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Clinical View on the Importance of Dendritic Cells in Asthma

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Summary

Allergic asthma is characterized by airway hyperresponsiveness and inflammation and may lead to airway remodeling in uncontrolled cases. Genetic predisposition to an atopic phenotype plays a major component in the pathophysiology of asthma. However, with tremendous role of epigenetic factors and environmental stimuli in precipitating an immune response, the underlying pathophysiological mechanisms are complicated. Dendritic cells are principal antigen presenting cells and initiators of the immune response in allergic asthma. Their phenotype, guided by multiple factors may dictate the immune reaction to an allergic or tolerogenic response. Involvement of the local cytokine milieu, microbiome and interplay between immune cells add dimension to the fate of immune response. In addition to allergen exposure, these factors modulate DC phenotype and function. In this article, integration of many factors and pathways associated with the recruitment and activation of DCs in the pathophysiology of allergic asthma is presented in a clinical and translational manner.

Keywords

Allergic asthma; Dendritic cell; microbiome; antigen tolerance

1. Introduction

Surpassing initial physical barrier of the upper airways, inhaled antigens may get deposited on the epithelium of trachea, bronchi or alveoli. At this stage, allergenic fate of the antigen is not yet sealed. It could be cleared by mucociliary transport or taken up by sentinel cells, surveying contact points to find these foreign bodies. Among sentinel cells, dendritic cells (DCs) are the most important and primary antigen presenting cells (APCs). They take up the antigen, process it and present the processed antigen to T-lymphocytes [1]. Based upon the

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nature of the antigen and cytokine milieu, different types of DCs polarize CD4⁺ T lymphocytes towards Th1, Th2, Tregs or tolerance to antigen. The T-lymphocytes interact with DCs in a multi-molecular level through numerous cross signaling events, deciding the fate of immune response at the inflammatory site. Allergic asthma is predominantly a Th2 type response involving various pro-inflammatory cells (eosinophils, neutrophils, mast cells, basophils, plasma cells, and epithelial cells), cytokines (including TSLP, IL-4, IL-5, IL-6, IL-9, IL-13, IL-17, IL-25, IL-33), chemokines (including eotaxin, IL-8, MCP), and other pro-inflammatory mediators (histamine, prostaglandins and leukotrienes) [2–4]. Asthma is characterized by airway hyper-responsiveness (AHR), increased bronchoconstriction, airway inflammation, and in chronic cases airway remodeling [5]. As integrity and compliance of the airways are compromised in asthma, it restricts the airflow in the lungs making it extremely difficult to breathe, which results in breathlessness, wheezing, and tightness in the chest. Apart from discomfort and inability to perform, serious asthmatic reactions may be fatal. Thus, it is utmost important to diagnose asthma, understand its phenotype and the underlying pathophysiological mechanisms and to develop better individualized therapeutic approaches.

The major question arises at this point is how do DCs recognize some antigens as allergens and polarize Th2 cells? And why a healthy person does not respond to allergens in a way an allergic individual does? The answer may lie on genetic as well as epigenetic factors, which regulate various gene expressions on DCs to recognize antigens as allergens. Some individuals are born with predisposition to allergic/atopic phenotype, and some acquire it over the years through exposure to environmental factors [6]. Remarkably, the acquired atopic phenotype can also be passed on to the next generation [7]. Mechanisms of allergenic activation of DCs are not yet fully understood. However, multiple studies have demonstrated various molecules present on DCs responsible for antigen uptake and signal transduction to induce downstream responses. Apart from certain microorganisms, including bacteria, eliciting tolerance to evade the host immune response, identification of antigens, which may direct DCs to a tolerogenic or even Th1 response, and could regulate the immune hyperresponsiveness in allergic asthma.

2. Phenotype of Dendritic Cells

Dendritic cells work as the principal APCs in the immune system, but their function might vary according to their phenotype and the nature of signal they transduce to T-lymphocytes. DCs are found throughout the lung environment, starting from nose, nasopharynx, trachea, bronchi, bronchioles to alveoli. In human, various lung DCs survey antigen-rich areas to sample and uptake antigen. Endogenous antigens that are created intracellularly, including viral and tumor antigens, are processed by DCs and presented via MHC class I molecules to CD8⁺ T-lymphocytes. Whereas, exogenous antigens, including bacterial antigens, pollen, and other allergens, that are taken up through endocytosis or phagocytosis are presented via MHC class II molecules to polarize CD4⁺ T helper lymphocytes.

While subtypes of human lung DCs are not yet completely understood, they can be divided into two major types- myeloid (conventional) and plasmacytoid dendritic cells (Figure 1). Myeloid DCs can be further divided into two subtypes based on their surface markers. The

mDCs are phenotypically CD11c⁺/hi, BDCA1⁺ (CD1c), and HLA-DR⁺ (MHC class II) or CD11c⁺/int, BDCA3⁺ (CD141), and HLA-DR⁺ [8]. The second major phenotype of DCs is plasmacytoid DCs (pDCs) that can be divided into multiple subtypes, based on location and surface marker expression. Lung pDCs are CD123⁺ (IL-3 receptor), CD11c⁻, BDCA2⁺ (CD303), BDCA4⁺ (CD304), HLA-DR⁺, and ILT7 (CD85g) [8–13] (Figure 1). Another subtype of pDCs has been found in tonsils and tumors with the expression of CD2^{high}. Its ability to secrete high levels of IL-12p40, and express high levels of co-stimulatory molecules, including CD80, postulates its role in antigen presentation to T-lymphocytes [13]. However, role of CD2^{high} pDCs in tolerance is yet to be established [14].

Mouse DCs have similar subsets, but their localization and function is known far better than their human counterparts (Figure 1). Type I mDCs in mice express mucosal integrin, CD103⁺, CD11c^{high}, CD11b⁻, langerin (CD207), and CD24⁻ [15]. They are close to the CD8α⁻ splenic DCs. These DCs are usually found above the basement membrane of tracheal epithelium. The main function of these mDCs is to take up the antigens and transfer them to lymph node DCs for communicating with CD4⁺ T-lymphocytes. On the other hand, type II mDCs in mice are CD103⁻, CD11b⁺, and CD11c⁺, and express sialoglycoprotein, CD24 [16,17]. Phenotypically, they resemble the CD8α⁺ splenic DCs. They are found under the basement membrane of submucosa, and are major APCs in the uptake and processing of the antigens to prime and stimulate CD4⁺ T-lymphocytes. Type II mDCs have huge amounts of TNF-α to support the T-lymphocytes, and CCL-17 to attract Th2 and CD8⁺ cytotoxic T-cells. Although, there is some ambiguity if these mDCs are involved in tolerance, it is evident from multiple findings that pDCs play a major role in the development of tolerance [18–20]. Mice pDCs have B-cell specific receptor B220 (CD45R) and express Ly6C, Siglec-H, and mPDCA-1 (BST2) [5,21,22]. They reside under the basement membrane of trachea and alveolar septum. As pDCs have huge IFN-α levels, they can oppose the Th2 response and thus help in the regulation of allergic responses [23]. However, the anti-Th2 response is not because of tolerogenic expansion of Tregs. In RNA virus infection, DCs (mDCs and pDCs) secrete IL-6 and IFN-α to induce antiviral response, which limits proliferation of Foxp3⁺ Treg cells [24]. Recently, lung pDCs have been subdivided into three populations based on the expression of CD8α and CD8β [14,25]. Lombardi *et al.* [25] demonstrated that CD8α⁻β⁻ pDCs contained immunogenic properties and expressed co-stimulatory molecules to support AHR, whereas CD8α⁺β⁻ CD8α⁺β⁺ showed tolerogenic properties and supported the development of Foxp3⁺ Tregs in the presence of TGF-β and retinoic acid. Other groups have also tried to decipher subpopulations of pDCs with CCR9 (liver and bone marrow) and CD9 (tumor cells) as specific markers [26,27]. However, immunogenic pDCs (CD8α⁻β⁻), as well as tolerogenic pDCs (CD8α⁺β⁻ and CD8α⁺β⁺) express comparable levels of CCR9, which is downregulated following TLR activation [25].

