Innate Immunity and Asthma

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Asthma remains a major health problem worldwide that has increased in developed countries. Much of the focus in asthma research in the past has been on adaptive, antigen-dependent immune responses. Recent work suggests that the innate, non-antigen-dependent immune system plays a critical role in asthma pathogenesis. Here we will highlight innate receptors and cells in the context of allergic responses. Reviewing animal models and human studies, we focus on interactions of innate and adaptive immunity.

Keywords: lung; airway disease; immunology; inflammation

Asthma is a disorder of profound clinical significance that afflicts at least 22 million people in the United States alone. There are estimated to be as many as 300 million individuals with asthma worldwide (1). Previously defined as a reversible disorder, asthma is a chronic inflammatory disorder characterized by airway inflammation and airway hyperresponsiveness (AR) to inhaled stimuli. Episodic wheezing, dyspnea, cough, sputum production, and bronchoconstriction characterize the acute clinical syndrome. When patients with asthma are prospectively examined from birth, most asthma begins in early childhood and has an allergic component (2). Patients with allergic asthma have eosinophilic inflammation in the lung, in parallel with increased mediators associated with an adaptive, allergen-dependent response (e.g., interleukin [IL] 4, IL-5, and IL-13) of the T helper cell (Th)2 rather than Th1 subset (e.g., interferon [IFN]- γ) (Figure 1), as well as elevated serum immunoglobulin (Ig)E. Recent attention has also focused on the Th17 subset that mediates neutrophilic inflammation and may play a role in asthma (3). Much of the focus in asthma research in the past has been on adaptive immune responses. Recent work suggests that the innate, non-antigen-dependent immune system plays a critical role in asthma pathogenesis.

Here we will highlight innate receptors and cells in the context of allergic responses. Reviewing animal models and human studies, we focus on interactions of innate and adaptive immunity.

ADAPTIVE AND INNATE IMMUNITY

The development of the adaptive immune response is an evolutionarily recent event present only in vertebrates and is characterized by events that require gene rearrangement. By contrast, the innate immune system consists of those elements of host defense against infection that are encoded in germline

DNA and do not require prior exposure to antigen (4). Thus, innate immunity is available for defense of the host at its initial encounter with infection. The innate immune system has been described as a primitive system, dating back hundreds of millions of years. It is present not only in animals but also plants. Seen a different way, the innate immune system has become highly refined over this time and highly preserved because of its efficacy. Adaptive immunity might be viewed as a luxury available only to vertebrates (paraphrased from Reference 5). Antigen recognition sites on antibodies and T cell receptors in adaptive immunity are thus created specifically for each new antigen encountered. Innate immune responses are rapid and transient, whereas adaptive immune responses are slower, but last longer. Notably, immunological memory is characterized as a component of adaptive immunity, with a more powerful and rapid response upon reexposure to the same antigen. Though distinguished by significant differences, the innate and adaptive arms of the immune system are tightly integrated as a single defense. Adaptive immune responses are dependent upon cytokine production and regulation by the innate system (6).

The innate immune system consists of afferent and efferent arms, with cellular and humoral elements. However, of particular importance is the afferent, sensing arm of innate immunity (5) because of its ability to identify specific components of microbial organisms. These components of microbes have been termed pathogen-associated molecular patterns (PAMPs); however, these are molecules rather than patterns and they need not originate from pathogenic organisms, but can also be present in nonpathogenic organisms (7). Thus, they are ligands of innate immunity receptors that are of microbial origin and specificity, with both humoral and cellular sensors (receptors).

