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Cockroach Allergen Exposure and Risk of Asthma

Danh C. Do[1], **Yilin Zhao**[1], and **Peisong Gao**[1,†]

[1]Division Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

Cockroach sensitization is an important risk factor for the development of asthma. However, its underlying immune mechanisms and the genetic etiology for differences in allergic responses remain unclear. Cockroach allergens identification and their expression as biologically active recombinant proteins has provided a basis for studying the mechanisms regarding cockroach allergens induced allergic sensitization and asthma. Glycans in allergens may play a crucial role in the immunogenicity of allergic diseases. Protease-activated receptor (PAR)-2, Toll-like receptor (TLR), and C-type lectin receptors have been suggested to be important for the penetration of cockroach allergens through epithelial cells to mediate allergen uptake, dendritic cell maturation, antigen presenting cell (APC) function in T cell polarization, and cytokine production. Environmental pollutants, which often co-exist with the allergen, could synergistically elicit allergic inflammation, and aryl hydrocarbon receptor (AhR) activation and signaling may serve as a link between these two elements. Genetic factors may also play an important role in conferring the susceptibility to cockroach sensitization. Several genes have been associated with cockroach sensitization and asthma-related phenotypes. In this review, we will discuss the epidemiological evidence for cockroach allergen-induced asthma, cockroach allergens, the mechanisms regarding cockroach allergens induced innate immune responses, and the genetic basis for cockroach sensitization.

Keywords

asthma; cockroach allergens; glycan; aryl hydrocarbon receptor (AhR); genetics

Introduction

Asthma is the most prevalent chronic illness in children with both increasing clinical and public health concerns (1). The prevalence of asthma in the United States has increased from 7.3% in 2001 to 8.4% in 2010 (2). Currently, asthma affects over 300 million people and one out of every 250 deaths worldwide is attributed to this disease. However, the reason for

†**Address correspondence to:** Peisong Gao, MD, PhD, Division Allergy and Clinical Immunology, 5501 Hopkins Bayview Circle, Room 3B.71, Baltimore, MD 21224, Telephone: 410-550-2124 / Fax: 410-550-2130, pgao1@jhmi.edu.

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Conflict of interest

All authors stated there is no conflict of interest.

this increased prevalence remains poorly understood. It has become apparent that interaction between environmental factors early in life and specific genetic factors is important in the development of asthma. Despite the numerous efforts to discover genes associated with asthma and allergy through various approaches, including genome-wide association studies (GWAS) and investigation of gene-environment interactions, so far, there has been no "genetic variants or specific genes" that are generally recognized. Although, genetic heterogeneity and ethnic differences may contribute to the failure in discovering these genetic factors for asthma, environmental factors, on the other hand, may be critical for the development of asthma in genetically susceptible individuals. Indeed, allergens trigger asthma attacks in 60-90% of children and in 50% of adults, and 75-85% of patients with asthma have positive skin tests. Exposure to indoor environmental allergens such as cockroach, house dust mite (HDM), pet dander, pollen, and mold can induce allergic asthma and atopy (3, 4). House dust mite and cockroach antigens are common, and exposure and sensitization have been shown to increase asthma morbidity. In particular, exposure to cockroach allergens appears to have a greater effect on asthma morbidity than dust mite or pet allergy among inner-city children with asthma (5). In this review, we will specifically discuss about the epidemiological evidence for cockroach allergen-induced asthma, major components for immunogenicity in cockroach allergens, and mechanisms regarding the cockroach allergens induced innate immune responses.

Cockroach allergen exposure and risk of asthma

Cockroach exposure has been linked to cockroach sensitization and allergic respiratory symptoms. In fact, sensitization to cockroach allergens has been identified as one of the strongest risk factors for the development of asthma in low-income urban populations (5). In studies comprising children and adults, the prevalence of cockroach allergy ranges from 17-41% in the United States (6, 7). Cockroach allergens are detected in 85% of inner-city US homes and 60–80% of inner-city children with asthma are sensitized to cockroach based on the skin prick testing (8). The levels of cockroach allergens measure in the home of these children are strongly associated with a greater risk for the development of cockroach sensitization (9, 10). This finding was supported by studies from the National Cooperative Inner City Asthma Study (NCICAS) and demonstrated a clear relationship between cockroach allergen exposures and sensitization in asthmatic children living in Baltimore inner cities (4). This suggests that cockroach sensitization is a specific and major contributor to asthma morbidity for individuals who are exposed to high levels of cockroach allergens. Indeed, studies in the New York City Neighborhood Asthma and Allergy Study (NAAS) have found that cockroach allergens were more prevalent in the bed dust from homes in neighborhoods with high prevalence of asthma compared to ones with low asthma prevalence (10). Further convincing evidence was provided from a recent meta-analysis study summarizing research findings published from 2000 to 2013 on indoor exposures and exacerbation of asthma through PubMed suggests a causal relationship between cockroach allergens exposure and exacerbation of asthma, especially in adults who are sensitized to cockroach (11). Moreover, cockroach-sensitized patients exposed to higher levels of cockroach allergens in their homes have greater asthma morbidity, particularly among children in the United States inner cities as compared to non-sensitized or non-exposed children. The rate of hospitalization for asthma was 3.4 times higher among children who

are skin test positive for cockroach allergens and whose bedrooms had high levels of cockroach allergens (12). These children also had 78% more visits to hospitals, significantly more wheezing, and missed more school days compared to children who were skin test negative to cockroach allergens (13).

Cockroach allergens exposures have also been reported in European urban communities, such as those found in the public housing units of Strasbourg, France (14). In Poland, approximately 25% of asthmatic children are sensitized to cockroaches and most of their homes have detectable levels of cockroach allergens (15). Among these children, there is an association between cockroach sensitization and a more severe asthma. In Asia, cockroach allergens are found in 11% to 98% of dust samples collected from 9 cities across the southern and tropical regions of China (16). In Taiwan, 58% of asthmatic patients are allergic to the cockroach allergen, Per a 2 (17). These studies implicated that cockroach allergens exposure and sensitization are clinically relevant across multiple continents.