Plasmacytoid DCs directly help in the generation of Tregs through several pathways including secretion of immunosuppressive cytokines like indoleamine 2,3-dioxygenase (IDO) [28], expression of programmed cell death ligand-1 (PD-L1) and retinoic acid. Presence of IL-10 during the differentiation of DCs helps in the development of tolerance [29]. Myeloid DCs also take part in the induction of tolerance and CD103⁺ mDCs in mesenteric lymph nodes might result in a tolerogenic response in the presence of TGF-β and

retinoic acid [30,31]. Multiple studies have shown that tolerogenic properties of DCs are usually linked to semi-mature DCs with high levels of MHC-II, but low levels of co-stimulatory molecules and pro-inflammatory cytokines [32,33]. Identification of subtypes of DCs with immunogenic or tolerogenic potential in humans is crucial in designing interventional approach to control allergy and asthma. Better understanding of specific markers on DCs responsible for tolerance would help in developing better therapeutic strategies.

3. Antigen versatility on DC phenotype

Availability of diverse DCs at various sites of antigen exposure or immune invasion depends on many factors. Based on the type of antigenic exposure, epithelial cells recognize them with their pattern recognition receptors (PRRs), including toll-like receptors (TLRs). The signal then drives production of different cytokines and chemokines to attract DCs at the site. These sentinels recognize surplus antigens through different cell surface PRRs, like TLRs, C-type lectins (such as DC-SIGN, MR, dectin-1, DEC-205 and langerin) [34,35], and NOD like receptors. As soon as the immune system is established early in the infancy and childhood, DCs start on sampling antigens in the cellular environment around basement membrane. Antigens, which induce immune response, are called immunogens, and if they elicit allergies (Type I hypersensitivity), they are referred to as allergens. According to the AllFam database of inhaled allergen families [201], there are now 137 allergen families originating from animals, plants, fungi and bacteria, containing a total of 526 inhaled allergens, and it continues to grow. These allergens have mostly been identified by their affinity to bind to IgE [201]. Based on the location, altitude, latitude, temperature and humidity, we find different aeroallergens in the environment [201]. The most common are Bet v 1 (*Betula pendula* or Birch pollen), Per h 1 (*Periplaneta americana* or American cockroach), Der p 1 (*Dermatophagoides pteronyssinus* or European house dust mite), and Amb a 5 (*Ambrosia artemisiifolia* or short ragweed) [201,36,37]. Potent Th2 response to these allergens depends on the allergen uptake, processing and presentation by DCs to T-lymphocytes [37,38].

Factors that might separate allergens from non-allergenic proteins include their protease activity and surface recognition features including glycosylation patterns. Cross-reactive carbohydrate determinants (CCDs) are one of the most common encountered epitope structures recognized by IgE [39,40]. These asparagine-linked carbohydrate moieties include xylose and core-3-linked fucose that are important part of IgE epitopes [39,41]. Since they are found only in plants, insects and certain parasites, their immunogenicity increases in humans. Recent investigations have pointed the importance of their structures compared to the amount in eliciting immune response [36,39]. Glycosylation of allergens is required for recognition and uptake through epithelial as well as DCs [36,37]. Mannosylation is the most common glycosylation pattern among allergens with an exception of Der p 2 (*Dermatophagoides pteronyssinus* or European house dust mite), which has N-acetylglucosamine, galactose and sialic acid [40]. Apart from Der p 1, Bla g 2 (*Blattella germanica* or German cockroach antigen), Can f 1 (*Canis familiaris* or dog allergen), and Fel d 1 (*Felis domesticus* or cat allergen) are mannosylated with 1–2, 1–3 and 1–6 mannose. The degree of mannosylation determines the efficiency of antigen uptake and allergenicity

[40]. Study from Al-Ghouleh and colleagues [36] demonstrated that recombinant hypermannosylated Der p 1 is taken up more efficiently by DCs than natural Der p 1. Demannosylating Der p 1 with sodium metaperiodate (a deglycosylating agent) reduces the uptake by DCs without modifying the protein structure [36]. Further understanding of CCDs present on allergens could give us an opportunity to target them for potential therapy of allergic asthma by modifying their structure to make them less immunogenic. Vaccine therapy can also be designed by careful manipulation of such carbohydrate chains.

Pollens release lipid mediators in addition to the proteins. These lipid mediators are also called pollen-associated lipid mediators (PALMs), and are capable enough to attract and stimulate innate and adaptive immune cells [42,43]. Phytoprostanes are products of auto-oxidation and consist of a characteristic prostaglandin-type ring structure. Hoffmann *et al.* [44] showed that *Betula alba* L. pollen extract among these phytoprostanes (PPE1, PPB1, and PPF1), only PPE1 was able to inhibit LPS-induced IL-12p70 in a dose dependent manner, mitigating Th2 response through modifying the function of DCs.

Mannose receptor (MR) and other c-type lectins on DCs interact with the glycosylated residues of these allergens. Degree of interaction of DCs with the cysteine protease-containing allergens determines the degree of DC activation and allergenicity. Recent developments have led us to believe that TSLP, released by the epithelial cells on exposure to allergens help DCs to drive the immune response to Th2 [45]. Additionally, Der p 1 exposure increases production of chemokines in epithelial cells [46]. Chemokines, including CCL2 (MCP-1), CCL5 (RANTES), CCL20 (MIP3A), CXCL8 (IL-8), and CXCL10 (IP-10), are increased in BEAS-2B cells and primary bronchial epithelial cells from non-atopic patients, whereas the production of CCL2, CXCL10 and CCL20 has been shown to be enhanced in primary bronchial epithelial cells of patients with allergic asthma following exposure to Der p 1 [46].

Environmental exposure and epigenetics add complexity to the genetic predisposition to allergic asthma. Maternal inclination to an allergic phenotype has higher risk of transmission to her children. Hypermethylation of DNA in splenic DCs has been seen in the offsprings. The altered methylation pattern makes them efficient in allergen-presentation and thus skewing the immune response to Th2 for atopy [7]. Exposure to diesel exhaust, pollution, free radicals, and ozone are added risk factors in allergic asthma. Their ability to mature the DCs to an allergic phenotype and enhance their activity for Th2/Th17 polarization increases the risk many folds when exposed to allergens [47,48]. Identification of allergens and respective changes in the genetic and epigenetic factors play an important role in understanding the phenotype in allergic individuals. Knowledge of these factors gives us an excellent opportunity to predict predisposition to asthma for a better management or a promising therapy against allergic asthma.

4. Effect of microbiome on DC phenotype

Presence of microflora modulates the microbiome of different organs including intestine and lungs. Every day we are exposed to billions of microorganisms through the environment. Trillions of these organisms inhabit our body. Their presence in our body is often translated

into effects, determining responses, specific to metabolism or immunity. *Helicobacter pylori*, being the most common bacterial infection worldwide, causes gastritis, gastric ulcer, and cancer. The chronic infection of this persistent and low pH resistant bacteria has, however, multiple protective effects on human beings, including protection against gastroesophageal reflux disease (GERD) [49], esophageal adenocarcinoma (EAC) [50], metabolic disorders and allergic diseases including allergic asthma and chronic inflammatory diseases [51,52]. Increasing clinical and experimental evidence suggest that *H. pylori* may protect the host from development of allergic diseases including allergic asthma [52]. The protective effect of *H. pylori* against allergic asthma is carried through DCs [33]. It eludes host adaptive immune response by reprogramming DCs to mature towards tolerance instead of immunity. As DCs continuously move to recognize and engulf the invaders, immature DCs interact with *H. pylori* through DC-SIGN. However, activation signal is transmitted through TLRs (TLR2) [19], and they are reprogrammed to tolerogenic DCs with high level of MHC-II expression and reduced co-stimulatory molecules expression in the presence of IL-18 [53]. Tolerogenic DCs then migrate to the lymph nodes to present the processed antigen to naïve T-cells. The *H. pylori* exposure results in the downregulation of co-stimulatory molecules, CD80 and CD86, and polarizes naïve T-cells towards Foxp3⁺ Tregs. Production of IL-10 and TGF- β from Tregs blocks atopic sequestration of the immune system by stopping Th2 response [33,53]. The findings from the studies of *Codolo and co-investigators* [54] suggest polarization of naïve T-lymphocytes towards Th1 by *H. pylori* neutrophil-activating protein (HP-NAP) in the presence of IL-12 and IL-23 through TLR2, and thus debilitating the Th2 response. Another way *H. pylori* could block atopy is by generating tolerance in DCs through virulence factors, γ -glutamyl transpeptidase (GGT) and vacuolating cytotoxin (VacA) [32]. *Bacillus* cells produce poly- γ -glutamic acid (γ -PGA), which activates NF- κ B and p38/MAPK signaling to upregulate CD40, CD86 and IL-12 in a TLR-4 dependent manner. Intranasal administration of γ -PGA in OVA-sensitized and challenged mice polarizes a Th1 type response and reduces AHR and granulocyte infiltration [55]. Konieczna *et al.* [56] demonstrated that administration of *Bifidobacterium infantis* 35624 in human volunteers increases expression of IL-10 and Foxp3 in the peripheral blood. Experiments done in vitro with *B. infantis* suggested an increase in the expression of IDO, and IL-10 in MDDCs (TLR2/6-dependent), mDCs (TLR2/6-dependent) and pDCs (TLR-9-dependent) [56]. Further investigation revealed that MDDCs and mDCs require retinoic acid, DC-SIGN and TLR2 to induce Foxp3⁺ Tregs, whereas pDCs need IDO [56]. Similarly, filamentous hemagglutinin (FHA) from *Bordetella pertussis* [57], phosphatidylserine and lysophosphatidylserine from *Schistosoma mansoni* [58] induce DCs to assist Tregs to develop tolerogenic response.