Innate Immunity: Asthma and Allergy

The prevalence of asthma has increased dramatically during the last 20 to 40 years in the "Western," industrialized world (8). Many hypotheses have been proposed to explain this increase. The "hygiene hypothesis" has received the greatest attention and support from the scientific literature. This hypothesis links the increase in allergy, asthma, and autoimmunity in industrialized nations during the last half century to the fact that patients are less frequently challenged with microbes or their products. This reduction in infectious challenge is purported to result from a less agrarian life style, smaller family size, better infection control, more immunizations, frequent antibiotic prescriptions, better sanitation, and less oro-fecal burden early in life (9). One postulate is that exposure to components of microbes early in life modulates the immune response and immunological phenotype of children from a predominant Th2 phenotype at birth to a Th1 phenotype as they proceed through childhood. As an extension of this concept, minimizing microbial exposure may support the development of the Th2 phenotype, and development of allergic asthma. However, New York City has a high microbial burden and yet asthma rates are high,

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Figure 1. Adaptive immune responses. Antigen-presenting cells (APC) bind, process antigen (Ag), and display it on their surface on the major histocompatibility complex (MHC). This is then able to bind an antigen-specific T cell receptor (TCR) on the surface of the naïve T cell (also known as signal 1). To respond to this antigen, the T cell must also be costimulated through additional receptors (costimulation, also known as signal 2). This dual stimulation can lead to a Thelper (Th)1 or Th2 response, depending on the antigen. The innate immune system plays a critical role in determining the type of T cell differentiation and, thus, the type of adaptive immune response. A newly described subset, Th17 cells, mediates neutrophil inflammation and may play a role in asthma.

suggesting that microbial exposure in relationship to asthma pathogenesis may be dependent upon a number of variables including, but not limited to, geographic location, genetics, and immune system interactions.

Receptors of Innate Immunity

Many microbes interact with the host through receptors that identify a specific pathogen or microbe-derived molecules. Microbes may limit the development of the allergic adaptive immune response through interaction with a group of these innate immune receptors, including receptors termed Toll-like receptors (TLRs), early in life. Thus, the innate immune system

appears to play a critical role in determining the phenotype of the adaptive immune response.

In addition to TLRs, cellular receptors for innate molecules identified to date include NOD proteins, Dectin, CD14, and collectins (5). Data have been published on 10 TLRs in humans thus far (10). TLRs function in microbial sensing, with each TLR sensing a separate set of ligands (Figure 2). TLRs are membrane proteins characterized by a cytoplasmic Toll/IL-1 receptor homology domain, or TIR domain, as well as ligand binding domain that contains a leucine-rich repeat sequence separated by a transmembrane domain (Figure 2) (10). TLRs are pattern recognition receptors that bind different specific

Figure 2. Toll-like receptors (TLRs), their ligands, and cellular location. TLR1, 2, 4, 5, and 6 are located on the plasma membrane, while TLR3, 7, 8, and 9 are located in intracellular compartments such as endosomes. Each TLR recognizes a discrete set of ligands and can form homo- or heterodimers, thus increasing the number of ligands recognized. Each TLR has a ligand-binding domain containing leucine-rich repeats. The cytoplasmic portion of the receptor contains a TIR domain that lacks signaling capability, but binds adaptor proteins when ligand is bound. dsRNA = double-stranded RNA; LPS = lipopolysaccharide; ssRNA = single-stranded RNA; TIR = Toll-like and interleukin 1 receptor.

ligands, but the exact nature of these ligand–receptor interactions is still evolving as additional data become available. These receptors not only recognize bacteria (at least TLR1, 2, 4, 5, and 9), but also fungi (TLR6), protozoa, and viruses (TLR3 and 9) (5). Some TLRs form heterocomplexes (TLR1 and 6 can bind with TLR2) and in turn can bind additional ligands. TLRs have no signaling domain, but bind adapter proteins that then initiate signaling cascades. There are five known adapter proteins, including MyD88, Mal/Tirap, Trif/Ticam-1, MyD88-4/TIRP, and MyD88-5 (5). Space prohibits the discussion of the signaling pathways involved in detail, but it should be noted that TLRs 1, 2, 6, and 9 are thought to signal exclusively through MyD88 or via a heterodimer including MAL/Tirap. TLR4 signals through MyD88 and Trif (11). Although these pathways overlap and both stimulate NF- κ B activation, only *Trif* leads to activation of IFN-releasing factor 3 (IRF-3) and the production of IFN- β (a Type I interferon) (14, 15). Binding of IFN- β to the Type I IFN receptor in turn leads to STAT1 activation in cells expressing this receptor, inducing nitric oxide synthase (NOS) expression and IP-10 production, to mention a few downstream responses.

