcot–Leyden crystal (CLC) protein
Secretory phospholipase A_2 ($sPLA_2$)
Bactericidal/permeability-inducing protein (BPI)
Acid phosphatase
Arylsulfatase
β-Glucuronidase

Lipid mediators
Leukotriene B_4 (negligible)
Leukotriene C_4
5-HETE
5,15- and 8,15-diHETE
5-oxo-15-hydroxy-6,8,11,13-ETE
Platelet-activating factor (PAF)
Prostaglandin E_1 and E_2
Thromboxane B_2

(Continued)

TABLE 1.6 Eosinophil Mediators—cont'd

Oxidative products
Superoxide radical anion (OH^-)
Hydrogen peroxide (H_2O_2)
Hypohalous acids
Enzymes
Collagenase
Metalloproteinase-9
Indoleamine 2,3-dioxygenase (IDO)
Cytokines[a]
IL-1α
IL-2
IL-3
IL-4
IL-5
IL-6
IL-9
IL-10
IL-11
IL-12
IL-13
IL-16
Leukemia inhibitory factor (LIF)
Interferon-γ (IFN-γ)
Tumor necrosis factor-α (TNF-α)
GM-CSF
APRIL
Chemokines
CXCL8 (IL-8)
CCL2 (MCP-1)
CCL3 (MIP-1α)
CCL5 (RANTES)
CCL7 (MCP-3)
CCL11 (eotaxin)
CCL13 (ECP-4)
Growth factors
Nerve growth factor (NGF)
Platelet-derived growth factor (PDGF)
Stem cell factor (SCF)
Transforming growth factor (TGF-α, TGF-β)

APRIL, A proliferation-inducing ligand; *ETE*, eicosatetraenoic acid; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *HETE*, hydroxyeicosatetraenoic acid; *IL*, interleukin.
[a]Physiologic significance of these cytokines needs to be confirmed.

CONTRIBUTION OF STRUCTURAL CELLS TO ALLERGIC INFLAMMATION

While structural cells, such as epithelial, bone, smooth muscle cells, or fibroblast, have their proper function, they produce cytokines, chemokines, lipid mediators, and growth factors which control mobility of immune cells and local inflammatory milieu. Symptoms of allergic airway disease, such as sneezing, rhinorrhea, unproductive coughing, episodic bronchospasm, and sensations of breathlessness, are neuronally mediated in response to inflammation. Accordingly, these structural cells play crucial roles in the pathogenesis and symptoms of allergic disease and asthma in concert with immune cells.

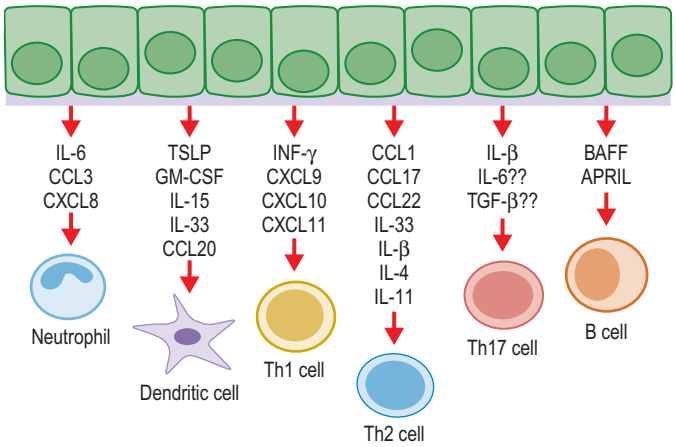

Fig. 1.12 Interaction between airway epithelial cell–derived cytokines and inflammatory cells. *APRIL*, A proliferation-inducing ligand; *BAFF*, B cell–activating factor of the TNF family; *CCL*, C–C chemokine ligand; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *IFN-γ*, interferon-γ; *IL*, interleukin; *TGF-β*, transforming growth factor-β; *Th*, helper T cell subset; *TSLP*, thymic stromal lymphopoietin.

