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Allergy and hypersensitivity

Nature versus nurture in allergy and hypersensitivity

Editorial overview

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Raif Geha investigates signals that
trigger isotype switching to IgE, atopic
dermatitis and immunodeficiency
diseases.

Abbreviations

AD	atopic dermatitis
ADAM33	a disintegrin and metalloproteinase 33
AHR	airway hyperreactivity
DC	dendritic cell
EC	epicutaneous
IFN	interferon
IL	interleukin
LN	lymph node
LPS	lipopolysaccharide
NF-κB	nuclear factor κ B
PAMP	pathogen-associated molecular pattern
TCR	T-cell receptor
Th	T helper
TLR	Toll-like receptor

Introduction

Allergic diseases affect up to 20% of the population in developed countries. Ominously, the incidence of allergic diseases continues to rise. They are the most common cause of school absence, a substantial cause for absenteeism from work, and they interfere in the quality of life of adults. Allergic diseases pose an enormous burden on the economy because of their dual impact on health care cost and productivity. A better understanding of the pathogenesis of these diseases, and of the molecular mechanisms that underlie them, is essential to devise strategies to prevent their occurrence and to effectively suppress their manifestations when they take root.

The following series of articles explores the contribution of genetics and environment to allergic diseases, and suggests novel approaches to prevent and treat them.

The genetics of allergy and asthma

It has been known for centuries that allergic diseases have a strong genetic component. For example, clinical observations indicate that 70% of offspring from parents who are both asthmatics will suffer from asthma. Furthermore, members of a family may develop asthma, hay fever, eczema or any combination of the three, suggesting an inherited susceptibility to develop an IgE-mediated antibody response, as well as a tissue-specific predisposition to allergic inflammation. Asthma, although often defined as a single disease, in reality includes several different phenotypes, each of which is likely to reflect different pathogenic mechanisms. Indeed, an important reason why the analysis of the genetic components of asthma

has proven so difficult probably lies in our inability to define the phenotypes strictly enough to identify genetically homogenous populations. In the first article of this series, Vercelli [1] reviews the current knowledge of genetic polymorphisms in allergy and asthma.

Linkage studies have identified more than a dozen genomic regions linked to asthma and/or increased IgE levels [2]. For some of these regions (e.g. the T helper 2 [Th2] cytokine locus on chromosome 5q31), identifying the genes responsible for the linkage signal was relatively straightforward because the pathogenetic role of these genes was already known. In other cases (e.g. *ADAM33*), deciphering linkage revealed the existence of novel genes [3]. ADAM (for a disintegrin and metalloprotease) proteins are membrane-anchored metalloproteases involved in the shedding of cell-surface proteins such as cytokines and cytokine receptors. ADAM33 is expressed in lung fibroblasts and bronchial smooth muscle, but not in bronchial epithelial or immune cells, suggesting a role for ADAM33 in airway remodeling rather than immune-mediated inflammation. Mice with disruption of ADAM33 are no doubt in the making and should shed light on its role in asthma.

Recent studies on the polymorphisms of genes that encode components of the Toll-like receptor (TLR) signaling pathway in asthma have begun to shed light on the intricate interactions between genes and environment. Both epidemiological data and mouse experiments suggest that lipopolysaccharide (LPS) from Gram-negative bacteria, the ligand for TLR4, can exert opposing influences on the development of a Th2-dominated allergic response [4]. As detailed in the review by Bottomly and co-workers [5], low-dose LPS favors Th2 responses, whereas high-dose LPS exposure suppresses them. CD14 is a cell-surface molecule essential in the recognition of LPS by TLR4. On the basis of studies into CD14 polymorphisms in asthma, Vercelli [1] proposes an 'endotoxin switch' theory. According to this model, there is a complex dose-dependent, nonlinear relationship between environmental exposure to bacterial products and the outcome of immune responses. Polymorphisms in genes at the host-environment interface — CD14 is a prototypical one — would modulate immune responses and reposition the dose-response curve along the bacterial load axis. Each haplotype would have a distinct dose-response curve and a distinct pathogen concentration required for the switch.