Home-based environmental interventions to decrease the exposure to indoor cockroach allergen has led to a reduction in asthma-associated morbidity (19, 20). These findings demonstrated the relevance of cockroach allergen exposure and sensitization in the contribution to the higher asthma prevalence observed in the United States. The studies also support the necessity of cockroach testing and consideration of this allergen in the treatment of allergic respiratory diseases.

Cockroach testing, immunotherapy, and current limitations

Cockroach allergy is diagnosed with cockroach crude extract via skin testing and/or by measurement of specific IgE to cockroach allergens. Cockroach allergen-specific IgE levels have been shown to be correlated with allergens exposure among sensitized participants and a range of inflammatory, physiologic, and clinical markers (20). However, the lack of immunodominant allergen(s) and complex patterns of IgE responses to multiple cockroach extracts have made it difficult to produce standardized cockroach allergenic extract with content that would promote high efficacy for those heterogeneously sensitized patients (21). Thus, it is essential to have the standardized cockroach extracts with reliable potency and contents for the diagnosis of cockroach allergy. Similarly, cockroach immunotherapy for cockroach allergy holds promise as a treatment strategy with immune-modulatory and clinical effects in a limited number of trials (22-25), but the lack of standardized cockroach extracts limit their potential to provide optimal clinical efficacy to patients. Thus, further works are needed to identify major allergenic components in cockroach and clone immunodominant cockroach allergens in order to provide therapeutic cockroach allergen products with enhanced clinical efficacy.

Cockroach allergens

Over 4,000 cockroach species have been identified. However, only a few species live in people's homes and have been the focus for cockroach allergen-related research. These cockroaches include American cockroach (*Periplaneta americana*), German cockroach (*Blattella germanica*), oriental cockroach (*Blatta orientalis*), brown-banded cockroach (*Supella longipalpa*) and smoky brown cockroach (*Periplaneta fulliginosa*). In particular,

both German and American cockroaches are the predominant species that infest human dwellings (23). Predominant sources of environment cockroach allergens include cockroach saliva, fecal matter, spermatophore, shredded skin, and desiccated remains of the insect. Inhalation of these cockroach allergens can cause allergic responses in human. Thus, it is essential to identify major determinants in cockroach that induce allergic responses leading to asthma. In the past decade, many cockroach allergens have been identified, sequenced, purified, and produced as biologically active recombinant proteins from German and American cockroaches. There have been 9 German cockroach allergens (Bla g 1-8 and Bla g 11) and 9 American cockroach allergens (Per a 1-3, Per a 6-7, and Per a 9-12) (www.allergen.org) (29, 30) identified thus far as listed in **Table 1**. For example, the recombinant cockroach allergen Bla g 1 has been expressed in both *E. coli* and *P. pastoris* (31, 32), while Bla g 4 (33), Bla g 5 (34-36), Per a 1 (37), and Per a 3 (38) have been produced in *Escherichia coli*, and Bla g 2 (39), Bla g 4 (40), Per a 1 (41), and Per a 7 (38) were made in the yeast *Pichia pastoris*, thus providing a way of controlled cockroach allergy diagnosis and experimentation compared to traditional methods that relied on the use of heterogeneous cockroach extract. A novel allergen, a chymotrypsin-like serine protease, has been recently identified from the German cockroach. The amino acid sequence of the novel allergen showed 32.7 to 43.1% identity with mite trypsin and chymotrypsin allergens, and serum from 28.6% German cockroach allergic subjects showed IgE binding to the recombinant protein (42). It is worth noting that there is a substantial degree of homology and variable IgE cross-reactivity between recognized German cockroach allergens and some homologous groups from the American cockroach allergens. Additionally, individual IgE responses vary in regards to multiple conformational allergic epitopes contained within a single allergen such as Bla g 2 (40, 43). In addition to IgE-mediated allergic responses, these purified allergens can induce allergic inflammations that are not mediated by IgE interactions. For instance, the human beta-defensin 3 has been shown to bind Bla g 2 and could modify the ability of Bla g 2 to induce localized allergic inflammatory and mucosal responses (44, 45). Bla g 7 can potently induce T cell immunoglobulin mucin domain (TIM) 4 expression on dendritic cells (46), which plays a critical role in T cell proliferation and Th2 cell development (47, 48). Per a 7 has been demonstrated to up-regulate the expression of protease-activated receptors, thereby, triggering Th2 cytokines secretion (e.g., IL-4 and IL-13) (49). Additionally, Per a 7 can reduce the production of IL-12 and the expression of the Toll-like receptor (TLRs) 9 (50). At present, these newly-characterized cockroach allergens have led an improvement in knowledge of the structure and function of cockroach allergens, and are crucial for the development of novel strategies for diagnosis and therapy.

Glycans in cockroach allergens may be a major determinant for immunogenicity

Despite the rapid increase in knowledge about the action of these purified and biological active cockroach allergens, the contribution of other potential virulence factors (i.e., macromolecules such as lipids and carbohydrates) that could exist in cockroach excrete and cockroach allergens and its clinical relevance to the development of human asthma remains unknown. Glycans are sugar modification attached to glycoproteins and glycolipids. They are generally complex heteropolymers, in contrast to the storage homopolymers that made up glycogen and amylose. More recently, intravenous and subcutaneous immunoglobulin preparations contain carbohydrate-specific IgG antibodies to microbial antigens, tumor-