Consistent with the hygiene hypothesis proposed by Strachan [59] in 1989, children growing up around farms have lesser incidence of allergy and asthma than the same age children in urban settings [60]. To unravel this cause-and-effect mystery, few studies have linked some bacteria that act as protectors while trying to survive in the host. Bacteria found in farm cowshed, including *Acinetobacter iwoffii* and *Lactococcus lactis*, prime the DCs to induce a Th1 polarization, thus protecting from allergies [60]. Cowshed dust extracts containing molecules such as synthetic lipopeptide from *Bacillus cereus*, LPGerD, induces TLR-2/IRAK-M signaling in bone marrow-derived DCs [61]. Such activation of TLR-2 nullifies the

LPS stimulus leading to a tolerant immune response. *Staphylococcus sciuri* W620, derived from farm dust may protect against the pathophysiological features of allergic asthma in house dust mite and ovalbumin-sensitized and challenged mouse models of allergic asthma [62].

On the other hand, certain microorganisms could be inducers of AHR, and their presence could pose a higher risk in incidence of childhood asthma. Cold-assisted viral bronchiolitis in infants is due to respiratory syncytial virus (RSV). The infection is approximately 70% in the first year and increases to nearly 100% by 2 years of age. Mechanistic aspects of this infection linked to the development of asthma in children remain unclear, but data suggest that up to 13% of childhood asthma cases could be prohibited by clearing bronchiolitis in infants [63]. Similarly, human rhinovirus (RV)-induced wheezing illnesses is also linked to a greater risk of asthma development in children as young as 6 years old [64]. There is a high probability that these viruses interact with DCs through PRRs and facilitate their maturation towards immunogenic mDCs, which under appropriate cytokine environment polarizes a Th2 type response for atopy. In addition to the immature DCs developing an immunogenic phenotype, Ghosh *et al.* [65] showed that transcription factor E2-2 deletion might result in the development of immunogenic mDCs from mature peripheral pDCs. At this stage, exposure to environmental allergens adds fuel to the fire in the apposite atmosphere and the host immune system puts up a full-fledged hyperresponsive and inflammatory retort. However, an interesting finding came out from a study related to smoking and DC response. Chronic smoking alters the balance and functionality of DC subtypes in the periphery, and drives them towards a tolerogenic phenotype [66]. On the contrary, another study reports that smoking promotes *Chlamydomphila pneumonia* infection and thereby increases the risk of allergic asthma [20]. The common finding among these groups was that pDCs could suppress the Th2 response and thus can restore the homeostasis. Adding the complexity to the general notion of pDC-associated tolerance and explaining the respiratory virus-associated higher prevalence of asthma, some studies have shown that pDCs in asthmatics have impaired ability to produce IFN- α with RV and influenza infection [67–69]. This may be due to the cross-linking of Fc ϵ RI (high affinity IgE receptor) on pDCs [69], which is expressed more in allergic individuals, and tends to negatively regulate TLR9 and TLR7 with CpG and influenza infections, respectively [68,69]. The counter-regulation of TLRs and reduced IFN- α production from pDCs results in weak antiviral response and leads to increased expression and production of Th2 cytokines and asthma exacerbation. The variety of effects of microbiome on immune response makes it a hotspot for potential targets in allergic asthma. Replacing bacteria that induce tolerance could help patients with allergic asthma.

5. Role of Pattern Recognition Receptors on DC-Driven Immune Response

5.1 Toll-like Receptors

Presence of numerous PRRs on DCs helps them recognize a plethora of antigens, encountered by human during the lifetime. TLRs, one of the PRRs, are expressed on DCs based on the type and maturity level (Figure 2). Most of the TLRs promote Th1 response. However, in some cases, certain microbial products induce Th2 or even Tregs. Certain

bacteria, including *Mycobacterium tuberculosis*, activate TLR2/TLR1 on DCs to cause MyD88-dependent activation of NF- κ B, and increase the production of pro-inflammatory Th1 cytokines, including TNF- α and IL-12 [70]. *Y. pestis* virulence factor and zymosan induce Tregs through TLR2/TLR6 pathway leading to a protective effect in allergic asthma [71,72]. Exposure to dsRNA stimulates TLR3 on mDCs. Their interaction with NK cells results in production of IFN- γ and TNF- α to clear infection and cancer cells [73] and oppose Th2 polarization. In addition to bacterial LPS, air pollutants, like ozone and diesel exhaust, activate DCs to atopic phenotype through TLR4 [48]. These pollutants may work as epigenetic modifiers to increase the susceptibility to allergic asthma. Bacterial protein flagellin, abundant in household, acts as an adjuvant to normal allergens like HDM and OVA. In a TLR5-dependent mechanism, flagellin primes mDCs for a strong response to indoor allergens resulting in allergic asthma [74]. A gram-negative infection from *Brucella abortus* is recognized by TLR6 with TLR2 on DCs to induce host innate immune response through a MyD88 dependent activation of NF- κ B leading to the production of TNF- α and IL-12 [75], polarizing a Th1 response. Activation of TLR-7 on pDCs can result in the suppression of IL-5, thus inhibiting the Th2 response. This immunomodulatory effect may take place through both IFN-dependent and IFN-independent pathways. IFN-dependent suppression of IL-5 is directly through IFN- α in the presence of IL-10. Whereas, IFN-independent pathway involves Notch signaling [23]. HIV-1 uses TLR8 and DC-SIGN on DCs to evade the host innate immune response by expression of integrated provirus in a NF- κ B dependent pathway [76]. This might be another pathway of co-morbidity of HIV and asthma. Bacterial DNA containing CpG motif can selectively activate DCs through TLR9. This pathway is important in cross-presentation of endogenous or exogenous antigens in mDCs as well as pDCs, which depends on the timing of TLR ligation [77]. The production of the type I interferons (IFN- α and IFN- β) in pDCs is dependent on TLR7 and TLR9 stimulation to impart protection against viral infections [78]. Recognition of *Toxoplasma gondii* profilin is dependent on TLR11 on mice DCs. As a result, IL-12 is produced. Production of IL-12 and IFN- α through TLR12 in pDCs induce NK cells to start secreting IFN- γ to fight against the infection [79]. This cytokine profile directs T-lymphocytes towards a Th1 response. It recognizes ssRNA present in the peptidyl transferase loop of 23S rRNA of certain bacteria in mDCs [80] and responsible for the immune response. However, humans do not express this receptor and thus has less significance in human asthma. Recognition of foreign molecules, and signaling events through TLRs are important in precipitating a particular immune response. This interaction is of particular interest in devising therapy as modulation (activation/suppression) of TLRs can change the immune repertoire to resist allergic asthma.

5.2 C-type Lectins

These Ca²⁺-dependent PRRs are found on DCs to recognize carbohydrate moieties present on the antigens. Depending on their structure and function, they can be divided into various groups. However, based on the orientation of their N-terminus, they can be divided into type I and type II transmembrane receptors. Type I transmembrane receptors have multiple carbohydrate recognition domains (CRDs). These receptors include MR (CD206), DEC-205 (CD205), Endo 180 (CD280), and PLA2, and play an important role in pathogen recognition and DC maturation. MR is responsible for DC maturation through Notch signaling following

allergen exposure [81]. Type II C-type lectins, including DC-SIGN, work as cell adhesion molecules as well as PRRs. Targeting antigens to induce c-type lectins such as DEC-205 on DCs can induce Foxp3 expression on T-lymphocytes to develop tolerance [31], and thus can help in allergic asthma.

