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REVIEW ARTICLE

Alarming Dendritic Cells for Allergic Sensitization

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ABSTRACT

Allergic patients mount a Th2 response to common allergens, like house dust mite (HDM), pollens, molds and animal dander. Most inhaled antigens are immunologically inert, however if these antigens are accompanied by microbial or endogenous danger patterns (alarmins), they can be recognized by inflammatory cells. Dendritic cells are the most potent antigen presenting cells, which express a wide variety of receptors on their cell surface, recognizing these microbial patterns, damage induced molecules and cytokines. Dendritic cells become reporters of the microenvironment if exposed to the allergen, subsequently migrating to the draining lymph nodes where they activate naïve T lymphocytes. Dendritic cells could also be indirectly activated by epithelial cells, which express various receptors and secrete a variety of cytokines early after allergen exposure. Upon HDM exposure these cells secrete chemokines to attract monocytes and immature dendritic cells, and GM-CSF, TSLP and IL-33 to activate dendritic cells, mast cells and basophils. Danger signals which alert dendritic cells and epithelial cells comprise many proteins and molecules, contributing to an enhanced immune response to inhaled allergens. This review focuses on the role of dendritic cells and alarmins in the sensitization to inhaled allergens in allergic asthma.

KEY WORDS

alarmins, asthma, danger signals, dendritic cells, IL-1

ALLERGIC ASTHMA

House dust mite, pollens, molds, animal dander are common allergens that cause chronic illness like allergic rhinitis, asthma, and atopic eczema. These diseases are increasing in prevalence. Several risk factors for becoming allergic have been identified and include family history, allergen exposure levels, lifestyle (e.g. inner city versus rural living), infection history, cigarette smoking and environmental pollution.[1] Allergic patients mount a T helper 2 (Th_2) type response to allergens, which is measured clinically by allergen-specific serum IgE levels and a positive skin-prick test. Allergic asthma is characterized by attacks of wheezing and breathlessness due to bronchoconstriction, mucus secretion, airway hyper responsiveness to non-specific stimuli, airway wall thickening and eosinophilic and $CD4^+$ Th_2 cell influx in the airway wall. Recruited inflammatory cells in asthmatics as well as in mouse models of the disease produce various cytokines like interleukin (IL)-4, IL-5 and IL-13.[2] In experimental settings, blocking these cytokines with specific antibodies revealed that every single cytokine contributes to one of the features of asthma.[3,4] However, Th_2 cells do not react directly to inhaled antigen, as their T cell receptor can only recognize antigens that are processed into peptides for presentation on major histocompatibility complex (MHC) molecules.[5] One of the most important antigen presenting cells is the dendritic cell (DC), a cell type previously reported to be important in allergic asthma.[6] This review focuses on the role of danger factors in initiating an immune response to allergens mainly through targeting of antigen presenting dendritic cells.

SENSITIZATION INDUCED BY DENDRITIC CELLS

Naïve $CD4^+$ T cells only differentiate into Th_2 cells if inhaled allergens are presented in MHC class II complex molecules.[5] DCs are considered to be the most powerful antigen presenting cells (APCs) and play a

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Table 1 Examples of pathogen associated molecular pattern (PAMP) and damage associated molecular pattern (DAMP) receptors expressed on dendritic cells and lung epithelial cells

	Dendritic cells	Lung epithelial cells
PAMP receptors		
Toll like receptors	TLR1-10	TLR1-6
Intracellular receptors	NLRs, TLR 3, 7, 9	NLRs, TLR 9
C-type lectin receptors	Dectin-1, -2, DEC205, BDCA-2 Macrophage mannose receptor	
RIG-I-like receptors	MDA5, LGP2	MDA5
Protease activated receptors	PAR 1-3	PAR 1-4
DAMP receptors		
Complement receptors	hCR1, hCR2, hCR3, mC3aR, mC5aR	mC3aR, mC5aR
Prostanoid receptors	DP1, EP2, EP4, IP	
Neuropeptide receptors	NK1, CGRPR	
Purinergic receptors	P2X, P2Y	P2X, P2Y
HMGB1 receptor	RAGE	RAGE
Heat shock protein receptors	CD14, CD36, CD91	