Microbes and allergy

The 'hygiene hypothesis' ascribes the increased prevalence and severity of allergic diseases and other diseases of immune dysregulation (e.g. Th1-mediated autoimmune diseases) in industrialized countries to decreased exposure to microbes as a result of modern public health practices [6]. This has resulted in the loss of a major

source of immune provocation, with a consequent increase in pathogenic immune responses and their associated diseases. In the second article in this section, Horner and Raz [7] explore the mechanisms by which microbes that activate innate immunity affect the pathogenesis of allergic disease. Mononuclear cells, and in particular antigen presenting cells (APCs), express pattern-recognition receptors (e.g. TLRs), which interact with microbial components that have been termed pathogen-associated molecular patterns (PAMPs).

Ten mammalian TLRs and a number of their ligands have been identified [8]. TLR2 interacts with peptidoglycan, lipopeptides and other products from Gram-positive bacteria, acid fast bacteria and fungi, as well as LPS from select bacterial species, whereas TLR4 recognizes LPS produced by a majority of Gram-negative bacteria. TLR5 recognizes bacterial flagellin and TLR3 recognizes double-stranded RNA, a product of many viral infections. TLR9 recognizes certain DNA sequences that are significantly under-represented in mammalian genomes, but that occur at predicted frequencies in the majority of bacterial and viral genomes. The signaling pathways used by TLRs universally lead to nuclear factor κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) activation, cytokine gene transcription (e.g. IL-6, IL-10 and IL-12) and co-stimulatory molecule expression (e.g. CD40 and B7). All TLRs studied to date signal through the shared MyD88/MAL adapter complex to activate IL-1-receptor-associated kinase (IRAK1), which is linked via TNF-receptor-associated factor 6 (TRAF6) to the NF- κ B-activating complex, inhibitor of NF- κ B kinase (IKK). TLR3 and TLR4 also use an independent signaling pathway mediated by the adapter TRIF, which activates IFN gene expression [9]. There is little doubt that additional pathways will be found in the years to come.

Horner and Raz [7] review the evidence that high levels of environmental LPS protect against atopy. They indicate that a higher LPS level might be an indicator of increased exposure to microbial products in general. A complete understanding of how TLR ligands shape adaptive immunity and predisposition to allergy will require the additional epidemiological study of all TLR ligands found to be present at biologically significant levels in the environment. Again, the theme of differential effects of LPS concentration is raised. The observation that MyD88-knockout mice are prone to develop a Th2 response [10] leads the authors to speculate that a MyD88-independent LPS signaling pathway induces Th2-cell development and is responsive to LPS at low concentrations, whereas the MyD88-dependent pathway dominates at high LPS concentrations and favors Th1-cell development.

The potential therapeutic value of immunostimulatory sequence oligodeoxynucleotide (ISS-ODN), which binds

to TLR9, is also reviewed by Horner and Raz [7]. ISS-ODN induces an innate response dominated by cytokines (e.g. IL-10, IL-12, type 1 IFNs, IFN- γ) that are known to inhibit the allergic phenotype. ISS-ODN has proven to be more effective than corticosteroids in attenuating the hypersensitivity responses of asthma, allergic conjunctivitis and allergic rhinitis in mice [11]. The results of ongoing studies in humans are eagerly awaited.

Dendritic cells and the initiation of the allergic response

The dendritic cell (DC) is an essential player in CD4⁺ T-cell priming and is thought to play an important role in T-cell differentiation. DC priming of Th1 responses is well understood. The uptake of antigen in peripheral tissues by a DC in the context of a PAMP leads to DC maturation and migration to the lymph nodes (LNs) where it presents the antigen to T cells. Concomitant IL-12 production results in Th1 differentiation of T cells. Although DCs are also essential for Th2 responses, the induction of these responses is less well understood.