associated carbohydrate antigens, and host glycans (51), implicating the importance of these modifying macromolecules in human health and disease. Furthermore, polysaccharides, widely concerned as bioactive macromolecules in recent centuries, have been proved to benefit the intestinal health. Dietary polysaccharides can regulate the intestinal microenvironment and stimulate the macrophages or lymphocytes in gut tissues to fight against diseases like cancer (52). A recent study by Shade *et al*. had revealed that the ability of IgE to trigger an allergic reaction through its interaction with mast cells is dependent on a single site of antibody glycosylation (53), suggesting a possible route to the selective disruption of IgE glycosylation sites for the treatment of allergic diseases. Importantly, it has been suggested that glycan may be crucial in cockroach allergen-induced allergic asthma. For example, surface epitopes mapped from a murine monoclonal antibody against Bla g 2, 4C3, was found to contain a carbohydrate moiety (54, 55) and the prevention of Bla g 2 glycosylation by nucleotide point mutation significantly reduces IgE binding, Th2 cytokine IL-13 production, and increased IL-10 (32, 44). Our recent studies have also demonstrated that Bla g 2 specific IgE from patients with cockroach allergy may be, at least partially, due to glycans (unpublished data). In addition, profiling of N-linked glycans from Bla g 2 using matrix-assisted laser desorption/ionization-mass spectrometry revealed a predominance of tri-antennary N-linked core di-fucose modified glycans with mannose-, galactose-, and/or N-acetyl glucosamine- (GlcNAc) terminated moiety (**Figure 1**). Thus, we suspected that these glycan determinants are of insect (i.e., cockroach) due to the fact that di-fucosylation of the innermost GlcNAc moiety is commonly present in insects (56). These studies give a glimpse into the potential association between immunogenicity and particular structural features of glycans and their possible contributions to allergic diseases. Furthermore, recent progress has made it possible to gain a precise understanding of structure-function relationships with a series of the systematic synthesis of high-mannose-type glycans (57).

Mechanisms underlying the cockroach allergen-induced allergic inflammation

Allergic inflammation is widely accepted as the fundamental driving force in the development of allergen sensitization that can ultimately leads to asthma. Like many other indoor/outdoor allergens (e.g., house dust mite, fungi, pollen, and animal dander), cockroach excrete particles can gain access to the lungs by lodging across the nasal/oral cavities, where it can provoke allergic type inflammation by allergen-induced epithelial damage or direct contact with cells of the epithelium (58, 59). Although much more is known about the allergen-triggered early immune events, little is known about the allergen-derived signals that initiate allergic inflammation. Here, we summarized the cockroach allergen-triggered signaling events that may contribute to the development of allergic inflammation. As illustrated in **Figure 2**, cockroach allergens can directly activate epithelial cells and induce the production of epithelial cells derived cytokines and chemokines (e.g., TSLP, IL25, IL33, and TGFβ1), which recruit inflammatory cells to the allergen-damaged airway for repairing and inflammation suppression. On the other hand, cockroach can disturb airway epithelial integrity through proteinase-activated receptor-2 (PAR-2), which would lead to an increased penetration of allergens, resulting in activation of innate immune cells [e.g. dendritic cells (DCs) and mesenchymal stem cells (MSCs)], through C-type lectin receptors (CLRs), Toll-like receptors (TLRs), and aryl hydrocarbon receptor (AhR) (60-63). These activated innate immune cells will lead to an imbalance of the adaptive immune system toward a more Th2

and Th17 phenotypes. Furthermore, the epithelial cell-derived cytokines TSLP, IL25 and IL33 can interact with their respective receptors expressed in innate lymphoid cell type 2 (ILC2), leading to the secretion of IL5 and IL13 and subsequently allergic inflammation (64). In addition, it is well known that genetic or epigenetic factors are also major determinants for the development of cockroach allergy (65). Thus, it is likely that these genetic determinants may modify or convey the susceptibility to cockroach allergens-induced allergic responses in patients with cockroach allergy and asthma.

Proteinase-activated receptor-2 (PAR-2) and environmental allergen-induced asthma

Like many airborne allergens from house dust mite *Dermatophagoides pteronyssinus* and *Aspergillus fumigatus*, cockroach allergens also contain protease activity (12, 66). Indeed, measurement of protease activity in German cockroach frass and whole body extract confirmed the presence of serine protease activity, which can induce pro-inflammatory cytokines production, especially TNF-α and IL-8, from challenged airway epithelial cells via PAR-2 (67). PAR-2, a major member in a family of proteolytically activated G-coupled receptors, is expressed on a variety of cell types located throughout the airways (67, 68), and PAR-2 activation is a critical early step in the development of allergic asthma. This was well-supported by studies on proteases from *Alternaria alternata* that PAR-2 plays a role in proteases-induced rapid [Ca2+] increases in human airway epithelial *in vitro* and cell recruitment *in vivo* (69). However, the mechanisms regarding the PAR-2-mediated cockroach allergen-induced allergic response have not been fully elucidated. Recent studies suggest that the dual oxidase-2 (DUOX2)-ROS pathway in airway epithelial cells plays a crucial role in mediating the activation of PAR-2-stimulated airway reactivity, inflammation, oxidative stress and apoptosis in cockroach allergen-induced mouse model of asthma (70). These data suggest that proteases may link the innate and adaptive immune responses via PAR-2 activation and signaling. However, although Bla g 2 shares sequence homology with the aspartic proteinase family of proteolytic enzymes, it lacks proteolytic activity in a standard milk-clotting and hemoglobin assay using casein as a substrate (40, 71, 72), suggesting that Bla g 2 is enzymatically inactive and perhaps other factors, beside proteolytic activity, may play a crucial role in allergen-induced immunological responses.

Toll-like receptors (TLRs) mediate allergen-induced sensitization and inflammation

TLRs are transmembrane proteins highly expressed in DCs and the recognition of molecular signatures of potential pathogens via TLRs plays an important role in mediating allergen induced innate and adaptive immune responses (73). For instance, exposure to exogenous pathogen components could activate DCs through TLRs, which then can tailor the adaptive immune response to the nature of the pathogen. Conversely, antigen presentation by DCs lacking of TLRs generally leads to tolerance (74). TLR4 activation in airway epithelial cells by house dust mite (75) has been demonstrated to be sufficient in promoting allergic sensitization via the release of innate cytokines such as IL-25, IL-33, and TSLP. Together, these findings implicate that TLR signaling is critical in mediating antigen-induced immune responses. Studies have also demonstrated a role for TLRs in mediating cockroach allergen-induced allergic responses. For example, German cockroach frass contains a TLR2 ligand that can directly activate cells of the innate immune system, leading to the release of MMP-9 and decreased acute allergic responses in experimentally induced asthma in mice (76).