central role in the initiation of primary immune responses,[7,8] and in the enhancement of secondary immune responses.[9,10] Under basal conditions, DCs can be found throughout the conducting airways, lung interstitium and vasculature.[6] Inhaled allergens can be recognized by airway DCs lining the epithelial layer. They are able to "fish" and endocytose antigens from the airway lumen. This was initially shown in the gut where intravital imaging DCs in MHCII-GFP knock-in mice were able to extend protrusions through the epithelial layer and probed the lumen for antigens.[11] We recently confirmed this scenario in the airways, using tracheal explants from the same mouse strain. However, in the trachea DCs showed the capacity to move in the upper layers of the pseudostratified epithelium to reach the airway lumen (unpublished data and[12]). Airway DCs which have captured antigen migrate to the T cell area in the draining mediastinal lymph nodes (MLN). On their way to the MLN, DCs process these captured antigens, display them as peptides on MHC class II molecules and subsequently present them to naïve CD4 Th cells in the paracortex of the draining node.[13] During this process, DCs acquire a mature phenotype, meaning that they upregulate their expression of costimulatory molecules necessary for optimal naïve T cell activation, and they acquire the capacity to stimulate an effector response.[14-18]

The DCs therefore become a reporter of their earlier microenvironment and have the potential to induce a polarized Th_1, Th_2, Th_{17} or regulatory T cell (Treg) type of response.[7,19] Many factors are determining the outcome of the DC-induced T-helper cell polarization, such as the type of antigen captured, the presence of microbial patterns or endogenous danger signals (also called alarmins) or the route of exposure and the genetic background of the host.[15,20,21]

ACTIVATION OF DENDRITIC CELLS

DCs do not initiate an immune response to inhaled antigen randomly. Most inhaled particles are immunologically inert, and therefore the usual outcome of their inhalation is tolerance and inflammation does not develop upon chronic exposure to the same antigens. In the absence of inflammatory triggers, DCs that take up these harmless antigens do not properly express costimulatory molecules, consequently fail to reach the threshold necessary to induce T cell activation and instead induce an abortive T cell response. DCs express a wide variety of receptors recognizing a wide array of antigens or contaminants in soluble antigens, like Toll-like receptors (TLR), cytokine receptors, NOD-like receptors, protease activated receptors (PAR) and C-type lectin receptors (Table 1). Triggering of these receptors activates an intracellular signaling cascade and influences the phenotype and functions of DCs.[22,23] Additionally, the dose of inhaled allergen is also playing a role in the type of immune response generated. As a result, when high amounts of antigen are administered the majority of antigen reactive T cells are deleted after dividing. This process is referred to as deletional tolerance. Animal studies have shed some light on how tolerogenic responses are initiated and regulated. In the lung, tolerance is a feature of DCs present in steady state conditions and is shown best for the model antigen ovalbumin (OVA). In the most commonly used models to induce allergic asthma, OVA is administered either in conjunction with an adjuvant, such as aluminium hydroxide or by repetitive injections at a low concentration.[24] After challenges with OVA aerosol via the lung or droplet aspiration via the nose, tissue eosinophilia occurs, and infiltrates of inflammatory cells develop around the bronchi. However,

when OVA is administered without an adjuvant, mice become tolerant to this antigen and the development of airway inflammation is prevented, this is a feature of true immunologic tolerance.[25,26]

In mice DCs were first described as CD11c and MHCII positive cells. However, it has become clearer that a broad range of markers are needed to divide DCs into various subsets, that possess different functions.[27,28] Recent studies from our group have demonstrated that tolerance is induced by particular DC subsets. Indeed, conventional DCs (cDCs) were shown to be important for inducing Th_2 responses in the lung, whereas plasmacytoid DCs (pDCs) were able to suppress T cell effector generation and to promote tolerance to inhaled antigens.[25] Interestingly, we have shown that pDCs anti-inflammatory irrespectively of their maturation state and their protective effects are mediated through programmed death (PD)-1/PD ligand 1 interactions.[28]

How sensitization to natural allergens occurs is still under study. DCs will only start a T helper response if there is some sort of adjuvant activity on board at the time of exposure to the allergen. This activity provided by the presence of pathogen associated molecular patterns (PAMPs), damage associated molecular patterns (DAMPs) and cytokines released upon cell activation, necrosis or oxidative stress (e.g. cigarette smoking, ozone exposure, diesel particles). This adjuvant signal can also be found in the allergen itself. Indeed, house dust mite (HDM), cockroach and many other allergens have proteolytic enzymes that can directly activate DCs or epithelial cells, and in this way promote Th_2 sensitization.[29,30]