Airway Epithelial Cells

The epithelium constitutes the interface between the external environment and the internal milieu of the lung. It is the site of first contact with inhaled particles, pollutants, respiratory viruses, and airborne allergens. Consequently, the epithelium plays an important role as a physical and immune barrier. The epithelium senses PAMPs on inhaled foreign substances via their PRRs and regulates airway homeostasis through the production of a multitude of mediators, such as GM-CSF, TSLP, IL-25, and IL-33, which promote a Th2 bias in DC precursor (Fig. 1.12). In other words, epithelial cells bridge the innate and adaptive immune responses by translating environmental exposures into disease phenotypes.

Epithelial cell structure and function are abnormal in patients with asthma. At a gross level, the composition of the asthmatic airway epithelium is different from that of the non-asthmatic population. For example, goblet cell hyperplasia and excessive mucus production are common features of asthma that contribute significantly to morbidity and mortality. Moreover, epithelial cells isolated from patients who have asthma have a deficient innate immune response from type I antiviral IFNs, particularly of IFN-β release during rhinovirus infection. Changes of epithelial cell structure and function occur early in disease pathogenesis. These findings place the epithelium at the forefront of asthma pathogenesis, and understanding the mechanisms that underlie these abnormalities will have short- and long-term clinical significance for the treatment of this disease.

When the epithelial cells are exposed to an external insult, such as allergens, pollutants, viruses, fungi, and bacterial toxins, epithelial barrier is damaged, epithelial cytokines (TSLP, IL-25, and IL-33) called alarmins are released. IL-25 and IL-33

activate ILC2s to produce IL-4, IL-5, and IL-13. Rhinovirus can also induce IL-33 and promote type 2 inflammation. The epithelial barrier is disrupted by Th2 cells, type 2 ILCs, and their cytokines IL-4 and IL-13 in human bronchial epithelium. Meanwhile, CPG-DNA administration strengthens the tight junction (TJ) integrity of the bronchial epithelial barrier. In addition, TSLP-stimulated $CD11c^+$ DCs can activate $CRTH2^+$ Th2 effector memory cells and undergo further Th2 polarization to magnify their role in allergic inflammation. Periostin is secreted by stimulated airway epithelial cells. It is an ECM protein and is considered a biomarker of type 2 inflammation. Periostin gene expression is increased by IL-13 and IL-4 in bronchial epithelial cells. Periostin functions on fibroblasts to promote airway remodeling, increase mucus secretion, and recruit eosinophils.[37]

Epithelial TJs seal the epithelia and form an essential part of the barrier between the inner tissues and the external environment. They control the paracellular flux and epithelial permeability and prevent the entrance of foreign particles, such as allergens and toxins to subepithelial tissues. They form complexes with members of the claudin family, the marvel family, and the junctional adhesion molecule (JAM) family spanning the membrane and forming homo- and heterodimeric connections between adjacent cells. Scaffold proteins, such as the zonula occludens (ZO) family, link the TJ complex to the actin cytoskeleton. Epithelial barrier TJ defects are reported in several allergic and inflammatory disorders, such as AD, asthma, and chronic rhinosinusitis, and a role for TJ in smooth muscle cells is described in asthma pathogenesis.[38–45]

Epithelial TJs are very sensitive to environmental factors. A recent study with laundry detergents demonstrated the devastating effects on TJ barrier integrity and cellular toxicity of human bronchial epithelial cells, even at very high dilution, without affecting epigenome and TJ gene expression.[46]

Airway Smooth Muscle Cells

In asthma, the ASM contracts in response to multiple stimuli, but it also produces ECM proteins, proteases that modulate these proteins, and myriad growth factors and cytokines. These collectively lead to airway remodeling—the pathology that characterizes asthma and consists of thickening of the airway wall, increased angiogenesis, mucous cell hyperplasia, thickening of the basement membrane, and increased bulk of muscle. It was previously thought that remodeling was a response to chronic airway inflammation, but it seems more likely that inflammation and remodeling develop along separate pathways. This is consistent with the finding that bronchoconstriction alone in the absence of an inflammatory or allergic stimulus can lead to airway remodeling.