Studies from our group on gene expression profiles in cockroach allergens treated DCs demonstrated that, among all TLR genes included for array analysis, both TLR2 and TLR8 were up-regulated in patients with cockroach allergy in comparison to healthy individuals (Manuscript in preparation). Thus, it would be of interest to extensively investigate the role and possible mechanisms of TLRs in mediating cockroach allergen-induced allergic responses.

C-type lectin receptors (CLRs) recognize glycans in allergens

C-type lectin receptors (CLRs) are pattern recognition receptor with at least one carbohydrate recognition domain (CRD) (77). The CRD that contains the conversed residue motifs determines the carbohydrate specificity, thus, CLRs are implicated to be crucial in the recognition allergenic glycans present on allergens and have been evolved to facilitate the endocytosis and presentation of pathogens (78, 79). In fact, signaling through CLRs has been shown to induce T-cell activation, tolerance and modification of cellular responses via cross-regulation of the TLR-mediated effect (80). This has been clearly illustrated by DC-SIGN (dendritic cell-specific, CD209) (80) and MRC1 (81). Thus, the expression of distinct CLRs on immune cells (i.e., dendritic cells and macrophages) may broaden the pathogen recognition profile to induce tolerance or activate immunity.

The fact that most allergens contain complex glycan modifications raises the possibility that allergenic glycan-CLR signaling may be important for allergenic immune responses. For instance, study on peanut allergens suggests that Ara h 1 (82), a major peanut allergens, is able to polarize Th2 response by interacting with DC-SIGN on monocyte-derived DCs (83). Bovine serum albumin (BSA) coupled with a common glycoform (fucosylated glycan lacking the alpha1,3-linked mannose) of allergens, including BG60 (Cyn dBG-60; Bermuda grass pollen) and Der p2 (house dust mite) showed significant bindings to DC-SIGN and its receptor, L-SIGN (84). The interaction between BG60 and DC-SIGN activated Raf-1 and ERK kinases leading to an increased expression of TNF-α (85). *MRC1*, encoding the mannose receptor, has been shown to mediate the uptake of diverse native allergens by DCs and determines allergen-induced T cell polarization through the modulation of indoleamine 2,3 dioxygenase (IDO) activity (85). Furthermore, MRC1 is able to mediate cat allergen Fel d 1-induced allergic responses (86). While the direct interaction between allergenic glycan and CLR has not been demonstrated, we previously reported a functional interaction for MRC1 and cockroach allergens in antigen binding, antigen recognition and downstream immune responses (87). Our ongoing study has led to a novel observation that the deletion of *MRC1* in mice (MR−/−) may exacerbate cockroach allergen-induced lung inflammation and play a role in regulating allergen-induced macrophage polarization (unpublished). However, MRC1 lacks a signaling motif and the mechanisms underlying MRC1-mediated macrophage function remains unknown. Interestingly, a very recent study suggests that miRNAs may have the ability to shape the balance of M1 and M2 macrophage polarization (e.g., miR-155, miR-146) and skewing the immune response (88, 89). miR-511-3p, the functional strand of miR-511, is an intronic miRNA encoded within the *MRC1* gene correlates with MRC1 expression in both tissue-resident and tumor-associated macrophages (90). As illustrated in **Figure 3** an intronic miRNA encoded within *MRC1* is processed by the miRNA machinery to generate the mature miR-511-3p sequence. miR-511-3p then

directly targets several genes and indirectly modulates the expression of several genes and regulate macrophage polarization, subsequently leading to allergic diseases and asthma. Indeed, miR-511-3p has been shown to directly target Rho-associated coiled-coil containing protein kinase 2 (ROCK2), a serine-threonine kinase that regulates the cell cytoskeleton contractility (91). ROCK2 can phosphorylate IRF4 and promote alternative activation of macrophages (92). These studies provide evidence for future more in-depth studies on the mechanisms with the focus on these identified miR-511-3p targets to identify their association with macrophage polarization, function and macrophage-driven lung inflammation in asthma.

Air pollution boosts cockroach allergy and asthma

Cockroach allergens are a major contributor to the increased risk in developing allergic asthma, particularly in urban areas. Exposure air pollution, particularly diesel exhaust and other combustion-related byproducts, can increase the likelihood of developing cockroach allergy (93, 94). This was further supported by studies showing that prenatal exposure to either diesel exhaust particulates (DEP) or polycyclic aromatic hydrocarbons (PAHs), is associated with a greater risk for the development of allergic sensitization, early childhood wheeze, and asthma (95, 96). Particularly, prenatal exposure to cockroach allergen was associated with a greater risk of allergic sensitization and this risk was increased by exposure to nonvolatile PAHs (97). Similarly, recent studies demonstrated that exposure to traffic-related air pollutants during childhood (i.e., PAH) is associated with the development and exacerbation of asthma with increasing likelihood of sensitization to cockroach allergens in urban inner-city children (98). Together, these findings suggest that exposure to environmental pollutants may exacerbate the allergen-induced allergic sensitization and asthma. However, the underlying molecular mechanism remains unknown.