PAMPs STIMULATE DC INDUCED SENSITIZATION

Charles Janeway proposed 20 years ago that the immune system cannot recognize every single unique feature of every microbial pathogen, since the required information is enormous and would rapidly become out-of-date because of selection pressure and spontaneous mutations.[31,32] Multicellular organisms have developed mechanisms to counteract life-threatening events such as infections and tissue injury, as well as to restore tissue homeostasis. Immune cells recognize broad molecular patterns rather than detailed features of specific pathogens. PAMPs comprise molecular structures found in microbes but not in host tissues. In the setting of infection, microorganisms initiate a series of host events promoted by their derived products. PAMPs are recognized by membrane-bound, cytoplasmic or endosomal pattern-recognition receptors (PRRs), including the TLRs, NOD-like receptors (NLRs) and RIG-like receptors (RLRs). Signalling through TLRs strongly activates DCs to upregulate costimulatory molecules (CD80 and CD86) and to produce pro-inflammatory cytokines (TNFα, IL-1, IL-6, and IL-12).[33,34] PRRs 'sense' bacterial products and activate intracellular cascades that lead to an inflammatory response.[35,36] PAMPs, sensed by host inflammatory cells early during infection, are potent stimuli for innate immunity and are often referred to as 'exogenous danger signals'. In allergic setting, antigens such as the experimental allergen OVA, do not have any intrinsic activating properties, like HDM. For these antigens, additional signals from contaminating molecules (like LPS[33]) or environmental exposures (respiratory viruses, air pollution or cigarette smoke) might pull the trigger on DC activation.[37,38]

The existence of a TLR-dependent mode of Th_2 generation is supported by Eisenbarth *et al.* Using a murine model of asthma, characterized by airway inflammation, eosinophilia, and mucus secretion in response to intranasal exposure to antigen, they found that the dose of LPS that is contaminating most commercially available batches of OVA used in mouse models of asthma regulates the induction of Th_2 versus Th_1 responses.[33] Intranasally administered antigen required a concomitant low-dose LPS signaling through TLR4 to induce allergic pulmonary Th_2 responses. MyD88, a common TLR adaptor molecule required for signalling, is an essential innate component in the induction of TLR4-dependent Th_2 responses to antigens, by inducing the expression of inflammatory cytokines like IL-6, IL-12 and TNF-α.[33,39-41] The fact that endotoxin in experimental mice models promotes allergic sensitization via effects on DCs might have direct clinical relevance, since most inhaled allergens, such as allergens derived from cockroaches and house-dust mites are contaminated with LPS. We have recently shown that Th_2 responses induced by HDM were mediated through TLR4.[12] Surprisingly however, the endotoxin contamination of HDM extracts used to induce allergic asthma in this study was in the subnanogram range, which is much lower than the dose described to promote Th_2 responses to OVA.[12] Therefore another molecule was expected to contribute to TLR4 signalling by HDM. TLR4 signalling by LPS leading to NF-κB activation will only take place in presence of extracellular proteins as CD14 and myeloid differentiation protein 2 (MD2). CD14 helps to form LPS-MD2-TLR4 complex and therefore signalling via the TLR4 receptor.[42] Analysis of the main HDM-allergen Der p2 shows functional homology to MD2, which facilitates TLR4 signalling and thus NF-κB activation even in absence of MD2.[43] These experimental and clinical observations suggest that direct or indirect activation of DCs by PAMPs (like TLR agonists) is a critical component of sensitization to some allergens.

DAMPs STIMULATE DC-INDUCED SENSITIZATION

Oxidative stress or tissue damage can trigger inflammation even in the absence of pathogens. Inflamma-