Bottomly and co-workers [5] review how DCs elicit a Th2 response in a mouse model of immunization induced by inhaled antigen. Inhalation of pure antigen fails to elicit DC migration to LNs; in the absence of DC migration, Th2-cell sensitization to inhaled antigens does not occur. Concomitant inhalation of LPS at low concentrations, however, induces DC migration to LNs and results in a Th2 response to antigen [12]. In contrast, concomitant inhalation of LPS at high concentrations results in a Th1 response. It is, therefore, of great interest to examine the gene expression profile of DCs treated with low versus high doses of LPS.

On the basis of these results, Bottomly challenges the existence of specialized DC subsets precommitted to induce one type of Th response [5]. She proposes that a single subtype of DC is able to initiate Th1 or Th2 responses to subsets of immune stimuli, thereby providing both flexibility and specificity to an environmental challenge. She discusses two alternative theories; one states that Th2 induction by DCs represents a default pathway, whereas the other proposes the active differentiation and maturation of DCs into APCs that direct Th2 development. A comparison of the gene expression profiles between unstimulated DCs, DCs activated with a high dose of LPS, and DCs activated with a low dose of LPS may help to reveal potential candidates for the elusive DC-derived molecule(s) that prime Th2 cells.

Regulatory T cells in allergy and asthma

The term 'regulatory T cell' refers to cells that actively control or suppress the function of other cells, generally in an inhibitory fashion. Four major types of CD4⁺ regulatory T cell have been described: Th3 cells, T_R cells,

CD4⁺CD25⁺ cells and NKT cells. Th3 cells are CD4⁺ T cells that are induced by oral antigen in the mesenteric LNs. They produce TGF- β and varying amounts of IL-4 and IL-10, and they suppress the development of auto-reactive T cells that mediate experimental autoimmune encephalomyelitis (EAE; [13]). T_R cells are elicited by chronic activation of CD4⁺ T cells in the presence of IL-10, and they suppress the proliferation of CD4⁺ T cells in response to antigen [14]. CD4⁺CD25⁺ cells play a critical role in the prevention of organ-specific autoimmunity, allograft rejection and the maintenance of self-tolerance. They suppress immune responses through direct cell-cell contact in a process that is dependent on signaling via cytotoxic T lymphocyte antigen 4 (CTLA-4), and the secretion of TGF- β [15]. They express glucocorticoid-induced TNF receptor (GITR) and their development depends on the transcription factor Foxp3. Lack of Foxp3 results in an X-linked autoimmune and allergic disease (XLAAD; X-linked autoimmunity allergic dysregulation syndrome), which is also called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X linked syndrome). NKT cells are either CD4⁺ or CD4⁻CD8⁻ double negative, and depend on IL-15 for survival [16]. NKT cells express a limited T-cell receptor (TCR) repertoire and an invariant V α 14-J α 281 TCR in mice and V α 24-J α 15 TCR in humans. Through this TCR, NKT cells recognize glycolipid antigens presented by the nonpolymorphic MHC-class-I-like protein, CD1d. Most importantly, when activated, NKT cells rapidly produce large quantities of IL-4 and IFN- γ .

In the fourth article of this section, Umetsu and co-workers [17] discuss the role of regulatory T cells in allergy and asthma. Exposure to inhaled allergen results in tolerance mediated by IL-10-producing DCs, which elicit T_R cells that secrete large quantities of IL-10, little IL-4 and no IL-13 [18]. He proposes that that, under normal circumstances, exposure to respiratory allergen results in the development of T_R cells and subsequent tolerance. Th2 cells could develop as an aberration of T_R-cell development, possibly due to inadequate production of IL-10 or enhanced IL-4 and IL-13 production, which would then lead to the development of allergy and asthma.