5.3 DC-SIGN

DC-SIGN is one of the most important receptors on DCs involved in the recognition of foreign bodies. Like TLR2, they can also recognize and activate DCs on bacterial exposure. However, they work by suppressing NF- κ B [70]. House dust mite can decrease the expression of DC-SIGN in mDCs resulting in the polarization of Th2 response [35]. DC-SIGN is a major molecule that binds to gp120 of HIV-1 infection. It activates Raf pathway to phosphorylate NF- κ B and uses the host immune system for its own proliferation and dissemination [76]. Gingo and colleagues [82] in their cohort study have comprehensively described that asthma is the most commonly diagnosed pulmonary disease in HIV-infected outpatients, standing at 20.6%, compared to 8.2% in general adult population. The precise mechanism of co-morbidity of HIV and asthma is not yet known. However, HIV-1 binding to DC-SIGN, abnormal regulatory T-lymphocyte function, and similar cytokine profile including IL-4, RANTES, MIP-1 α and MIP-1 β in HIV infection may result in higher incidence of asthma [82]. On the other hand, DC-SIGN interaction with *Lactobacillus reuteri*, *L. casei* and *Mycobacteria* results in a tolerogenic response similar to *H. pylori* and *L. acidophilus* via Tregs to increase the production of IL-10 and induce tolerance [33,83–85]. Modulating signaling pathways through DC-SIGN can help in controlling allergic responses in asthmatic patients. However, this approach poses considerable risk of compromised immunity against pathogens because of its importance in the recognition of microbes and host defense.

5.4 Dectin molecules

Dectin-1 present on DCs is important in antifungal innate immunity. It binds to β -glucans of fungi, including yeast. House dust mite (Der p 1) and *Aspergillus* allergens can bind to Dectin-2 on DCs through Fc γ R to activate its arachidonic acid metabolism and production of cysteinyl leukotrienes, IL-6 and TNF- α [86]. Dectins are potent ROS activators and thus may involve NF- κ B or AP-1 (redox transcription factors) to cause DC maturation and activation to a specific phenotype, and thus are important players in the pathogenesis of allergic asthma.

5.5 NOD-like receptors

These PRRs recognize pathogen-associated molecular patterns (PAMPs) as well as endogenous signals, stimulating host immune response under cellular stress. They have a tripartite-domain organization with a conserved nucleotide binding oligomerization domain (NOD) and leucine-rich repeats (LRRs) [87]. Their engagement results in the release of cytokines and chemokines to attract innate and adaptive immune cells, and thus could be used as therapeutic target in asthma.

6. Chemotaxis of DCs

Movement of DCs is precisely controlled by chemokines milieu and concentration. Expression of different chemokine receptors at different stages of DC maturation is a key event in the mobilization of selective DCs based on their type and maturation (Figure 2). Lymphatic endothelium is the principal source of CCL21 – a ligand of CCR7. Expression of CCR7 is gained in the mature DCs to be able to find their way into draining lymph nodes. CCR7 has two ligands, CCL19 and CCL21, but intravasation of mature DCs to the draining afferent lymph nodes is only dependent on CCL21, not CCL19 [88].

Interestingly, immature and mature DCs, both express CCR8, but in spite of a comparative lower level of CCR8 expression, mature DCs show greater responsiveness to the CCL1 compared to immature DCs [89]. Exposure to bacterial LPS decreases membrane expression of CCR8 on DCs possibly by receptor internalization through β -arrestin. In a knockout mice study, Robays and investigators [90] showed the importance of CCR2, but not CCR5 or CCR6 in the migration of DCs in lungs during allergic inflammation. Plasmacytoid DC-specific CCR9 expression increases as they differentiate into a mature phenotype. Mucosal epithelial cells along with DCs produce CCL25, the ligand for CCR9 to mobilize mature pDCs to induce tolerance [91].

After antigen uptake DCs have to find their way to lymph nodes to present the processed antigen to T-lymphocytes. Apart from the involvement of CCR7 and CCR8 chemokine receptors in the migration of antigen-carrying lung DCs to draining lymph nodes [89], we have recently found that calcium-activated potassium channel, KCa3.1, is a key player in regulating the chemotaxis of DCs in the lungs [92]. Migration of DC via KCa3.1 is modulated at two levels where by CCR7 activation is modulated by the activation state of KCa3.1 via CCL19/CCL21-dependent intracellular calcium release. Higher expression of CCR7 assists in the activation of KCa3.1. Furthermore, higher expression levels of KCa3.1 in lung DCs under atopic conditions necessitate its involvement in DC migration [92]. Further understanding on the molecular and chemical signals to attract different DC subsets could help us devise better therapies for allergic airway inflammatory conditions..

7. DCs interaction with airway epithelial cells

Epithelial cells serve as barrier with the formation of tight junction including zona occludens (ZO), occludin and claudins [93]. As the epithelial barrier is breached by antigens, including microorganisms or allergens, through proteases, the epithelium starts secreting cytokines and chemokines to attract DCs to the site of contact or breach (Figure 3). DCs extend their processes through epithelium without compromising its integrity [94] to take up the foreign body for further processing and presentation to T-lymphocytes to decide the fate of immune response. Experimental evidence suggests the role of epithelial cells in regulation and differentiation of local DCs by upregulating co-stimulatory molecules and increasing the antigen uptake of DCs under Th2-rich cytokine conditions. Similarly, epithelial cells can also modulate DC differentiation to resist Th2 polarization under LPS-activation (IL-12/ TNF- α) or in the presence of IL-6/ IFN- α [95]. The direct and indirect interaction of

epithelial cells with DCs can be targeted to mitigate the inflammatory response in allergic asthma.

7.2 Role of allergen protease activity

Ragweed pollen contains serine proteases, whereas other pollens including cedar and cypress have cysteine and aspartic proteases [96]. House dust mites produce cysteine (Der p 1 and Der p 3) and serine proteases (Der p 6 and Der p 9). However, Der p 2 does not have any protease activity. It interacts with TLR-4 as MD2 (TLR-4 cofactor) on DCs to cause its effects independent of protease activity [97]. American cockroach contains a 28kDa trypsin-like serine protease (Per a 10), whereas Bla g 2 from German cockroach has aspartic protease activity [98]. Involvement of serine protease activity has also been observed in cockroach antigens. Epithelial cell breach by inhalation of fungi is mostly related to the serine proteases [97]. These proteases damage the epithelium by degrading ZO-1 and occludin leading to disruption in the tight junction [97]. Der p 1 can cleave tight junction though sites found in an extracellular domain of occludin, and claudin-1 [97,99]. It may also damage the tight junction indirectly by activating surface zymogens on epithelial cells [100]. Allergens with protease activity may also exert their effect in a protease-independent manner by sensitizing to a non-protease protein like OVA [97]. This observation is very important in understanding why some innocuous agents might turn to inducers of allergic asthma, and a possible explanation to some failed replication of asthmatic phenotype in clinics.

7.2 Role of cytokines and chemokines

Epithelial cells express pattern recognition receptors (PRRs) to recognize pathogen associated molecular patterns (PAMPs) on microbes and damage-associated molecular patterns (DAMPs) by tissue damage or stress [101]. Microbial recognition or damage to the tight junction and breach in epithelium causes production and release of numerous chemokines and cytokines to attract innate and adaptive immune cells [100–102]. Der p 1 causes production of CCL2, CCL20, and IL-12p40 from epithelial cells to attract monocytes and immature DCs [101,103]. Activation of TLR-4 by Der p 1 also causes production of TSLP, IL-25, IL-33 and granulocyte-macrophage colony stimulating factor (GM-CSF) to favor Th2 immune response [103]. However, Chu *et al.* [105] suggested that HDM-induced allergic asthma is primarily dependent on IL-33 and not on TSLP or IL-25, and discussed how IL-33 might increase the expression of OX40L on DCs to exhibit Th2 immune response. Cytokines, TSLP and IL-33, play a major role in DC maturation towards atopic phenotype [2–4]. IL-33, an IL-1 family cytokine induces mDCs to produce the pro-inflammatory cytokines, IL-6, IL-1 β , TNF α , and chemokines like CCL17 to attract T-lymphocytes. It also increases the expression of co-stimulatory molecules, CD40, CD80, OX40L and chemokine receptor CCR7 [3]. Also, IL-33 activates T1 (ST2) receptor, thereby inducing Th2 response [101]. Similar to IL-33, TSLP, an IL-7-like cytokine produced by epithelial cells following allergen breach also results in the maturation of mDCs by upregulating CD40, CD80 and CD86 [2] to polarize Th2 cells and production of IL-4, IL-5 and IL-13 [45, 106] (Figure 3). Production of TSLP by the action of various inducers on epithelial cells is an important determinant in allergic phenotype [101]. Its receptor, TSLPR, is present on epithelial cells and DCs. Various single nucleotide polymorphisms (SNPs)