tion triggered by tissue damage in the absence of infection is often referred to as sterile inflammatory response. It is now understood that immune cells react to molecules released by injured or necrotic, but not apoptotic, cells.[44] These molecules alert our body defence system of an impending danger, and are therefore also referred to as 'alarmins', 'endogenous danger signals' or DAMPs.[45] These DAMP molecules contribute to the induction of inflammation by recruitment of innate inflammatory cells and interact with PRRs, shared with the exogenous danger signals. The actual repertoire of DAMPs in damaged tissues can vary greatly depending on the type of cell (epithelial or mesenchymal) and injured tissue. Heat shock proteins (HSP), high mobility group box 1 (HMGB1) protein, uric acid and adenosine triphosphate (ATP) are a few examples. We have recently summarized the contribution of ATP to allergic sensitization.[46,47] Many intracellular proteins secreted actively through nonclassical pathways and endowed with inflammatory activity so-called leaderless secretory proteins (LSPs) can be released by dying cells and behave as DAMPs. HMGB1 is a prototypical LSP that is passively released by injured or necrotic cells, or by immune cell responses to endotoxin, promoting tissue inflammation.[48] A study on PBMCs however showed that HMGB1 alone cannot induce detectable levels of IL-6, except after co-administration of LPS, CPG-ODN, PAM3CSK4 or IL-1β.[49] Compelling evidence suggests that a tight collaboration between PAMPs and DAMPs is needed to start an immune response to allergens.[50,51] More research nowadays focuses on how the immune system regulates danger. In a model of liver necrosis, Chen *et al.* showed that CD24 partners with Siglec-G (Siglec-10 in human) to negatively regulate the immune response to proteins released by damaged cells, but not ligands of microbial origin (like LPS and Poly-IC). CD24 is a membrane protein expressed by immune and stem cells and Siglec-G is a c-type lectin. CD24 does not contain a cytosolic domain, and signals through Siglec-G, which contains an immune receptor tyrosine-based inhibitory motif (ITIM). ITIMs are cytosolic domains that reduce activation of NF-κB. CD24 and siglec-G deficient DCs showed an increased secretion of IL-6 and TNF-a in response to HMGB1, HSP-70 and -90 as compared to wild-type DCs.[52] In contrast to necrotic cells, apoptotic cells retain HMGB1 in their nuclei and so do not activate inflammation.[53] All these data together suggest that there are some similarities between infectious and sterile inflammation, since PAMPs and DAMPs seem to share many receptors.[36]

ALUM-INDUCED Th_2 RESPONSES

One recent illustration of the potential implication of endogenous danger signals to the process of allergic sensitization comes from our studies on the mechanism of action of alum adjuvant. Alum is used in mouse models of asthma as a prototypical Th_2 adjuvant, whose mechanism of action is poorly understood. When added to DCs *in vitro*, alum poorly activates APC function with the notable exception of IL-1β induction.[54] *In vivo* however alum strongly recruits and stimulates inflammatory DCs and boosts their potential to induce Th_2 responses, associated with production of bio-active IL-1β.[55]

We found that alum induces the release of uric acid, an endogenous danger signal released by dying cells or cells exposed to oxidative stress.[56-58] Uric acid is known to induce the release of IL-1β, to promote Th_2 polarizing responses by DCs and to induce IgG_1 responses.[59] The activation of IL-1β release requires the presence of a TLR agonist, IL-1 receptor I or TNF receptor I/II signalling acting on APCs to promote activation of NF-κB and transcription and translation of pro-IL-1β.[60] Subsequently pro-IL-1β is cleaved by caspase-1 in the cytoplasm, whose activation in turn depends on triggering of the NLR NALP3 (also known as cryopyrin) via endogenous danger signals, which activates caspase-1.[55,61,62] Recently, it was shown that NALP3 activation occurs in cells undergoing necrosis *in vitro* and *in vivo*, resulting in the production of mature IL-1β.[63] In addition, extracellular ATP has been known for years to activate caspase-1, and several studies have demonstrated the requirement of $P2X_7$ receptors (in a complex pannexin-1) for ATP-induced caspase-1 activation and subsequent IL-1β maturation.[61,64,65] Double stranded DNA which is released by necrotic cells, is also potently able to induce caspase-1 activation as soon as it is cytosolic. Recently PYHIN (pyrin and HIN domain-containing protein) family member absent in melanoma 2 (AIM2) is described as a receptor for cytosolic DNA to regulate caspase-1 activation via NALP3.[66]