ASM is a functional part of the innate immune system. It expresses messenger RNAs (mRNAs) for TLR1 through TLR10 and functional TLR2 and TLR3, indicating ASM can respond to bacterial and viral infections. ASM modulates leukocyte trafficking and function in asthma by activating cell adhesion molecules and secretion of chemokines and cytokines. When the response from cells obtained from people with asthma and people without asthma were compared, higher levels of cytokines and profibrotic factors were observed in the asthma-derived cells.

Neuronal Control of Airway Function

Both the immune system and the nervous system are critical to host defense within the airways. The immune system uses cellular and humoral mechanisms to protect the peripheral air spaces from invasion and colonization by microorganisms. The nervous system protects the airways by orchestrating reflexes, such as sneezing, coughing, mucus secretion, and bronchospasm in response to inflammation. Therefore the nervous system serves as the principal transducer between immunologic aspects of allergic inflammation and the symptomatology of immediate hypersensitivity.

Nerve–immune interactions can be inappropriate and deleterious, as with allergy; the immune response triggered by allergen exposure can recruit the nervous system in a way that is not beneficial to the host and causes or exacerbates the symptoms of allergic disease: irritation, pruritus, sneezing, coughing, hypersecretion, reversible bronchospasm, and dyspnea. Relatively little is known about the specific pharmacology of allergen–immune–nerve interactions, but the mediators likely include histamine, arachidonic acid metabolites, tryptase, neurotrophins, chemokines, and cytokines. In addition, the allergic reaction in the respiratory tract is associated with overt activation, increases in electrical excitability, as well as phenotypic changes in sensory, central, and autonomic neurons. Future research into the mediators and mechanisms of allergen-induced neuromodulation will not only increase our basic understanding of the pathophysiology of allergic disease but also suggest novel therapeutic strategies.[47]

CYTOKINE NETWORKS IN ALLERGIC INFLAMMATION

Cytokines play a key role in the orchestration and perpetuation of allergic inflammation and are now targeted in therapy (Fig. 1.13).[48] Allergic inflammation is characterized by the secretion of Th2 cytokines, including IL-4, IL-5, IL-9, and IL-13, which are secreted mainly by Th2 cells. The use of biologic immune response modifiers that target and neutralize cytokines is beginning to shed new light on the role of individual Th2 cytokines. IL-4 and IL-13 play a key role in IgE synthesis through isotype switching of B cells and appear to play a critical role in animal models of asthma. Thus far, blocking IL-4 and IL-13 or their common receptor IL-4Rα has not yet been shown to be of clinical benefit in asthma, but many clinical trials are currently under way. IL-5 is of critical importance in the differentiation, survival, and priming of eosinophils. A humanized monoclonal IL-5 neutralizing antibody, mepolizumab, induced a profound decrease in eosinophils in the blood and in induced sputum in patients with mild asthma but had no effect on the response to inhaled allergen. Clinical trials of anti–IL-5 in unselected symptomatic asthmatic patients showed no overall clinical improvement. Yet in highly selected patients with severe asthma and sputum eosinophilia, despite high doses of inhaled or oral corticosteroids, mepolizumab decreased the frequency of exacerbations and reduced requirements for oral corticosteroids, although it did not lessen symptoms or AHR.