have been identified in the promoter region of TSLP gene [107]. However, targeting TSLP for therapeutic approach is not viable because of its role in epithelial repair and other biological processes [101]. The interaction of antigen/allergen and DC through PRRs also determines the type of immune polarization. If it is an allergen, DCs mature towards an immunogenic phenotype and secrete cytokines appropriate for a proper Th2 response. Production of IL-25 in epithelial cells is dependent upon proteolytic cleavage by MMP7, which is also produced by epithelium upon damage/activation [108]. There is some experimental evidence that IL-25 might activate DCs by upregulating Jagged-1 expression and thus promoting Th2 response in RSV-infected mice [109]. In an attempt to show the direct effects of epithelial cell-derived cytokines on DC differentiation/maturation, Regamey *et al.* [110] used airway epithelial-conditioned media to differentiate monocytes into functional DCs. This is an important observation suggesting increase in the number of DCs in the airways, following allergen exposure. With monoclonal antibody against IL-15, they were able to demonstrate the role of epithelial-derived IL-15 in DC differentiation and function [110]. Such evidence suggests that cytokine milieu provided to DCs by the epithelial cells is paramount in deciding the immune response [2–4,95,110], and manipulation of this microenvironment could give us opportunity to modulate the inflammatory immune response in allergic asthma.

8. Interaction of DCs with various immune cells

Dendritic cells interact with different immune cells to dictate the immune response. This interaction may be direct (T-cells), or indirect (with B-cells, eosinophils, neutrophils, mast cells and basophils). The microenvironment around the interaction point is also of utmost importance as it may direct the immune response in different directions. In an atopic response, all the immune cells, under an atopic environment produce pro-inflammatory mediators in a feedback manner to produce an efficient hyperactive response. In this section, we will discuss how these cells interact with DCs under various microenvironments.

8.1 DCs interaction with T-lymphocytes

Under appropriate atopic environment, matured mDC interacts with naïve T-cells to polarize them towards Th2 phenotype, where T-cells secrete IL-4 in an autocrine manner for clonal selection of the Th2 cells. The interaction of DCs with T-lymphocytes takes place via a multi-molecule immune synapse starting with antigen presentation via MHC class I/II on DCs to the TCR of T-lymphocytes. This interaction is further supported by CD3 on T-lymphocytes. But, to complete the molecule repertoire, interaction between OX40L-OX40, CD40-CD40L, CD80/86-CD28 and ICAM-1-LFA-1 is required [111]. With completion of molecular circuit with DCs, T-cells polarize towards Th1, Th2, Th3, Th9, Th17, Th22 or Tregs (Figure 4).

8.1.1 Role of co-stimulatory molecules—Primary signal provides antigen specificity to the developing immune response. However, secondary signal through co-stimulatory molecules is required to completely activate T-lymphocytes. These co-stimulatory molecules on DCs usually can be classified under B7 superfamily (CD80, CD86, CTLA-4, ICOS-L and PD-L1/L2), and TNF superfamily (CD27, CD30-L, CD40, Fas, HVEM/

LIGHT, 4-1BB-L and OX40L) or Ig superfamily (B7/CD28, and CD2) [111–115]. Co-stimulation with CD28 in T-lymphocytes is required for efficient immune response [111]. However, knockout experiments in mice suggested that CD28 is not the only driver of this signal. Another B7 molecule that shares DC counter receptors (CD80/CD86) is CTLA-4 [111]. Conversely, it is a negative regulator of the T-lymphocyte activation and helps in the development of tolerance. Several single nucleotide polymorphisms have been detected in CTLA-4 in asthmatic patients suggesting its role in anergy [111]. Patients with acute asthma have higher levels of soluble CD86 (transmembrane domain deleted) compared to chronic asthmatics or healthy individuals, which decreases with corticosteroid treatment. Another B7 family member ICOS present on T-lymphocytes together with ICOS-L on DCs regulate cytokine production, airway inflammation, smooth muscle cell constriction and mucus production from goblet cells [113]. Interestingly, ICOS/ICOS-L is also involved in co-stimulation of Tregs to produce tolerance [113]. In the presence of IL-10, signal through co-stimulatory molecules CD28 and ICOS is hampered by src homology 2 domain-containing protein tyrosine phosphatase-1 (SHP-1) phosphorylation leading to tolerance [116]. Co-stimulatory PD-1 on T-lymphocytes involves PD-L1 or PD-L2 on DCs [117–120]. Allergen driven augmentation of PD-L2 (B7-DC) in mDCs directly decreases IL-12 production. The counter receptor of PD-L2 – PD-1, however, is not involved in this response. IL-12 is responsible for the suppression of signaling events transcribed through IL-13. Thus, PD-L2 on mDCs may lead to the exacerbation of AHR [121].

The expression of co-stimulatory molecules on different subsets of DCs may regulate the immunity in different directions to impart immunogenicity or tolerance [122]. Mouse knockout studies with PD-1 show development of autoimmune diseases suggesting its role in maintenance of tolerance. On the other hand, absence of PD-L2 expression leads to inflammation and AHR [118,119]. By blocking PD-L2 with monoclonal antibodies, investigators have shown that it is involved in the development of tolerance and works opposite to PD-L1, which conversely enhances AHR and Th2 cytokine production [111,118,119]. Interaction between PD-1/PD-L1 reduces IFN- γ production, and may be because of that it skews the response to a Th2 type [111]. Double knockout studies with PD-L1/PD-L2 showed development of inflammation and AHR comparable to the wild-type mice suggesting neutralization of the PD-L1 knockout [118]. Lung DCs have increased expression of PD-L2 with OVA challenge and is upregulated in the presence of IL-4. Increased expression of PD-L2 causes decrease in IL-4 production in a feedback manner, modulating the immune response [118,119]. On the other hand, IFN- γ increases expression of PD-L1, and increased PD-L1 decreases IFN- γ production [111,118]. A group from Germany recently showed that the expression of PD-L1 is regulated by TLR/p38/MAPK/STAT3 pathway in DCs to modulate cytokines for the development of tolerogenic DCs [120]. Our group has demonstrated that Flt3 ligand treatment in OVA-sensitized and challenged mice increases PD-L1 and PD-L2 expression levels in CD11c^{high}, CD11b^{low} DCs [123]. The positive correlation of Flt3 treatment with PD-L2 expression might be responsible for decrease in T-lymphocyte proliferation. With similar expression profiles in humans and mice, PD-L1 and PD-L2 may be considered as a therapeutic target in allergic asthma [111].

Dendritic cells as well as T-lymphocytes express LIGHT/HVEM. Deficiency in LIGHT leads to weak T-lymphocyte activation, whereas loss of BTLA or HVEM causes increased inflammatory response and implicated in autoimmune diseases [124]. Interaction of OX40-OX40L may change the immediate cytokine microenvironment modulating T-lymphocyte differentiation to Th2 type in presence of IL-4 or TSLP [113,116]. However, in the presence of IL-12 and IFN- α , the differentiation is skewed towards Th1 [113]. Knowledge of co-stimulatory molecules taking part in immunogenic or tolerogenic immune response can help in tailored therapy for atopic individuals.

8.2 DCs interaction with B-lymphocytes

DCs usually do not directly interact with B-lymphocytes; they modulate B-lymphocytes by secreting cytokines and other chemical mediators while interacting with epithelial cells or T-lymphocytes. However, Chappell and colleagues [125] found DC-induced B-lymphocyte activation and migration in mice. They delivered antigen to CD8 α ⁻ DCs in marginal zone to see an immediate upregulation of B-lymphocyte activation markers along with chemokine receptors (CXCR5), and accumulation of the activated antigen-specific B-lymphocytes in the extra-follicular splenic bridging channels [125], suggesting a direct interaction. B-lymphocytes can be differentiated into three different phenotypes – memory B-lymphocytes, regulatory B-lymphocytes (B10), and effector B-lymphocytes (Figure 5). Upon antigen exposure, B-lymphocytes imprint a memory to recognize the antigen the next time the host comes across. This happens in presence of IL-10 and TGF- β . However, in an atopic response, effector B-lymphocytes may undergo class switching to IgE in the presence of IL-9 and IL-13. IL-4 also helps in the stimulation of these B-lymphocytes as they transform to plasma cells, secreting antibodies, which then bind and neutralize the antigen/allergen (Figure 5). Recently, another type of B-cell came to light, which was very similar to Tregs and secreted IL-10. These B10 cells are responsible for inducing tolerance in the presence of IL-10 and IL-21 [126].