Aryl hydrocarbon receptor mediates allergen-induced exacerbation of asthma

Aryl hydrocarbon receptor (AhR) is a multifunctional regulator that senses and responds to environmental stimuli and has been shown to play a role in normal cell development and immune regulation (99-101). Environmental pollutants such as DEP and PAH can activate AhR signaling leading to changes in target gene transcription (e.g., cytochrome P450 cyp1a1, cyp1b1) and a variety of immunotoxicological effects (102-107). Recent studies found that bacterial compounds can also act as potential AhR ligands and that recognition of these virulence factors by AhR contributes to host defense against invading microbial pathogens (64, 100, 106). Therefore, AhR not only elicits protection against environmental toxic molecules, but also serve as a sensor for invading pathogenic microbes (AhR-microbiome). Studies from our own group have suggested a critical role of AhR in controlling mast cell differentiation, growth, and function (108), and cockroach allergens induced immune responses (107). Furthermore, AhR deficiency led to exacerbation of lung inflammation when exposed to cockroach allergen in our well-established asthma mouse model (Xu e*t al*. J Immunol 2015, In Press). Especially, cockroach allergens can directly induce activation of AhR signaling in bone marrow-derived MSCs, and AhR regulates MSC migration and allergic immune suppression. These findings suggest that AhR protects lungs from cockroach allergen-induced inflammation though MSCs and, therefore, is a potential target for the treatment of allergic asthma. In addition, AhR was increased in patients with

allergic asthma compared to healthy controls (64), and plays a critical role in mediating the pro-inflammatory effects of traffic-related particulate matter (PM) (109). Together, these studies suggest a critical role for AhR in environmental pollutant and allergen-induced allergic inflammation and asthma. AhR may serve as a link between environmental pollutants and cockroach allergens contributing to the increased risk of developing allergic diseases like asthma.

Genetic determinants in the development of cockroach allergy

It has been suggested that there is a genetic basis for allergen-induced sensitization (110, 111). However, only a handful of studies have been performed to identify genetic factors specifically for cockroach sensitization. A genome wide screen demonstrated linkage between the HLA-linked marker DRB1*0101 and DRB1*0102 in the Hutterites, a white founder population, and African American population, respectively. Genome wide quantitative-trait loci (QTL) analysis of 533 Chinese families with asthma, provided evidence of linkage at a possible QTL D4S1647 for skin reactivity to cockroach defined by skin prick tests (SPT) (112). Furthermore, evidence of linkage between IgE and cockroach sensitization was found on chromosome 5q23 where TSLP is located (113). Single-nucleotide polymorphisms (SNPs) in several genes including mannose-binding lectin (*MBL*), *IL-12A*, *TLR6*, *C11orf30*, *STAT6*, *SLC25A46*, *HLA-DQB1*, *IL1RL1*, *LPP*, *MYC*, *IL2* and *HLA-B* were associated with cockroach allergy (114-116). We performed analysis for 895 single nucleotide polymorphisms (SNPs) in 179 candidate genes in a total of 631 children from Boston Birth Cohort and identified several genes that are associated with cockroach sensitization including *JAK1*, *JAK3*, *IL5RA*, *FCER1A*, and *ADAM33* with the strongest association for *FCER1A*(117). Interestingly, when analysis was performed for allergic sensitization to house dust mite, *JAK2*, *MAML1*, and *NOD1* showed significant association to HMD but not cockroach, suggesting that sensitization to different allergens may be determined by their unique loci. Furthermore, environmental exposure has been suggested to play a critical role in asthma by interacting with genetic factors in genetically susceptible individuals. Thus, it is essential to assess the gene-environment interactions to determine if the associations for cockroach sensitization are modified by cockroach allergens exposure in the future.

Conclusion

Cockroach sensitization has been established as an important risk factor for the development of asthma. The identification of cockroach allergens from cockroach excrete and their molecular cloning and expression as biologically active recombinant proteins has allowed for a better our understanding in the mechanisms of cockroach allergens causes allergic disease, like asthma. There has been a potential association between immunogenicity and particular structural features of glycans. Glycans in cockroach allergens may be major determinants for immunogenicity. Several receptors (PAR-2, TLRs, and CLRs*)* and their signaling pathways have been found to be important in the penetration of cockroach allergens through epithelial cells, mediating allergen uptake, and signaling T cells to activate inappropriate immune responses. Environmental pollutants, which often co-exist with allergen, could synergistically elicit allergic inflammation that leads to asthma. Recent

studies suggest that cockroach allergens can active AhR signaling, which may be crucial in environmental pollutant promoted cockroach allergen-induced allergic diseases. Genetic factors play a crucial role in allergic sensitization. SNPs in or near several genes have been associated with allergic sensitization (e.g., *TLR6, STAT6, HLA-DQB1, IL1RL1, IL2* and *HLA-B*) and cockroach sensitization (e.g., TSLP, MBL2, CD14, IL-12A, JAK1, JAK3, IL5RA, FCER1A, and *ADAM33*). We believe that continuous studies on characterizing cockroach allergens and exploring the mechanisms regarding allergen- induced immunity and gene-environment interaction will add value to the existing research investment. These studies will offer novel insights into the molecular mechanisms that cause cockroach sensitization and subsequently asthma. Findings from these studies will contribute to the development of novel therapeutics and diagnostics of cockroach allergy that could ultimately lead to the prevention and treatment of allergic asthma.

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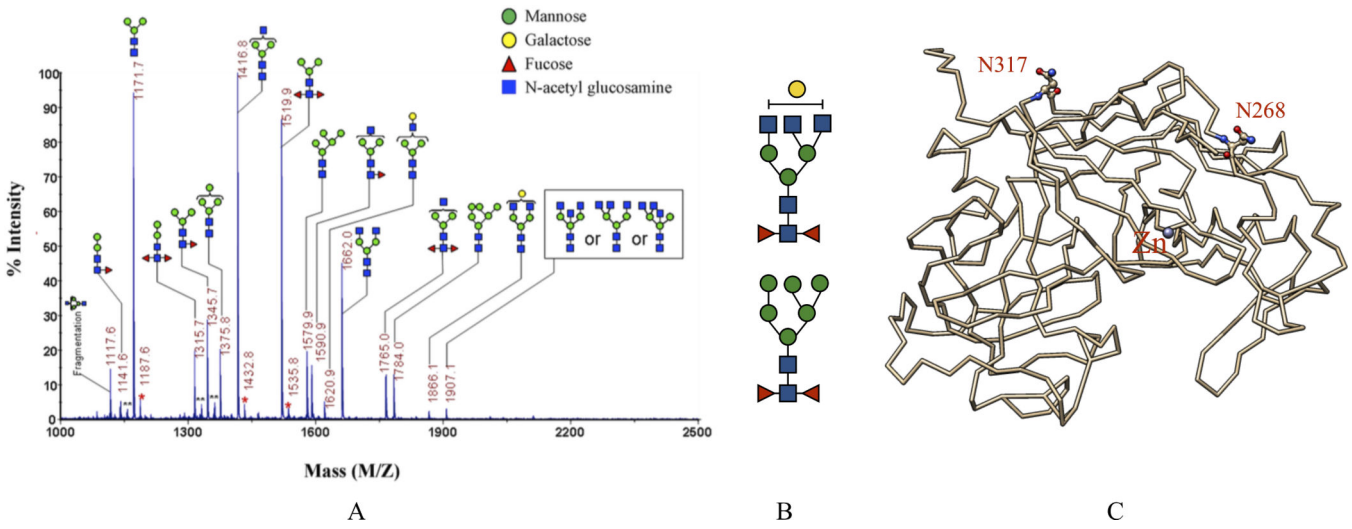