Lipopolysaccharide (LPS), a ligand of TLR4, and apparently other innate immunity ligands, can serve an adjuvant role via the Trif adaptor protein with its downstream signaling pathway (14). Antigen is presented to cells by antigen-presenting cells (APCs) via MHC II, but requires costimulatory molecule expression (e.g., CD80, CD86, and CD40) to generate an adaptive immune response. One of the most important functions of Trif, mediated via triggering the downstream production of IFN- β , is costimulatory molecule expression (14, 16, 17). The failure of this innate signal may be involved in the development of allergy and asthma, although a mechanism for this remains to be determined.

LPS, a TLR4 ligand, is also termed endotoxin, and a significant component of gram-negative enteric bacterial cell walls. LPS exposure appears to both protect against and promote asthma. Epidemiologic studies indicate that exposure of children to LPS, in a rural setting or in bed sheets, or domestic pets within the first 6 months of life is associated with a decreased incidence of asthma, consistent with the hygiene hypothesis (18, 19). In contrast, adults that get exposed to very high concentrations of LPS in occupational settings (grain workers, farming occupations) develop asthma that is temporally related and made worse by additional exposure to LPS. LPS can inhibit the development of an allergic response in animal models. For example, LPS-containing, commercially available allergen preparations induce a less intense airway response in an animal model of asthma when compared with LPS-free allergens (12). Similarly, as stated above, environmental endotoxin exposure in children inversely correlates with allergic asthma (19). These findings point to the adjuvant role of innate immunity ligands and the role that they may play in allergic disease (13), but by no means demonstrate that LPS is the only ligand capable of this response or that TLR4 is the only receptor involved. Many of these receptors trigger similar, if not identical, responses, but research on this topic has been clouded by contamination of innate ligands with ligands for other receptors in the innate immunity family. Finally, not all patterns may be the same. Ligands for TLR2 stimulate the release of IL-13 and IFN- γ , whereas ligands of TLR4 induce production primarily of IFN- γ and modest amounts of IL-13 in *in vitro* studies in mice and humans (22).

TLRs and Asthma

Some investigators have found that activation of TLR2 is associated with increased allergic inflammation and AR in a murine allergic models (14). Other studies have found that

TLR2 and TLR4 ligands decrease allergic response (15). These studies underscore the complex response to LPS, and probably other innate immunity ligands. The timing and dose of LPS, as well as the genetic and environmental background of the host, appear to be important. This may help to explain how LPS can induce an asthma phenotype independent of antigen (16). Thus, as a component of organic grain dust LPS can participate in the pathogenesis of asthma in adults and may exacerbate disease in individuals with allergic asthma (26). These responses appear to be independent of the adjuvant role of LPS or other innate immunity ligands.

NOD Proteins

NOD proteins are intracellular, cytoplasmic receptors that are characterized structurally by a CARD (caspase activation and recognition domain) domain, a centrally located nucleotide-binding oligomerization domain (NOD) and multiple C-terminal leucine-rich repeats (17). There are two NOD proteins that are known to exist in humans: NOD1 and NOD2. NOD1 has the natural ligand bacterial diaminopimelic acid (abbreviated iE-DAP) that is present in gram-positive and gram-negative bacteria. The NOD1 gene is on chromosome 7p14 and this region has been strongly linked to asthma in multiple linkage analyses performed in humans (28). Moreover, the protective effect of living on a farm from birth for reducing the prevalence of asthma is lost in patients that have a mutation in this gene (18). In a large cohort of adult Germans, those with a mutation in this gene had a higher frequency of atopy and asthma (30). While data suggest that NOD1 may play a protective role in asthma, the influence of additional geographic locations and genetic background as well as underlying mechanisms remain to be investigated.