8.3 DCs interaction with eosinophils

Eosinophils are one of the most pathogenic cells in allergic asthma, capable of producing extensive damage and inflammation in the airways. Presence of eosinophils has been correlated with the induction of Th2 response [127]. IL-5 secreted by Th2 cells is a major cytokine in the differentiation, maturation and migration of eosinophils. Another indirect effect of DCs on eosinophils is through epithelial cells, which along with T-cells secrete GM-CSF to promote eosinophils, neutrophils and monocytes (Figure 6). Eotaxin and TGF- β secreted from epithelial cells and other sources cause further migration and activation of eosinophils. With continuous atopic cytokine milieu in the vicinity, eosinophils release pre- and newly-formed mediators, including MBP, ECP, EDN, EPO and more than a dozen cytokines including TGF- β , revealing their damaging potential on airway epithelium. In the chronic condition of allergic asthma, eosinophils cause airway remodeling to display severe form of allergic asthma, in which the airway loses compliance and patient may succumb to death. Eosinophils are always known as the ultimate effector granulocytes. However, several studies suggest even bigger role of eosinophils in the pathophysiology of asthma. As eosinophils migrate to draining lymph nodes and express MHC class II and co-stimulatory molecules like DCs, they may function as DCs or with DCs to form an immune synapse

with T-lymphocytes [127,128]. Moreover, their ability to secrete IL-12 to differentiate Th0 cells into Th1, Th2 cytokines, including IL-4, IL-25 and immunosuppressive cytokines, including indoleamine 2,3-dioxygenase, also expressed in immature DCs [28], makes them versatile in their immunomodulatory role in allergic asthma. Further understanding of the molecular mechanisms underlying the migration and activation of eosinophils is warranted.

8.4 DCs interaction with neutrophils

Interaction of DCs with epithelial cells secretes IL-8, which acts as a potent chemoattractant for neutrophils (Figure 6). Complement factor C5a, leukotriene B4, GM-CSF and IL-4 add fuel to the fire and promote neutrophils to cause damage [129]. Neutrophils are mostly involved in acute inflammatory phase through their azurophilic and specific granules containing mediators potential enough to cause serious damage to the airway epithelium. In chronic allergic airway inflammation, especially following house dust mite challenge, significant number of neutrophils is found in the bronchoalveolar lavage. Thus, further knowledge on the the migration and activation of neutrophils and their role in acute versus chronic allergic airway inflammation is critical to develop better therapeutic approaches..

8.5 DCs interaction with mast cells

The activated mast cells, another source of IL-5, release both pre-formed and newly-formed mediators similar to eosinophils. Mast cells secrete massive amounts of histamine, prostaglandin D2, leukotriene C4, tryptase, chymase, heparin and platelet activating factor (PAF) with other cytokines to cause vascular permeability, edema, bronchoconstriction and inflammation while eliciting the chemotaxis of granulocytes in response to release chemoattractants and the granulocytes further induce damage and destruction. IL-13 along with IL-4 contributes to the development of mast cells and aids in the induction of IgE synthesis. Additionally, IL-9 secreted from Th2 cells is the major promoter and activator of mast cells, but interaction of DCs with mast cells goes a little farther compared to other immune cells (Figure 6). Antibodies secreted from plasma cells bind to the high affinity FcεRI on mast cells. On subsequent exposure to allergens, antibodies bound to FcεRI on mast cells cross-link causing a signal transduction leading to the activation of mast cells releasing pre-formed mediators from their granules together with many newly formed mediators [130,131]. Molecular signals to reduce the activation of mast cells can be promising to control inflammatory response.

8.6 DCs interaction with basophils

Similar to mast cells, basophils also have the unique ability to produce histamine and heparin. In addition, they have high affinity FcεRI and are abundant source of IL-4. With their granules containing proteolytic enzymes, leukotrienes and several cytokines, they also contribute to the inflammatory damage to the airway epithelium. IL-3, IL-4, IL-33, MCP-2, RANTES, and insulin-like growth factors (IGFs) are major cytokines and chemokines involved in the differentiation, migration and activation and thus, indirectly interact with DCs through these mediators [132]. TSLP secreted by epithelial cells promotes differentiation and growth of basophils, which are early source of IL-4 to assist DCs for Th2 polarization. Controlling the activity of basophils can be therapeutically beneficial in early-stage asthma.

9. Potential checkpoints for therapeutic intervention

Since DCs are the major drivers of immune polarization, they may pose as potential therapeutic targets in immune diseases including allergic asthma, HIV and cancer.

9.1 Targeting the molecules involved in antigen recognition

The process of targeting molecules is one of the most important features of DC-driven immune response. Based on the expression of their surface molecules, DCs recognize antigens. Modulation of this interaction to a favorable conduit could have a therapeutic potential. This may be done in a two-way targeting of the interactions between antigens and PRRs. Recombinant protein or synthetic structure generation of known allergens and their modification to generate a tolerant immune response could be a promising target. Secondly, blocking atopy-committed PRRs and inducing tolerance-producing PRRs on DCs could further strengthen this approach. Among the soluble PRRs, collectins (collagen-containing c-type lectins), surfactant protein D (SP-D) binds to CD14 impeding Der p binding and induction of NF- κ B through TLR4. SP-D can also regulate the DC-SIGN expression to amend the airway inflammation [34]. Mite allergen-specific immunotherapy could change the expression of co-stimulatory molecules (CD86, HLA-DR, and TLR4) on DCs to modify the pathophysiological features of allergic asthma [65]. However, this therapy comes with numerous side effects. To compensate for the side effects, one group of investigators proposed to use carbohydrate-modified allergens in combination with targeting DCs with hypoallergenic substances [133]. This requires low dose of allergen-specific immunotherapy with reduced risk of side effects. Indeed, efficient uptake of mannan-conjugates by DCs results in a shift from IgE to IgG in B-lymphocytes [133]. NLRP10, a NOD-like receptor, lacks the general ligand binding leucine-rich repeat domain found in other members, and it has been found to be a negative regulator of other NOD-like receptors. It may modulate DCs through an inflammasome to regulate caspase-1 activity leading to reduced Th2 response [87].

9.2 DC maturation

Another approach could be the targeting of key molecules involved in DC maturation. On antigenic exposure and completion of proper signaling repertoire, DCs mature to a specific phenotype. Identification of signaling events responsible for the development of DCs into an atopic or a tolerogenic phenotype could be promising in targeting them for a desirable response. Transcription factor E2-2 is required in the maintenance of interferon-producing mature pDCs, and its deletion can result in an immunogenic mDC phenotype [65]. TLR7/9 signaling has been shown to induce production of IFN- α in pDCs [23,68,69]. Similarly, expression of CCR9 is a key event in the maturation of DCs to pDCs [26,91]. Through receptor agonists, genetic manipulation or stem cell therapy, the population of pDCs can be restored for homeostasis and tolerance. Experimental evidences suggest hypermethylation of multiple genes, including *zbtb41* and *Foxo6*, in CD11c⁺ splenic DCs in allergen-naïve offspring of asthmatic mother, suggesting possible therapeutic target with epigenetic modifications [7]. However, site-specific methylation or demethylation cannot be achieved at this point, limiting its therapeutic application in allergic asthma.

We found that the administration of Fms-like tyrosine kinase 3 ligand (Flt3-L) reverses the AHR and airway inflammation in murine models of allergic asthma using OVA, HDM or cockroach antigens. The administration of Flt3-L increased regulatory DCs ($CD11c^{high}CD8\alpha^{high}CD11b^{low}$) and Tregs ($CD4^{+}CD25^{+}ICOS^{+}Foxp3^{+}IL-10^{+}$) in addition to a decrease in Th17 ($CD4^{+}IL-17^{+}IL-23R^{+}ROR-\gamma^{+}CD25^{-}$) cells in the lungs [5,134,135]. This treatment could be a promising therapy for allergic asthma. Neuropeptide Y (NPY) levels have been found to be elevated in the lungs of allergic asthmatic patients, mostly in chronic condition. Activation of NPY receptor- 1 (NPY-Y1) on DCs is needed for efficient antigen uptake, and T cell priming. In addition, NPY regulates the motility of DCs [136,137]. Recently, we found the expression of NPY-Y receptors on structural and immune cells of the airways suggesting a potential paracrine-autocrine signaling in these cell types leading to exacerbation of asthma. Thus, targeting a specific NPY receptor may also be a therapeutic target to mitigate asthma [136].