Figure 1.

Glycans in cockroach allergens. Surface epitopes mapped from a murine monoclonal antibody against the cockroach allergen Bla g 2 was found to contain a carbohydrate moiety (references 33, 44) and the prevention of glycosylation significantly reduces IgE binding to Bla g 2 (references 21). (A) MALDI-TOF mass spectrum of N-linked glycans prepared from purified natural Bla g2 glycoprotein (adopted from Tsai et al, 2013) demonstrated a predominance of (B) tri-antennary core di-fucose modified glycans with mannose-, galactose-, and/or N-acetyl glucosamine- (GlcNAc) terminated moiety. (C) These tri-antennary core di-fucose modified glycans are predicted to decorate Bla g 2 (1YG9) at asparagine (ball-and-stick) 268 and 317 (N268, N317). Glycan compositions were assigned based on the measured m/z values with the m/z values of the putative composition of permethylated glycans. **is undermethylated glycans. *is unknown peaks.

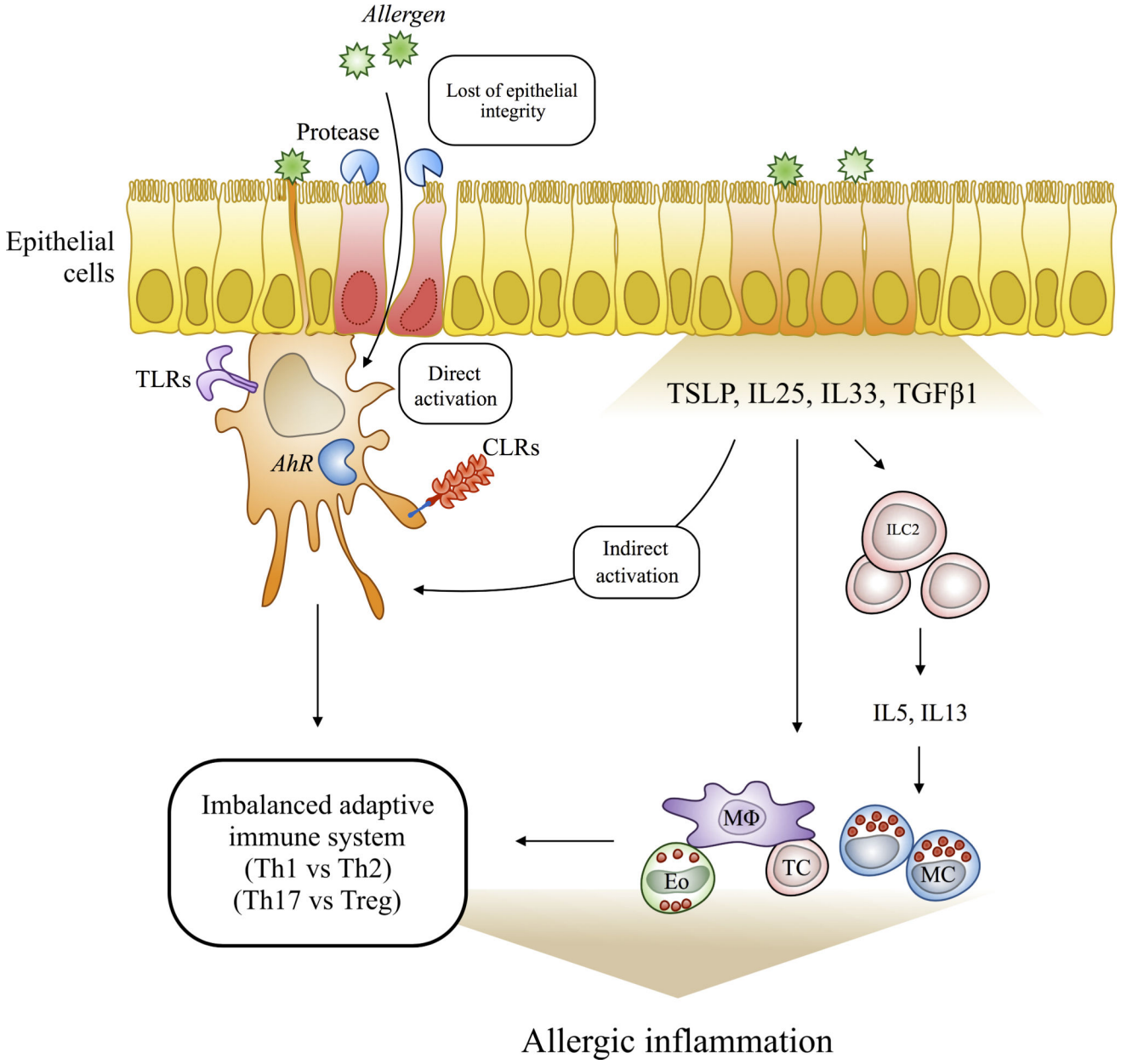

Figure 2.