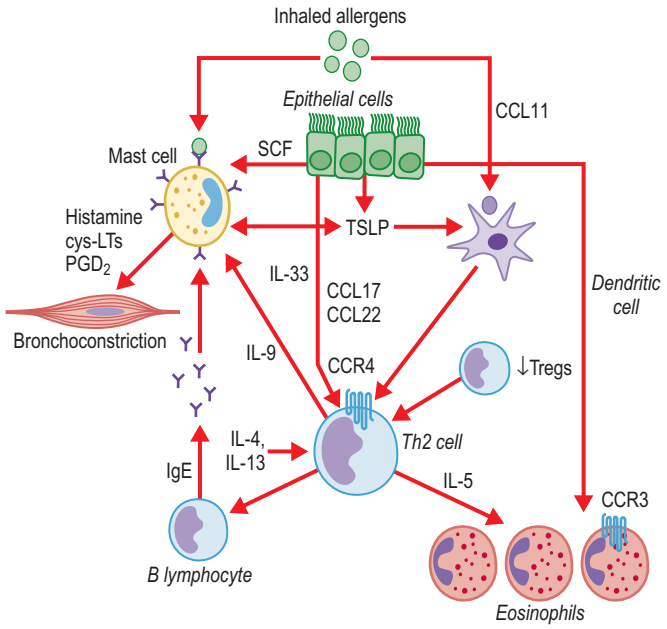

Fig. 1.13 Inflammation in allergy. Inhaled allergens activate sensitized mast cells by cross-linking surface-bound immunoglobulin E *(IgE)* molecules to release several bronchoconstrictor mediators, including cysteinyl leukotrienes *(cys-LTs)* and prostaglandin D_2 *(PGD_2)*. Epithelial cells release stem cell factor *(SCF)* (i.e., Kit ligand), which is important for maintaining mucosal mast cells at the airway or skin surface. Allergens are processed by myeloid dendritic cells, which are conditioned by thymic stromal lymphopoietin *(TSLP)* secreted by epithelial cells and mast cells to release the chemokines CCL17 and CCL22, which act on CCR4 to attract T helper 2 *(Th2)* cells. Th2 cells have a central role in orchestrating the inflammatory response in allergy through the release of interleukin *(IL)*-4 and IL-13 (which stimulate B cells to synthesize IgE), IL-5 (which is necessary for eosinophilic inflammation), and IL-9 (which stimulates mast cell proliferation). Epithelial cells release CCL11, which recruits eosinophils via CCR3. Patients with allergic disease may have a defect in regulatory T cells *(Tregs)*, which may favor further Th2 cell activation. *CCL*, C–C chemokine ligand; *CCR*, C–C chemokine receptor.

This observation suggests that blockade of individual cytokines may provide clinical benefit only in carefully selected patients.

Several proinflammatory cytokines have been implicated in allergic diseases, including IL-1β, IL-6, TNF-α, and GM-CSF, which are released from a variety of cells, including macrophages and epithelial cells, and may be important in amplifying the allergic inflammatory response. Although available evidence is persuasive that TNF-α may be important in patients with severe asthma, and earlier small clinical studies with anti–TNF-α therapies were promising, a large placebo-controlled trial of an anti-TNF antibody (golimumab) in severe asthma showed no overall benefit. Some of the subjects may have been responders, however, and patients with greater bronchodilator reversibility showed an apparent reduction in exacerbations. IL-17 also is increased in severe asthma, but anti–IL-17 antibodies have not yet been tested in asthma patients.

Interest has now focused on upstream regulatory cytokines in the pathogenesis of asthma because it is thought that they may have greater therapeutic potential. TSLP is an upstream IL-7–like cytokine that may initiate and propagate allergic immune responses and plays an important role in immune responses to helminths. TSLP is produced predominantly by airways and nasal epithelial cells and by skin keratinocytes and also stimulates immature mDCs, which express the heterodimeric TSLP receptor to differentiate into mature DCs. TSLP-activated DCs promote naive $CD4^+$ T cells to differentiate into a Th2 phenotype and promote the expansion of Th2 memory cells through the release of Th2 chemotactic cytokines CCL17 and CCL22 and expression of the costimulatory molecule OX40 ligand. In addition, TSLP suppresses the IL-12 p40 receptor in DCs and, by suppressing Th1 responses, further enhances Th2 responses. TSLP also promotes allergic inflammation by activating the differentiation IL-4 gene transcription in Th2 cells and the production of IL-13 from mast cells, by recruiting eosinophils and by amplifying responses of basophils. TSLP may therefore play a pivotal role in the initiation of allergic asthma, rhinitis, and AD. It is highly expressed in the airways of asthmatic patients, and its expression is correlated with disease severity and the expression of CCL17. TSLP is also expressed in epithelial cells of patients with AR and AD. Overexpression of TSLP in skin keratinocytes of mice amplifies the inflammatory response of inhaled allergen in sensitized animals, thus providing a mechanism for the "allergic march" whereby AD commonly precedes the development of asthma in children.