9.3 Chemokine receptors

Chemokine receptors on DCs direct them to the required site based on their ligand concentration, released from different immune cells including epithelium. Understanding of the expression and activity of different chemokine receptors on DCs at different maturation stages as well as in different DC phenotype would enable us to develop therapy based on chemoattraction of DCs. The chemokine receptor CCR8 expressed on DC is of major importance in allergic asthma. Both mature and immature DCs express CCR8, but only mature DCs respond to CCL1. CCR8 antagonists, such as diazospiroundecane, can inhibit migration of DCs, T-cells and eosinophils to reduce inflammation in allergic asthma [89]. Bellinghausen *et al.* [138] showed that enhanced production of CCL18 by tolerogenic DCs suppresses the Th2 driven airway inflammation. Thus therapies targeting DCs to express CCL18 could be beneficial in allergic asthma. Therapy directed to express more CXCR3/4, which is specific for pDCs could bring tolerance in allergic people. Furthermore, expression of CXCL9-12, ligands for the chemokine receptors, could attract the therapeutic pDCs to the site. The major drawback in this approach is that both HIV and cancer use the same chemokine receptors for invasion and migration. So, therapy devised should be carefully selected and studied extensively before application.

9.4 Antigen presentation

Antigen presentation through MHC molecules present on DCs requires TCR and other co-stimulatory molecules. If the immune synapse between these cells is incomplete or insufficient, polarization of T-lymphocytes to a specific phenotype for a proper immune response is abated. The important aspect in targeting this molecular interaction is that this interaction is integral to our host defense against pathogens. However, therapeutic potential of this interaction could be significant if the targeting a site modulates the response instead of stopping it. Targeting PD-L2 on DCs, which directly reduces the IL-12p40 production on allergen exposure, could modulate IL-13, and thereby help in ameliorating the DC-driven allergic response [138]. By adoptive transfer of naturally occurring Tregs ($CD4^{+}CD25^{+}$) and inducible Tregs ($CD4^{+}CD25^{-}$) isolated from lungs and spleen of BALB/c mice into cockroach antigen-sensitized and challenged mice, we found that program death-1 (PD-1) regulates AHR and airway inflammation, and thus could be a target for therapeutic

intervention [123]. Gamma-interferon-inducible lysosomal thiol reductase (GILT) reduces disulfide bonds in proteins taken up by DCs for optimal processing and presentation on MHC class II molecules. Targeting GILT could reduce the Der p 1 antigen processing and presentation ameliorating the allergic response associated with HDM [37].

9.5 Immune modulation through microbiome

Microbiome-induced immunomodulation could be another potential therapeutic approach where microorganisms inducing tolerance can be used in atopic patients. As we discussed in earlier section that some of these microorganisms, including *H. pylori*, modulate the host immune response to evade and disseminate [33]. Virulence factors of *H. pylori*, γ -glutamyl transpeptidase (GGT) and vacuolating cytotoxin (VacA), help in the reprogramming of DCs to a tolerogenic phenotype [52] (Figure 7). Downregulation of co-stimulatory molecules on DCs and polarization of Tregs further strengthens the immune response away from Th2. This survival trait can be harnessed for host benefit by selecting harmless strains that may induce tolerance and introduce them in an atopic individual (Figure 7). As the bacterium is harmless, it would not cause damage to the host, but by inducing tolerance it may relegate the allergic phenotype. *Staphylococcus sciuri* W620 isolated from farm dust has been shown to have protective effect in murine HDM- and OVA-models for allergic airway inflammation, possibly through the activation of TLR2 and NOD2 on DCs [62]. Viral infections, such as respiratory syncytial virus, may prime the immune system to respond inappropriately to allergens. One of the ways to reduce eosinophilia in these cases is by blocking cysteinyl leukotrienes in DCs to reduce the production of RANTES (CCL5) [139].

9.6 Interaction of DCs with immune cells

This involves multiple signaling pathways involving various cytokines, chemokines and pro-inflammatory mediators. Modulation of these interactions in favor of tolerance rather than allergy can be achieved through targeting the molecules involved in such interaction at multiple stages. Both AP-1 and NF- κ B, the redox-sensitive transcription factors, are involved in multiple inflammatory pathways. Targeting these transcription factors could attenuate allergic response in asthmatics. Lysophosphatidic acid (LPA) overexpression in DCs of murine model of AHR hinders NF- κ B to negatively regulate DC activation and allergic airway inflammation [140]. The adoptive transfer of perforin-sufficient CD8⁺ T cells could mitigate the allergic response through secretion of IFN- γ and TNF- α . Additionally, they may target the allergen-presenting mDCs and deplete them to reduce the antigen presentation to Th2 cells and thereby decreasing the eosinophil infiltration [141]. Level of type III IFN- λ 2 (IL-28A), an antiviral cytokine, has been found to be low in allergic asthmatics. Exploiting this finding, studies have shown that overexpression of IL-28 in mDCs may lead to a Th1 polarization rather than Th2 in murine model of asthma [142]. Complement molecule, C5a protects from AHR by regulating DCs during allergen sensitization, whereas it acts as a potent pro-allergic molecule during the effector phase. Between the two receptors of C5a, C5aR and C5a receptor-like 2 (C5L2), C5L2 deficiency in mice has protective effects on the development of AHR and airway inflammation. C5L2 could be another potential target for therapy against allergic asthma [143].

9.7 Vitamin D

Vitamin D has emerged as a potent immunomodulator in recent years [144]. It modulates the immune cells through its active form calcitriol, also known as 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃]. The inactive form of vitamin D, 25(OH)D₃, is used as an indicator of circulating vitamin D level in an individual. However, effectiveness depends on the potential of a cell to contain the metabolizing enzyme, 1 α -hydroxylase (CYP27B1), to convert inactive 25(OH)D₃ into active 1,25(OH)₂D₃ [144,145]. Upregulation of CYP27B1 has been seen in DCs upon maturation with LPS or with T cell in an immune synapse [146]. Involvement of vitamin D binding protein (carrier protein), vitamin D receptor (VDR), and CYP24A1 (catabolizing enzyme) are also important in maintaining the effects of vitamin D in a particular cell [144,147]. Recently, it was demonstrated that through vitamin D binding protein, level of free 25(OH)D₃ available to DCs governs the balance between allergic and tolerogenic response to allergens [146]. Increase in intracellular vitamin D levels drive DCs to reduce expression of co-stimulatory molecules including CD80, CD83, CD86, and HLA-DR [145]. In addition, it also decreases the levels of TNF α and IL12 [145,148]. This effect may be correlated with reduced nuclear transport of activated RelA, an NF- κ B subunit through importin- α 3 (nuclear transporter) due to a decreased expression of importin α 3 under low levels of vitamin D [144].

9.8 Signaling pathways to induce tolerance in DCs and activate Tregs

With many interactions known to stimulate DCs to induce tolerance and activate Tregs, the nature of precise signaling events remains obscure. Along with vitamin D, vitamin A also has some role in immunomodulation. DCs express alcohol dehydrogenase (ADH) to oxidize vitamin A to retinaldehyde, which then is converted to retinoic acid in the presence of retinal dehydrogenase (RALDH) [31]. Retinoic acid is a known inducer of Foxp3 Tregs [31]. Unlike ADH, only a specific set of DCs (mostly CD103⁺) express RALDH. Retinoic acid increases the expression of RALDH in DCs in an autocrine manner through RAR/RXR signaling. In addition, certain microbial stimuli have been shown to induce RALDH expression through TLR-ERK pathway to induce tolerance via retinoic acid [31]. Intestinal DCs deficient in β -catenin has low levels of RALDH and reduced IL-10 production to assist Th2 polarization [31].

Wnt ligands bind to frizzled receptor to cause accumulation of β -catenin in the cytoplasm and translocation to the nucleus, which in turn regulates a number of genes to induce tolerance. Thus, activation of β -catenin signaling programs DCs to a tolerogenic type and helps in Treg production [149]. Experiments with monocyte-derived DCs have revealed that TAM receptor (MerTK, Tyro3 and Axl) activation can lead to an upregulation in the expression of suppressor of cytokine signaling 1 (SOCS1) and SOCS3 via IFNR/STAT1 signaling. This in turn causes suppression of TLR-mediated inflammatory signals, and supports Foxp3 Tregs to induce tolerance [31].

Ig-like receptors ILT3 and ILT4 can be activated by vitamin D, and immunosuppressant cytokines IDO and IL-10. ILT3 activation leads to phosphorylation of phosphatases, SHP-1 and SHIP-1, to cause inhibition of NF- κ B and p38/MAPK signaling pathways [31]. This results in the development of tolerogenic DCs that assist Tregs to induce tolerance.