INNATE CELLS IN ASTHMA

Bronchial Epithelial Cells

Human and nonhuman bronchial epithelial cells have been shown to express MHC Class II antigens that are essential for external presentation of antigen (19). Thus, these cells have the characteristics of APCs. Human bronchial epithelial cells also express CD40 and ICAM-1 in addition to MHC Class II, and these molecules can be up-regulated by IFN- γ (20). Bronchial epithelial cells are capable of inducing a proliferative response of mixed lymphocytes in the presence of IFN- γ (20). They also express TLRs including TLR1–6 and TLR9 (33). Although they do have MHC Class I on their surface, this receptor generates a weak proliferative response of lymphocytes. Diesel exhaust particles have been shown to induce the maturation of immature dendritic cells through the release of GM-CSF from airway epithelium (21), supporting a role for bronchial epithelial cells in the rise of allergic asthma.

Dendritic Cells

Dendritic cells (DCs) are APCs that play a central role in initiating and regulating adaptive immune responses (Figure 1) (22). These cells also serve as an important bridge between the innate and adaptive immune system. DCs arise from CD34+ bone marrow progenitor cells or CD14+ monocytes and differentiate into immature DCs of three types: Langerhan's cells, myeloid DCs (mDCs), and plasmacytoid DCs (pDCs). Immature DCs have the greatest capacity for uptake of antigen; however, DC maturation is associated with greater ability for antigen presentation. Maturation of DCs is stimulated by a variety of agents, including endogenous factors released by necrotic cells, cytokines, activated T cells that express CD40 ligand, and innate immunity ligands that are derived from

Figure 3. Regulatory T cells (Tregs) and adaptive immunity. Tregs differentiate from naïve T cells in response to antigen, and this may be influenced by TLRs binding their cognate ligands on APCs or T cells. Tregs are IL-10 dependent and they secrete IL-10 that exerts a suppressive effect on Th1 and Th2 phenomena. Substantial data also indicate that transforming growth factor- β is secreted by regulatory T cells and that this cytokine has important regulatory effects. Ag = antigen; MHC = major histocompatibility complex; TCR = T cell receptor; Th = T helper.

microbes. These factors induce decreased endocytosis and up-regulation of co-stimulatory molecule expression including CD80, CD86, and CD40 on APCs, as well as MHC Class II molecule expression. Tolerance to antigen has been shown to develop when immature DCs are exposed to antigen in the absence of co-stimulatory molecule expression (23). Interestingly, in the lung, tolerance to the allergen ovalbumin, induced by intranasal injection, is IL-10 dependent and results in the generation of CD4⁺ T regulatory cells that also produce IL-10 (24). Mature DCs, expressing inducible T cell co-stimulator (ICOS) ligand, CD80, and CD86, are crucial for a T regulatory cell-mediated decrease in AR (25). However, a substantial amount of data supports the concept that airway DCs are increased in asthma, that antigen-pulsed DCs induce and exacerbate asthma, and that removal of DCs in sensitized mice can attenuate the response to antigen (summarized in Reference 26).

T CELLS: ADAPTIVE CELLS THAT INTERACT WITH INNATE IMMUNITY

T Cells

The activation of T cells requires a first signal of antigen recognition and second costimulatory signal (Figure 1) (27). In allergic asthma, one critical event is the activation of CD4⁺ T cells, leading to a predominance of Th2 cytokine (e.g., IL-4, IL-5, IL-13) over Th1 cytokines (e.g., IFN- γ). Notably, as the rise in Th2-type disorders (asthma) is increasing, so are Th1-type disorders (type I diabetes, multiple sclerosis), indicating the necessity for intense investigation of pathogenic mechanisms (28). Recent studies suggest that Th1 as well as Th2 cytokines may promote asthma (29). Also, T cell subsets, in addition to Th1 and Th2, have been identified in asthma, including T regulatory and Th17 cells (30), and may modulate the asthma phenotype. While not the focus of this review, neutrophils have increasingly been noted to be associated with asthma pathogens, particularly severe asthma. Th17 cells mediate neutrophilic inflammation, as well as steroid-resistant airway inflammation in a murine model (3, 31–33).