Umetsu [17] proposes several mechanisms of protection against allergy by microbial PAMPs. Exposure to high levels of endotoxin enhances the development of Th1 responses and suppresses Th2 responses. Mycobacteria induce CD4⁺CD45RB^{lo} regulatory T cells, which produce IL-10 and TGF- β and inhibit the development of airway eosinophilia. *Bordetella pertussis* filamentous hemagglutinin protein stimulates the development of T_R1 cells that produce IL-10. Finally, infection with hepatitis A virus, which is associated with protection against asthma and allergy, induces protective immunity by binding to its receptor, TIM1 (T-cell immunoglobulin- and mucin-domain-containing molecule 1), which

regulates IL-4 production and airway hyperreactivity (AHR) in murine models [19].

NKT cells are present in the lungs of asthmatic individuals and produce high levels of IL-4 and IL-13. On the basis of his studies in NKT-cell-deficient mice, Umetsu suggests that NKT cells become activated by antigens encountered in the lung, and are a prerequisite for the development of AHR [20].

The relative role of regulatory cells in asthma is discussed by Umetsu, who favors a prime role for T_R1 cells, as DCs from the respiratory tract produce IL-10, which is required for T_R1 -cell development. $CD4^+CD25^+$ cells appear not to block the induction of AHR. Th3 cells are primarily involved in regulating gastrointestinal disease, possibly because DCs from the gastrointestinal tract produce both IL-10 and TGF- β , which may be required for the development of Th3 cells. NKT cells appear to be essential for the induction of AHR in mice, but their importance in human asthma has not yet been studied. This will surely be the subject of future investigations.

Nature and nurture in the pathogenesis of atopic dermatitis

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease that is characterized by pruritic, eczematoid skin lesions. The prevalence of AD is steadily increasing, especially in industrialized nations, where the current lifetime prevalence in children is estimated to be 10–20%. In the fifth article of this series, Leung *et al.* [21] review the evidence that AD results from interactions between susceptibility genes, the host environment, skin barrier defects, bacterial and viral skin infections, and immunological factors.

Genetic linkage analyses have identified several chromosomal regions with linkage to atopic dermatitis. Candidate genes that have been studied for their role in AD include the β chain of Fc ϵ RI, mast cell tryptase, the CC chemokine RANTES, SPINK5 (the serine proteinase inhibitor implicated in Netherton's disease), IL-4, IL-4 receptor (IL-4R), IL-13R and STAT-6 [22]. All of these, except SPINK5, are expressed in immune cells and/or mast cells. SPINK5 is expressed in skin; its loss results in dry, injured skin. The development of AD-like lesions in SPINK5 deficiency suggests that skin-specific genes may play an important role in AD. This is possibly because they lead to itching. Work from our laboratory in a mouse model of AD has clearly shown that the epicutaneous (EC) application of antigen to abraded skin results in a vigorous systemic Th2 response and allergic skin inflammation dominated by Th2 cells and eosinophils irrespective of the genetic background [23]. IL-10 expression is upregulated in skin following injury and it plays an essential role in Th2 skewing following EC sensitization [24].

Leung *et al.* [21] review the wide and complex network of cellular interactions that involve DCs, T cells and resident skin cells that underlie AD. As an example of these interactions, mechanical skin injury also results in the expression of the Th2-cell selective chemokines TARC (for thymus and activation-regulated chemokine) and macrophage-derived chemokine (MDC). This initiates a positive feedback loop in which Th2 cells recruited to the skin induce further expression of TARC and MDC by resident skin cells. There is good experimental evidence that implicates these two chemokines in human AD [25].

A number of triggers are known to contribute to the pathogenesis of AD. Food allergens, aeroallergens, bacteria and even emotional stress have all been implicated as immunological triggers for AD. Many patients with AD have increased numbers of superantigen-secreting *Staphylococcus aureus* cultured from their skin lesions, and antibiotic therapy can be a useful method of controlling AD [26]. Our recent observation [27] that EC sensitization with the superantigen SEB (*Staphylococcus enterotoxin B*) provokes an AD-like skin lesion in mice with a systemic Th2 response to superantigen further indicates that bacterial superantigens play a role in AD. Skin from AD patients is deficient in the production of keratinocyte-derived antimicrobial peptides, such as LL-37 and β -defensins [28]. This may be the result of increased levels of Th2 cytokines, which suppress the expression of antimicrobial peptides. These data suggest that eradication of *S. aureus* from AD skin in addition to treatment with topical anti-inflammatory agents (e.g. corticosteroids and calcineurin inhibitors) is important in treating this disease.