10. Expert commentary & five-year review

Considering the complex immune response to an allergen in atopic individuals involving multiple cells and multifarious signaling events, treatment is less likely to be a one shot formula. To come up with a viable clinical solution, it is critical to look deeper into the mechanism of allergic sensitization and the development of the airway inflammation. The first view in this regard focuses on the genetics, which determines the demonstration of atopy in individuals. But, epigenetic modifications due to environmental exposure bring intricacy to the development of allergic phenotype. Additionally, microenvironment rich in microbiome may modulate the immune response in different directions. With so many variables, the best approach is to understand the complex interactions and interplay of intra- and extra-cellular molecules, and target the hyperreactive pathways for a therapeutic application in allergic asthma. Dendritic cells, being the sentinel APCs, are principal initiators in an immune response. It would be critical to better understand the underlying mechanisms and the molecules involved in their migration to the lymph nodes to induce immune response. Thus, targeting the molecules that regulate the differentiation, maturation and migration of dendritic cell phenotypes with approaches discussed in this review at multiple stages in a holistic modus could be of potential therapeutic application in allergic asthma. However, careful consideration of the underlying signaling pathways must be given while designing such therapies. Modulation of surface receptors on DCs to mitigate allergic conditions could also lead to a compromised immunity against various pathogens.

11. Conclusion

In this article, multiple aspects of DC biology and development of asthma have been reviewed. Our attempt to tie DC phenotype change to the development of immunogenic or tolerogenic responses opens a vast area to explore into the modulation of its phenotype to regulate allergic asthma. Understanding the involvement of numerous co-stimulatory molecules on DCs with different immune and structural cells give us an opportunity to modify the immune response with monoclonal antibodies and small RNAs. However, such therapeutic approach should always be cautioned as these molecules play an important role in host defense against pathogens. Interaction of various immune cells with DCs may also result in particular immune response as various cytokines released by them have potential to drive them towards immunogenic or tolerogenic response. Also, further knowledge of microbiome is critical for therapeutic application. With understanding of various microorganisms and their immune response in our body enables us to take this approach from bench-to-bedside. Indeed, a number of commensal species inhabit our body and induce tolerance. Similarly, some microbial infections predispose us to an immunogenic response. Switching the immunogenic 'bad' microbiota with tolerogenic 'good' microbiota could be a way to control allergic asthma. However, recognition of these microbes by surface molecules on DCs adds another level of understanding to this complex repertoire. Different climatic conditions including altitude, temperature, humidity and geographical location give rise to different allergens in the environment, based on genetic or epigenetic modifications of a person, have their effect. Additionally, allergenicity of an allergen can be related to the modification of the allergen molecule with carbohydrate, lipid or protein molecules. Knowledge of exact modifications that turn the innocuous molecules to allergens, could give

us opportunity to reduce the possibility of an inflammatory response. Dietary modifications could also reduce allergenicity through vitamin A and D (retinoic acid and 25(OH)D₃), as discussed in detail in our review. Better understanding of the underlying cellular and molecular pathways involved in the induction of tolerance would allow development of promising therapies against allergic asthma.

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Key Issues

- Phenotype of dendritic cells may determine the type of immune reaction generated in response to allergen.
- Genetic, epigenetic and environmental factors dictate differentiation and maturation of a specific dendritic cell phenotype.
- Different types of antigens are recognized through pattern recognition receptors on DCs for immune precipitation to allergy or tolerance.
- Local microbiome can change the immune polarization to atopic or tolerogenic response through DCs.
- Environmental exposure of pollutants and reactive oxygen species, including free radicals, may modulate the activation of dendritic cells to generate an allergic response on exposure to allergens.
- Target therapy with tailored allergens and microorganisms, recognized by dendritic cells to favor Th1 or Tregs, can ameliorate allergic asthma.

	Mouse Lung DCs	Human Lung DCs
<p>Myeloid DC (CD103⁺/BDCA3)</p>	<p>Location: Above the basement membrane of trachea and large airways</p> <p>Function: Take up the antigens and transfer them to the lymph node DCs</p> <p>Markers: CD103⁺, CD11c⁺ (High), CD11b⁺ (Low), CD207 (Langerin)</p>	<p>Location: Precise location not known</p> <p>Function: Take up the antigens and present them to naïve T-cells</p> <p>Markers: CD11c⁺, BDCA3 (CD141), HLA-DR, TLR3/8</p>
<p>Myeloid DC (CD103⁻/BDCA1)</p>	<p>Location: Underneath the basement membrane airway submucosa</p> <p>Function: Take up the antigens and present them to naïve T-cells. Produce TNF-α, CCL-17 and CCL22 to recruit Th2 cells to lungs</p> <p>Markers: CD103⁻, CD11c⁺ (Low), CD11b⁺ (High)</p>	<p>Location: Precise location not known</p> <p>Function: Take up the antigens and present them to naïve T-cells</p> <p>Markers: CD11c⁺, BDCA1 (CD1c), HLA-DR</p>
<p>Plasmacytoid DC</p>	<p>Location: Under the basement membrane of trachea and alveolar septum</p> <p>Function: Take up the antigens and secrete massive amounts of IFN-α. Block Th2 response through Foxp3⁺ Tregs and induce tolerance</p> <p>Markers: B220, Ly6C, Siglec-H, CCR9 CXCR3/4, TLR9, CD8α⁻β⁻/CD8α⁺β⁺</p>	<p>Location: Precise location not known</p> <p>Function: Take up the antigens and present them to naïve T-cells. Block Th2 response through Foxp3⁺ Tregs and induce tolerance</p> <p>Markers: CD11c⁻, BDCA2 (CD303), BDCA4 (CD304), CD123, ILT7 (CD85g), HLA-DR, TLR7/9, CXCR3/4</p>

Figure 1. Classification of mouse and human lung DCs
Lung DCs in mouse and human are characterized by the presence of different epitopes. Their location and function vary depending upon their respective protein expression.

Figure 2. Maturation of DCs

Dendritic cells express different chemokine receptors and are responsive to different chemokines at different stages of their maturation. The progenitor DCs mostly express markers which allow them to migrate out of bone marrow to an environment where they may differentiate. Whereas immature DCs express proteins which assist them to interact with antigens. Mature DCs on the other hand express markers to migrate to lymph nodes to interact with T-lymphocytes and transduce molecular signal for a particular immune precipitation.

Figure 3. Epithelium breach and polarization of Th2 response

When proteases of allergens break the barrier of epithelial cells, they start secreting cytokines and chemokines to call for DCs to sample these allergens. TSLP and IL-33 released from epithelial cells mature the DC towards an atopic phenotype (mDCs). mDCs take up the allergens and migrate to the draining lymph node to present the processed allergen to T-lymphocytes. Proper cytokine milieu results in polarization of Th2 cells and allergic response.

Figure 4. Dendritic cell interaction with T-lymphocytes

Depending upon the antigen encountered and cytokine presence, T-lymphocytes may differentiate into Th1, Th2, Th9, Th17, Th22 or Tregs for appropriate immune response. The dendritic cell – T-lymphocyte interaction is dependent on many stimulatory and co-stimulatory molecules to exert various physiological effect.

Figure 5. Dendritic cell-driven B-lymphocyte response

Dendritic cell interaction with T-lymphocytes produce different cytokines. Memory B-lymphocytes imprint a memory for a naïve antigen to respond to it more effectively, when the body encounters it again. Effector B-lymphocytes could be of regulatory or immunogenic type. Regulatory B-lymphocytes, B10 develops under the environment rich in IL-10 and IL-21 to induce tolerance. On the other hand, immunogenic B-lymphocytes undergo class switching in presence of IL-4, IL-9 and IL-13, and differentiate into plasma cells to release IgE.

Figure 6. Effect of DCs on other immune cells

Cytokines and chemical mediators produced by epithelium, DCs and T-lymphocytes control the effector immune cells, including, eosinophils, neutrophils, mast cells and basophils to promote inflammation and exacerbation of asthma.

Figure 7. Bacteria-induced tolerance in DCs

Gut microbiome contain bacteria which may try to evade the immune system by reprogramming DCs and the immune responses in host. *H. pylori* produces HP-NAP, GGT, and VacA to polarize Th1 or Treg cells through PRRs. Production of Tregs results in a tolerogenic response in the host. These Tregs travel to the lung draining lymph nodes and protects the host from allergen-mediated allergic asthma by blocking Th2 cells.