It therefore comes as no surprise that mice deficient in NALP3, ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) and caspase-1 have a defect in crystal-induced IL-1β secretion and fail to mount Th_2 mediated inflammation *in vitro*.[55,67] This finding however has also been debated and it seems that NALP3 inflammasome activity is mainly necessary at the start of the alum induced Th_2 response.[68,69] There is indeed evidence that alum directly triggers the formation of the NALP3 inflammasome in a process that also requires the ASC protein.[55,67] However, *in vivo*, uric acid-mediated Th_2 cell development is an additional trigger. Certainly uric acid promotes the development of Th_2 responses when added to DCs *in vitro*.[55,59,67] Cleaving of pro-IL-1β into its bio-active form does not occur only intracellularly. Neutrophils which are attracted to inflammatory sites, secrete proteinase-3, an enzyme which is able to cleave pro-IL-1β extracellularly. Other proteases such as caspase-11, elastase, matrix metalloproteases, granzyme A and the mast cell chymase also generate active IL-1β.[70] Therefore

not all IL-1β induced responses are necessarily NALP3 dependent.

ROLE OF IL-1 β IN INFLAMMATION

Another cell type recruited during inflammation and found to be a dominant source of IL-1β is the monocyte. Whereas macrophages and DCs need a two way signalling to process pro-IL-1β into bio-active IL-1β, human monocytes are able to secrete bio-active IL-1β upon only a TLR stimulus.[71] However if these monocytes differentiate into other cell types, they loose this ability. Monocytes constitutively express active caspase-1, likely due to the fact that these cells are able to release endogenous ATP, therefore providing their own 'second signal' to release bio-active IL-1β, since it was shown to be dependent on ASC and NALP3.[71,72] The proinflammatory IL-1 cytokine family consists of 11 members, the best known being IL-1α, IL-1β and IL-1 receptor antagonist (IL-1Ra). All types can bind to IL-1 receptors I and II, whereas IL-1Ra and IL-1α/β compete for binding to these receptors. In healthy individuals there is a balance between IL-1Ra and IL-1α/β, IL-1Ra (Anakinra) has appeared very useful to treat patients with inflammatory disorders such as gout and rheumatoid arthritis.[73] Only signalling via IL-1RI results in NF-κB activation, since soluble IL-1RII is able to block inflammatory functions of IL-1.[74] Previous experiments using OVA alum sensitization as a model for asthma in mice deficient of IL-1α/β did not result in any differences in airway hyperresponsiveness (AHR) compared to wild-type mice. However, in a milder model by repetitive OVA injections intraperitoneally, a reduction in AHR in mice deficient of IL-1α/β was observed. In addition, mice deficient for IL-1Ra showed an increase in the influx of DCs to the lung, in AHR and in the levels of specific IgE and Th_2 responses.[75] Mice lacking IL-1RI had reduced features of asthma when the mild model was used, but not when alum adjuvant was added to sensitize the mice.[76] In another asthma model using toluene diisocyanate, AHR and specific IgG_1 levels in serum were partly reduced in mice treated with neutralizing antibodies to IL-1β, but this was not observed in mice treated with antibodies against IL-1α.[77] These data together suggest a role for IL-1β in Th_2 sensitization in mild models of asthma.

In clinical settings, levels of IL-1β are found to be increased in broncho-alveolar lavage taken from challenged asthmatics and IL-1β levels in serum were proposed to be useful as a biomarker during the symptomatic phase to distinguish allergic asthmatics form non-allergic asthmatics and COPD patients.[78,79] The main inflammatory cell types secreting IL-1β were found to be monocytes and dendritic cells.[78] A study of cell necrosis in mice revealed different chemotactic pathways for monocytes and neutrophils upon sterile inflammation. Injection of dead cells in IL-1R and MyD88 deficient mice resulted in a modest reduction of monocytic influx, whereas neutrophils numbers were significantly reduced compared to wild type mice. Therefore attraction of neutrophils seems to be regulated by IL-1β in sterile inflammation.[80] By using autoimmune prone NOD mice and IL-1Ra deficient mice O'Sullivan *et al*. showed that IL-1β drives proliferation and cytokine production by $CD4^+CD25^+$ effector and memory T cells, and in addition attenuates functions of regulatory T cells, and allows escape of autoreactive effector Tcells from suppression.[81] Taking together, these data suggest an important role for IL-1β in recruiting and regulating inflammatory cell functions, but the precise significance of these findings remain unknown.