IL-25 (IL-17E) is a member of the IL-17 family of cytokines and induces allergic inflammation through increased production of Th2 cytokines. Although originally shown to be produced by Th2 cells, it is now known to be released from many different cells, including mast cells, basophils, eosinophils, macrophages, and epithelial cells. Blockade of IL-25 is effective in animal models of allergic disease, and blocking antibodies are now in clinical development. IL-33 is another upstream cytokine and a member of the IL-1 family of cytokines, which is unusual in its localization within the nucleus, where it may regulate chromatin structure and gene expression. It appears to be released only on damage to epithelial or endothelial cells, presumably acting as an alarmin, and is constitutively expressed at mucosal surfaces such as the airways. It signals through a receptor, ST2, that activates NF-κB and MAPK pathways. Its relevance to allergic inflammation is that it enhances ILC2 and Th2 cell function, leading to eosinophilia, mast cell activation, and mucus hypersecretion, potentially acting as a bridge between innate and adaptive immunity in allergic inflammation. It also directly activates eosinophils, mast cells, epithelial cells, and DCs. It appears to switch alveolar macrophages to the alternatively activated form (M2) that has been found in animal models of asthma with increased secretion of CCL17, although whether this association is relevant to human allergic disease is uncertain. IL-33 shows increased expression in airway epithelium of asthmatic patients, and level of expression is related to disease severity. IL-33 is increased in the skin of patients with AD and is released into the circulation during as well as mediating anaphylactic shock. IL-33 also is expressed in mast cells after activation through IgE receptors and also activates mast cells, providing a means of maintaining mast cell activation. Antibodies that block IL-33 or ST2 are now in clinical development.

MICROBIOME AND IMMUNE SYSTEM

Bacteria can stimulate or suppress inflammatory events in many ways. Both bacterial cell wall components and some metabolites of the microbiome have been associated with immunoregulatory effects. *Bifidobacterium*, *Lactobacillus*, and *Clostridium* species have been shown to increase the proportion of Treg cells in animal models. Moreover, *Clostridia* stimulates ILC3s to produce IL-22, which results in a strengthening of the epithelial barrier in the gastrointestinal tract. Bifidobacteria and Lactobacilli increase the induction of Treg cells by promoting metabolic processes such as vitamin A metabolism and tryptophan metabolism in DCs. An exopolysaccharide from *Bifidobacterium longum* has been shown to suppress Th17 responses in the gut and lung. Ingestion of *B. longum* by healthy human volunteers stimulated Foxp3$^+$ Treg cells in peripheral blood. Administration of this bacterial strain to patients with chronic inflammatory diseases resulted in decreased levels of serum proinflammatory biomarkers. Bacteria-derived metabolites also have some effects on immunoregulatory processes. Short-chain fatty acids (SCFAs) produced by the gut microbiota have been shown to affect DC and T cell functions by epigenetic mechanisms which are inhibition of histone deacetylases. Biogenic amines produced by bacteria in the human gut can change immune and inflammatory responses. In recent studies, microbiota-originated taurine and histamine have been shown to influence host–microbiome interactions in different ways such as co-modulating NLRP6 inflammatory signaling, production of epithelial IL-18, and suppressing the AMP production.[49]