T Regulatory Cells

T cells were shown many years ago to suppress the immune response in an antigen-specific manner (34). Although the concept of suppressor T cells generated immense controversy (35), the existence of regulatory T cells is now reasonably well established and their function is beginning to be characterized (36). Recent immunological research has demonstrated that discrete regulatory populations of T lymphocytes (Treg) exist. These cells are identified by their cell surface markers (CD4⁺CD25⁺). Regulatory cells other than CD4⁺CD25⁺ cells also seem to exist. These include CD8⁺ regulatory cells and some spontaneously occurring regulatory cells, including CD25⁺CD62L⁺ T cells and natural killer (NK) cells. The latter two can be considered “innate” regulatory subsets of T cells because they occur spontaneously, but they are distinct from other cells of the innate immune system in that they express the T cell receptor (TCR). In the case of CD4⁺CD25⁺ cells, cell-cell contact appears to be required to induce suppression *in vitro* (37, 38). By contrast, the mediation of suppression (regulation) *in vivo* appears due in part to cytokine secretion. Indeed, Th1 cells have a suppressive effect on Th2 responses via the secretion of IFN- γ and Th2 cells have a similar suppressive effect on Th1 cells via secretion of IL-4. Tregs are IL-10 dependent, and they secrete IL-10 that exerts a suppressive effect on Th1 and Th2 phenomena. Th2 cells also produce IL-10. Substantial data also indicate that transforming growth factor- β is secreted by regulatory T cells and that this cytokine has important regulatory effects (Figure 3) (36). We review just the beginning of our understanding of afferent and efferent arms of immune regulation.

ADDITIONAL PATHWAYS THAT MODULATE INNATE IMMUNITY

There is heightened interest in understanding the pathways that regulate the regulators. We present two examples (cytotoxicity and collectins surfactant protein [SP]-A and SP-D) of distinct immune interactions between regulators and innate immunity.

For example, CTLA4 is a marker of Tregs that has the potential to decrease allergic responses, by activation of Tregs. CTLA4 is also a ligand for the costimulatory molecules CD80 and CD86 and, upon T cell activation, transduces a negative feedback signal to decrease immune responses (39). CTLA4 deficiency results in systemic autoimmunity, supporting the potent negative regulatory role of CTLA4 (46). Recent studies suggest that the CD45 receptor tyrosine phosphatase is a strong immunoregulator of CTLA4, induces allograft tolerance and decreases allergic adaptive responses (40).

Other innate molecules that have been shown to modulate allergic adaptive responses include the collection surfactants SP-A and -D. Both SP-A and SP-D are associated with decreased allergic responses, suggesting a potential negative regulatory role (41). Deficiency of SP-D leads to persistent T cell activation (47) and enhanced allergic immune responses (48). Whether manipulation of negative regulators such as CTLA4, SP-A, or SP-D will prove to be promising in control of allergic immune responses remain to be determined.

HUMAN IMMUNE INTERACTIONS: INNATE AND ADAPTIVE INFLUENCES

Studies from cord blood and children suggest important lessons regarding development of immunity. Parasite-infected children in Gabon, Africa have decreased atopy that correlated with IL-10 production, a cytokine associated with Treg function (42). In fetal cord blood, maternal atopy is associated with decreased Foxp3 levels (15). Foxp3 is a transcription factor characteristically expressed in Tregs. The concept of a current asthma epidemic, as well as reports of a potential decline in asthma, but not eczema (43), supports the critical need to understand asthma pathogenesis early in life.

APPROACHES TO INVESTIGATE INNATE AND ADAPTIVE INFLUENCES: LOOKING TOWARD THE FUTURE

There are myriad pathways and genes involved in innate and adaptive immune responses, thus compelling state-of-the-art investigative approaches. For example, TLR4 receptor-ligand interactions may have both pro- and anti-asthmatic effects. Sorting out the signal transduction pathways for these different responses can be daunting (44). At least 100 genes (in animal models) and 150 genes (humans) appear to be important in asthma (45). New approaches, such as systems biology and bioinformatics, offer important tools that may be critical for understanding innate and adaptive immune interaction relevant to allergic asthma.

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