Schematic diagram of the proposed mechanisms underlying the cockroach allergen-induced allergic inflammation. Cockroach allergens gain access to the lungs by lodging across the nasal and oral cavity, where it can directly activate epithelial cells and induce the production of epithelial cells derived cytokines and chemokines. These epithelial derived cytokines and chemokine can activate innate immune cells leading to an imbalanced adaptive immune response and the development of cockroach sensitization and allergic asthma. Proteases in cockroach extract can damage the epithelium leading to an increased penetration of allergens and activation of innate immune cells via TLRs, AhR, and CLRs. MC: mast cell, TC: T-cell, MΦ: macrophage, Eo: Eosinophil, ILC2: Innate lymphoid class 2 cell, CLRs: C-type lectin receptors, and TLRs: Toll-like receptors.

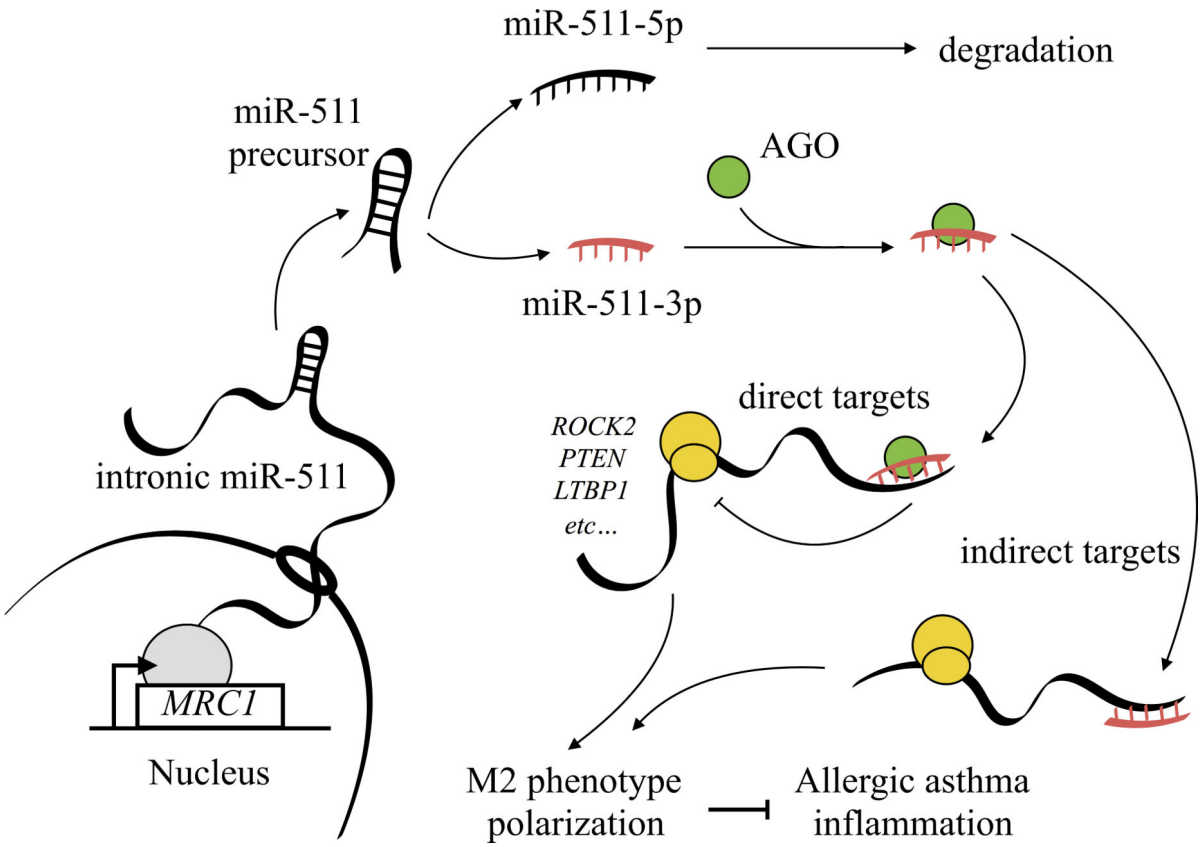

Figure 3.

Schematic diagram of the proposed mechanisms for miR-511-3p in modulating allergic inflammation in asthma. *MRC1* transcribes the primary intronic miR-511, and followed by the miRNA machinery to generate the mature miR-511-3p sequence. The miR-511-3p can directly targets several genes (e.g., *ROCK2*, *PTEN*, and *LTBP1*) and shape the balance of M1 and M2 macrophage polarization and skew the immune response. In addition, miR511-3p may also modulate the expression of several indirect targets. MRC1, macrophage receptor, AGO, Argonaut.