FOOD ALLERGY AS A MODEL FOR ALLERGIC DISEASES

Food allergy frequently develops during infancy and this is explained by the immaturity of the gastrointestinal mucosa.[50] For this reason, exposure to food allergens early in life may be protective towards the development of allergy, establishing oral tolerance before sensitization to the allergen. LEAP study showed that early introduction of peanuts decreased the probability of peanut allergy development among children at high risk and resulted in the induction of oral tolerance to peanuts.[51] Although GUT mucosa are continuously exposed to allergens and commensal microorganisms, the immune system are mostly capable of tolerating these antigens. Induced Treg cells (iTregs) and Tr1 lymphocytes play an important role in this immune tolerance. Tolerogenic CD103$^+$ DCs present the luminal antigens and induce Foxp3$^+$ Tregs in a TGF-β–dependent and retinoic acid–dependent pathway.[52,53] In children who outgrow or become tolerant towards cow's milk allergy, the level of Tregs has been found to be higher than those with active allergies.[54] Genetic and environmental factors shape the immune responses in the skin when an exposure to food allergens occurs. In two epidemiologic studies, AD and the filaggrin gene mutation have been identified as potential risk factors for the development of food allergy.[55,56] In experimental food allergy models, exposure of the skin to food allergens resulted in the promotion of intestinal food allergy development in a Th2-dependent manner before the establishment of immune tolerance.[57,58] Despite the advancement in studies, the mechanism to which allergic sensitization in the skin is able to disrupt oral tolerance and how it leads to the development of food allergy in the gut remains unclear. It is proposed that the triggering effect of food allergens stimulates TSLP, IL-33, and IL-25 production in the skin keratinocytes and these alarmins in turn results in the activation of ILC2s and DCs.[52,53,58–62] The migration of DCs to the lymph nodes triggers the proliferation of Th2 effector and memory cells.[32] Following the ingestion of sensitized food, these Th2 cells are likely to migrate into the intestine and communicate with ILC2s leading to the production of IL-13. Intestinal epithelial cells also produce IL-33 and IL-25, further stimulating ILC2s. As a result of this, an allergic immune response develops towards the sensitized food.[63,64]

Tregs regulate the functions of ILC2s and suppress their type 2 cytokine production. Reciprocally, ILC2s secrete IL-4, which downregulates the Treg functions and increases the mast cell activation.[65] In the steady state, this network functions towards the food tolerance side. However, some genetic and environmental factors like microbiota dysregulation may stimulate alarmin production from the intestinal epithelial cells, which results in ILC2 activation.[66] Additionally, peanut allergens have been shown to increase alarmin production leading to food allergy development.[67] ILC2s produce many Th2 cytokines like IL-4, IL-5, IL-9, IL-13. IL-4, and IL-9 that amplifies the mast cells response.[68] As a result, iTregs are inhibited by the effect of IL-4.[65] After re-exposure to food allergens, activated mast cells can stimulate IL-33 production and ILC2 activation. This forms a positive feedback loop on mast cell activation and a negative feedback loop on iTregs, promoting the persistence of food allergy.[69,70]

Commensal bacteria also have some indirect effects on host immune responses towards food antigens. Some *Clostridia* strains induce the accumulation of Tregs in the colon.[71,72] *Clostridia* also trıgger ILC3s to produce IL-22, strengthening the epithelial barrier. In mice, it was shown that *Clostridia*-containing microbiota suppresses the response to food allergy.[73] In response to the microbial signals, macrophages secrete IL-1β which mediates GM-CSF release from ILC3s. GM-CSF induces IL-10 and retinoic acid production by DCs and macrophages and subsequently promotes the induction of Tregs. Any interference with this crosstalk results in loss of oral tolerance to food allergens.[74]

RESOLUTION OF ALLERGIC INFLAMMATION AND MAJOR PATHWAYS

Inflammation resolution is a tightly regulated and active process essential for the restoration of tissue homeostasis after an inflammatory insult. Dysregulated resolution results in chronic inflammation, tissue remodeling, and fibrosis. Granulocyte apoptosis–mediated caspase family proteins are essential for the clearance of these infiltrating inflammatory cells; cell survival is increased during inflammation, and apoptosis is accelerated during the resolution phase.