Intervening with mast cell high-affinity IgE receptor signaling in the treatment of allergic diseases

The aggregation of antigen with the IgE bound to a high affinity receptor on mast cells or basophils initiates a complex series of biochemical events that result in the release of mediators that cause allergic inflammation and anaphylactic reactions. In the sixth article of this series, Siraganian [29] brings us up to date with the signaling pathways that are triggered by the high-affinity IgE receptor (Fc ϵ RI) on mast cells and basophils. He reviews recent work that shows that binding of IgE to Fc ϵ RI without the addition of antigen can also generate some signals that stimulate mast cell proliferation and mediator secretion without resulting in overt degranulation [30]. In this respect, recent evidence that the occupancy of Fc ϵ RI by monomeric non-antigen-specific IgE may be important for the development of a cutaneous hypersensitivity reaction (H Oettgen, personal communication). This is possibly because it triggers the secretion of TNF- α , which plays an important role in DC migration to regional LNs.

The biochemical pathways involved in mast cell activation following crosslinking of FcεRI by IgE and antigen are extensively reviewed by Siraganian [29]. Several kinases, biochemical intermediates and adapter molecules play key roles. They include src family protein kinases the tyrosine kinase Syk and their substrates the adapter proteins SLP-76 (for SH2-domain-containing leukocyte protein of 76 kDa) and LAT (for linker for activation of T cells), and their downstream effectors phospholipase Cγ (PLC-γ) and Vav, which are all indispensable for FcεRI signaling. There is also a host of regulatory proteins, which by themselves are not essential for FcεRI signaling, but modulate it either positively or negatively. For instance, Csk positively regulates FcεRI signaling by promoting the activation of src kinases, whereas PAG/Cbp negatively regulates FcεRI signaling by sequestering Csk in resting mast cells.

The essential role of calcium GTPases and SNARE (for synaptosomal-associated protein receptor) proteins in FcεRI-mediated granular fusion, mediator release and activation of gene transcription is also reviewed by Siraganian [29]. Recent data from our laboratory indicate that the Wiskott–Aldrich syndrome protein (WASP), which is activated by the small GTPase Cdc42 and its partner WASP-interacting protein (WIP), both of which are involved in cytoskeletal reorganization, is important for FcεRI-triggered mast cell mediator release and gene transcription [31].

Finally, Siraganian reviews the role of surface receptors that inhibit FcεRI signaling and mast-cell activation. FcγRIIB is a major inhibitory receptor. Recent studies in mice have shown that bifunctional molecules that crosslink FcγRIIB to FcεRI inhibit mast cell release [32]. More interestingly, a chimeric antigen–IgGFc fusion protein inhibits mast cell activation by antigen-specific IgE. It will be important to determine the clinical value of these inhibitory chimeric proteins.

Conclusions

Understanding the interplay between genes and environmental factors, particularly with respect to the microbial world, promises to be the key to the complex pathogenesis of allergic diseases, and the effective prevention and treatment of these diseases. The quest will be arduous because of the number of pathways and molecules that predispose to allergy in general, and to tissue-specific allergic inflammation in particular. The role of microbial agents also promises to be complex because different agents may have different effects on the development and expression of allergic inflammation. This is also because the same agent may exert opposing effects depending on the exposure dose and, more importantly, the genetic make-up of the host. Nevertheless, there is little doubt that efforts to unravel the complexity of allergic diseases are bearing fruit and

that much more information will be forthcoming in the near future.

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