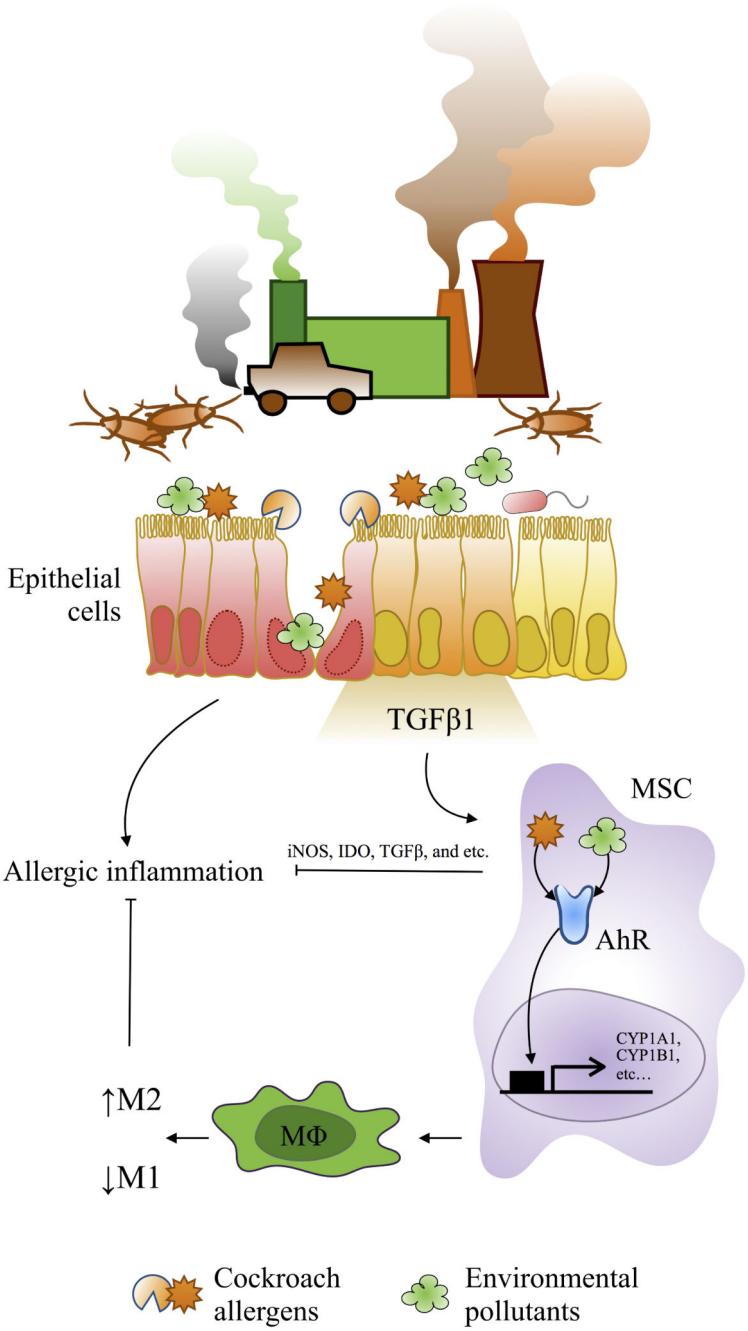

Figure 4.

Proposed model in the role of AhR in modulating environmental pollutant and allergen-induced allergic inflammation. Airway epithelial cells can be damaged after exposure to environmental pollutants and cockroach allergens and release cytokines and chemokines (e.g., TGFβ1), which can recruit MSCs and some other inflammatory cells to the epithelial damaged sites for tissue repairing/inflammation. The recruited MSCs activated through AhR by environmental pollutants or cockroach allergens or both synergistically release anti-inflammatory factors (e.g., iNOS, IDO, and TGFβ1) and suppress airway inflammation. On

the other hand, activated MSCs may modulate macrophage differentiation through AhR and inhibit airway inflammation. MSC: mesenchymal stem cell, AhR: aryl hydrocarbon receptor, MΦ: macrophage, M1: classically activated macrophage, M2: alternative activated macrophage, IDO: indoleamine 2,3-dioxygenase.

Table 1

Characteristics and functions of allergens from German and American cockroaches

Allergen	M.W.(*)	Function/Homology	IgE Prevalence	Major Linear IgE Epitopes	GeneBank Accession #
Bla g 1	46	• Lipids-associated and/or binding protein (118) (i.e. palmitic, oleic, and steric acids) • Nonspecific transport of lipid molecules in cockroach • Non-enzymatically active aspartic protease (34, 40, 119)	20-40%	a.a. 1-111, 289-403, and 394-491 (32)	AF072219 AF072221 L47595 AF072220
Bla g 2	36	• Glycoprotein, decorated glycans indicated to be important for IgE binding (55, 73) • Binds to human beta-defensin 3 (44)	40-70%	a.a. 1-75 and 146-225 (45)	U28863
Bla g 3	79(*)	• Homologous to hemocyanin and American cockroach allergen Per a 3 (120)	n.r.	n.r.	GU086323
Bla g 4	21	• Ligand binding protein, members of the calycin protein family (121)	17-40%	a.a. 34-73, 78-113, and 118-152 (34)	U40767
Bla g 5	23	• Sigma class glutathione S-transferase (35, 36, 122)	35-68%	a.a. 176-200 (37)	U92412
Bla g 6	21	• Homologous to muscle protein troponin C with four calcium-binding domains (35)	14%	Dependent upon calcium level, a.a. 96-151 (123)	DQ279092 DQ279093 DQ279094
Bla g 7	31	• German cockroach tropomyosin (124) • Can induce TIM4, CD80, and CD86 and increased IL-13 secretion in human DCs (125) • Potential involvement in DCs-induced Th2 polarization (47)	18%	n.r.	AF260897
Bla g 8	n.r.	• Calcium binding protein • Myosin light chain (47)	n.r.	n.r.	DQ389157
Bla g 11	57	• α-amylase			DQ355516 KC207403
Per a 1	45	• Homologous to the mosquito precursor protein, ANG12, which may be involved in digestion (123)	9-100%	a.a. 358-446 (38)	AF072222 U78970 U69957 U69261 U69260
Per a 2	42	• Inactive aspartic protease-like (126) • 42-44% homology to Bla g 2	81%	a.a. 57-86, 200-211, and 299-309 (17)	GU188391
Per a 3	72	• Homologous to insect hemolymph proteins, arylphorin/hemocyanin (127)	26-95%	a.a. 400-409, 466-471, 580-595, and 595-605 (39)	L40818 L40820 L40819 L40821
Per a 5(**)	25	• Glutathione S-transferase (128)	25%	n.r.	AY563004
Per a 6	17	• Homologous to insect troponin Cs and vertebrate calmodulins (129)	14%	n.r.	AY792950
Per a 7	33	• Tropomyosin (123) • Induce reduction of IL-12 production and expression of TLR9 in P815 mastocytoma cells (130)	13-54%	n.r.	Y14854 AF106961
Per a 9	43	• Arginine kinase (51)	80-100%	p. LTPCRNK	AY563004
Per a 10	28	• Serine protease and insect trypsins (131)	82%	n.r.	AY792954
Per a 11	55	• α-amylase (132)	83%	n.r.	n.r.
Per a 12	45	• Chitinase (133)	64%	n.r.	n.r.

(*)Mass determination by mass spectrometry

(**)Has not been officially reported in the official site for Allergen Nomenclature