ROLE OF IL-33 IN INFLAMMATION

A new member of the IL-1 cytokine family is recently identified, namely IL-33. This cytokine possesses a dual function like IL-1α and HMGB1, as a nuclear binding factor and it acts as a cytokine via ST2 receptor, which is expressed by many inflammatory cells.[82] IL-33 is released during inflammatory events and promotes Th_2 development and stimulates DCs to induce Th_2 responses.[6,83,84] Intratracheal administration of IL-33 induces an influx of eosinophils in the lung and increased immunoglobulin serumlevels.[82] Human eosinophils were shown to become activated by binding to the ST2 receptor *in vitro*.[85] In addition, in mice treated with an antibody against IL-33 in a mild asthma model, features of airway inflammation were inhibited.[86] IL-33 was found to be elevated in biopsies from asthmatics compared to control subjects.[87] This cytokine is also released by lung epithelial cells upon HDM challenge and levels are found to correlate with AHR.[12,88]

Recently this cytokine was found to be cleaved by caspase-1 as well as its family members IL-1β and IL-18. However, the cleaved protein was not able to bind to the ST2 receptor and induce signalling, unlike the intact IL-33.[89] These data together suggest a role for IL-33 in allergic asthma.

EPITHELIAL CELLS AS A SOURCE OF ALARMING CYTOKINES

Allergens in HDM and cockroach extracts possess protease activity of which the most studied is Der p1 in HDM. This peptide is shown to break intercellular tight junctions by cleaving occludin and claudin-1. Therefore epithelial permeability is increased allowing Der p1 to cross the epithelial barrier and to come into contact with DCs.[90] *In vitro* studies on human cell lines revealed the importance of TLRs and NOD receptors on epithelial cells. Lung epithelial cells for example express a wide variety of TLRs (TLR1 to 6 being the most abundantly expressed), and also express PARs which are involved in the recognition of allergens with enzymatic activity.[91] Recently it has shown by our group that TLR4 expression on struc-

tural cells is necessary for the development of HDM-induced asthma.[12] Protease activated receptors can be activated by inflammatory proteases, like tryptase and chymase, which are released upon activation of mast cells and allergens such as HDM and cockroach. PAR1-4 are expressed on epithelial cells, but only PAR-1, -2 and -4 activation lead to cytokine secretion.[92] PAR-2 expression is also found to be upregulated in lung and nose epithelial cells of asthmatics.[93] How epithelial cells control Th_2 sensitization and the subsequent development of allergic asthma remains unclear, but it might involve several inflammatory cytokines released very early after HDM exposure. As an example, the inhalation of HDM induces the release of GM-CSF, TSLP, IL-25 and IL-33 by epithelial cells within hours following HDM administration. GM-CSF is a growth factor that promotes DC differentiation and their maturation.[94] In previous studies the blockade of GM-CSF has been shown to prevent HDM-driven asthma.[95] TSLP is produced by epithelial cells, mast cells and basophils upon HDM challenge. This cytokine directly activates DCs to prime naïve $CD4^+$ Tcells.[96-98] IL-33 and IL-25 (IL-17E) are also cytokines released in the lung upon HDM exposure, by epithelial cells, basophils and eosinophils.[6,99] These cytokines are shown to play a role in the initiation of Th_2 differentiation and in the maintenance and restimulation of Th_2 memory cells.[99,100] In addition, it might be that the recruitment of specific inflammatory cell types to the airways by chemokines is another way of contributing to Th_2 sensitization. *In vitro* and *in vivo* studies have shown that exposure of airway epithelium to HDM resulted in the rapid secretion of CCL20, a chemokine attractant for immature DCs.[100] This CCL20 release showed to be protease-, TLR2- and TLR4-independent but relied on beta-glucan moieties within the HDM extract. Treatment of HDM with the enzyme beta-glucanase to break these moieties significantly reduces subsequent chemokine secretion by epithelial cells.[100] Moreover, HDM exposure is also accompanied by an increased production of CCL2, a chemoattractant for monocytes.[12] These recruited CCR2+ monocytes are the precursors for inflammatory DCs and it is very tempting to speculate that these cells are responsible for the sensitization to HDM.

CONCLUSION

The term alarmins or danger molecules covers a wide range of cytokines, molecules and proteins, which induce activation of the immune system. Allergens, either accompanied with danger signals or displaying proteolytic activity, are able to affect a broad range of inflammatory cells, as well as structural cells. Allergens containing proteases are able to activate dendritic cells directly or indirectly by stimulating epithelial cells. Further research on how DCs are instructed via their PAMP and DAMP receptors might lead to the discovery of new targets for therapy.

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