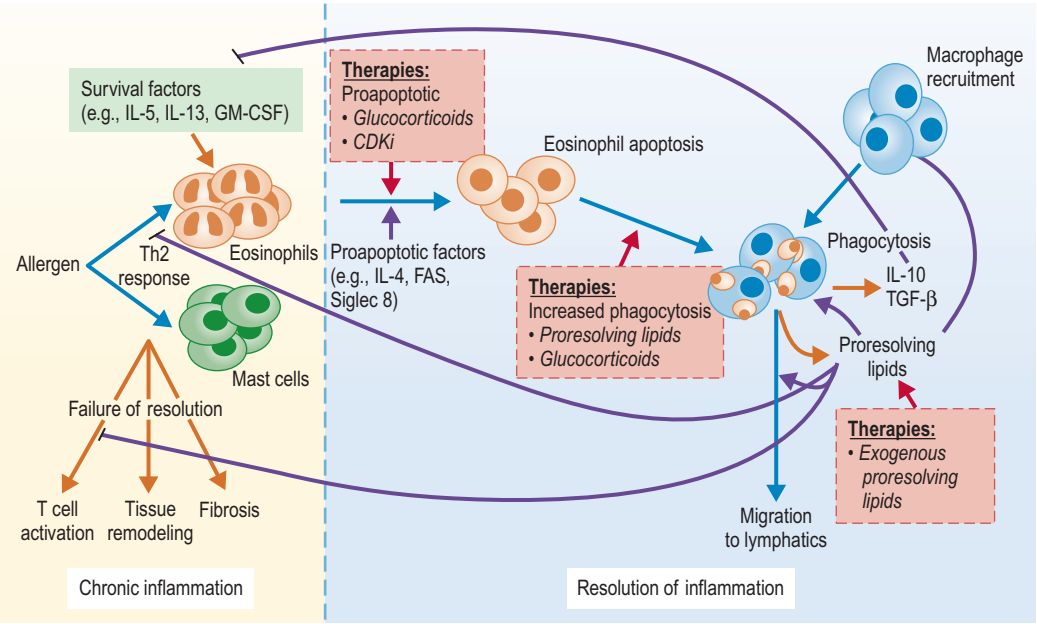

Fig. 1.14 Inflammation resolution and therapeutic opportunities. After the initial Th2-mediated proinflammatory events that occur in allergic inflammation and that are characterized by increased eosinophil recruitment, activation, and survival along with mast cell degranulation, progression to the resolution phase of inflammation allows return of normal tissue structure and function. Increasing proapoptotic factors drive eosinophil apoptosis for their timely clearance by macrophages, a process that is controlled by and increases the production of proresolving lipids. Apoptosis can be enhanced through the use of glucocorticoids, which can also increase the phagocytic capacity of macrophages and a variety of proresolving lipids. IL-10 released from a variety of cell types, including macrophages, can indirectly attenuate eosinophil survival and promote resolution. *CDKi*, Cyclin-dependent kinase inhibitor; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *IL*, interleukin; *Siglec*, sialic acid–binding immunoglobulin-like lectin; *TGF-β*, transforming growth factor-β; *Th2*, T helper type 2 cell.

Phagocytosis of apoptotic cells by macrophages ensures the safe disposal of dead and dying cells without release of toxic intracellular mediators. Engulfment of apoptotic cells signals to the phagocytosing macrophage that inflammation is coming to an end and alters macrophage mediator production from predominantly proinflammatory to proresolution, with enhanced production of cytokines with antiinflammatory properties, including IL-10 and TGF-β. This pattern contrasts with macrophage phagocytosis of necrotic eosinophils, which leads to enhanced proinflammatory mediator production such as GM-CSF.

Several proresolving lipids promote and control the resolution phenotype. The delivery of exogenous protectins, lipoxins, and resolvins has increased inflammation resolution and improved clinical outcomes in a variety of allergic murine models. Advances in our understanding of proresolving lipids, granulocyte apoptosis, and phagocytic clearance of dead and dying cells are creating new avenues for generation of novel proresolving agents with which to tackle allergic inflammation (Fig. 1.14).

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