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Review

Inflammasome–IL-1–Th17 response in allergic lung inflammation

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Allergic asthma has increased dramatically in prevalence and severity over the last three decades. Both clinical and experimental data support an important role of Th2 cell response in the allergic response. Recent investigations revealed that airway exposure to allergen in sensitized individuals causes the release of ATP and uric acid, activating the NLRP3 inflammasome complex and cleaving pro-IL-1β to mature IL-1β through caspase-1. The production of pro-IL-1β requires a toll-like receptor (TLR) 4 signal which is provided by the allergen. IL-1β creates a pro-inflammatory milieu with the production of IL-6 and chemokines which mobilize neutrophils and enhance Th17 cell differentiation in the lung. Here, we review our results showing that NLRP3 inflammasome activation is required to develop allergic airway inflammation in mice and that IL-17 and IL-22 production by Th17 cells plays a critical role in established asthma. Therefore, inflammasome activation leading to IL-1β production contributes to the control of allergic asthma by enhancing Th17 cell differentiation.

Keywords: asthma, NLRP3 inflammasome, IL-1, Th17 cells, IL-17, IL-22

Introduction

Allergic asthma is one of the most common chronic respiratory diseases in developed countries. It is characterized by acute and chronic inflammation of the airways in patients with a prevailing Th2 response characterized by expression of IL-4, IL-5, IL-13, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Allergic lung inflammation can be modeled in experimental animals by immunization and challenge with a variety of protein antigens (Wills-Karp, 1999). The main features of allergic inflammation are airway infiltration by eosinophils, Th2 lymphocytes, and mast cells, mucus overproduction, and smooth muscle cell proliferation. Hyperreactivity to cholinergic stimuli combined with increased mucus causes constriction of the small airways which may cause respiratory failure with hypoxia and death. The critical role of dendritic cell (DC) priming and memory Th2 response to inhaled allergen are well established (Lambrecht and Hammad, 2003; Hammad and Lambrecht, 2008). More recently, the role of structural cells in asthma pathogenesis has been highlighted (Eisenbarth et al., 2002; Hammad et al., 2009; Kouzaki et al., 2009). Basophils and mast cells play a central role during the effector phase, since allergen re-exposure leads to cross-linking of specific IgE antibody on these cells followed by degranulation and release of histamine and several other mediators that cause the acute symptoms of asthma (Wills-Karp, 1999). Using a high affinity histamine scavenger protein from arthropods, we confirmed a critical role of histamine in acute asthma (Couillin et al., 2004). However, other cells including eosinophils, B cells, NKT cells, and many inflammatory mediators are involved in the pathogenesis of asthma. We recently confirmed a role for TNF in allergic asthma and demonstrated the beneficial effect of dominant-negative TNF treatment in experimental asthma (Maillet et al., 2011). Further, the role of innate immune cells and pattern recognition receptors will be addressed in this review. Finally, Th17 cell functions in allergic asthma will be discussed.

Activation of toll-like receptors and lung inflammation

The lung is continuously exposed to environmental agents that are normally cleared by mucociliary transport and phagocytosed by alveolar macrophages that neutralize antigens. Inhaled microbial products can be sensed by pattern recognition receptor of the innate immune system such as toll-like receptors (TLRs) on epithelial cells, DCs, and monocytes that leads to cytokine and chemokine production and immune cell recruitment (Akira et al., 2006; Beutler et al., 2006). Microbial agonists may be of bacterial, viral, fungal, and parasitic origin and activate discrete TLR pathways. The TLR engagement by microbial products causes cell activation, which often results in a pro-inflammatory response.

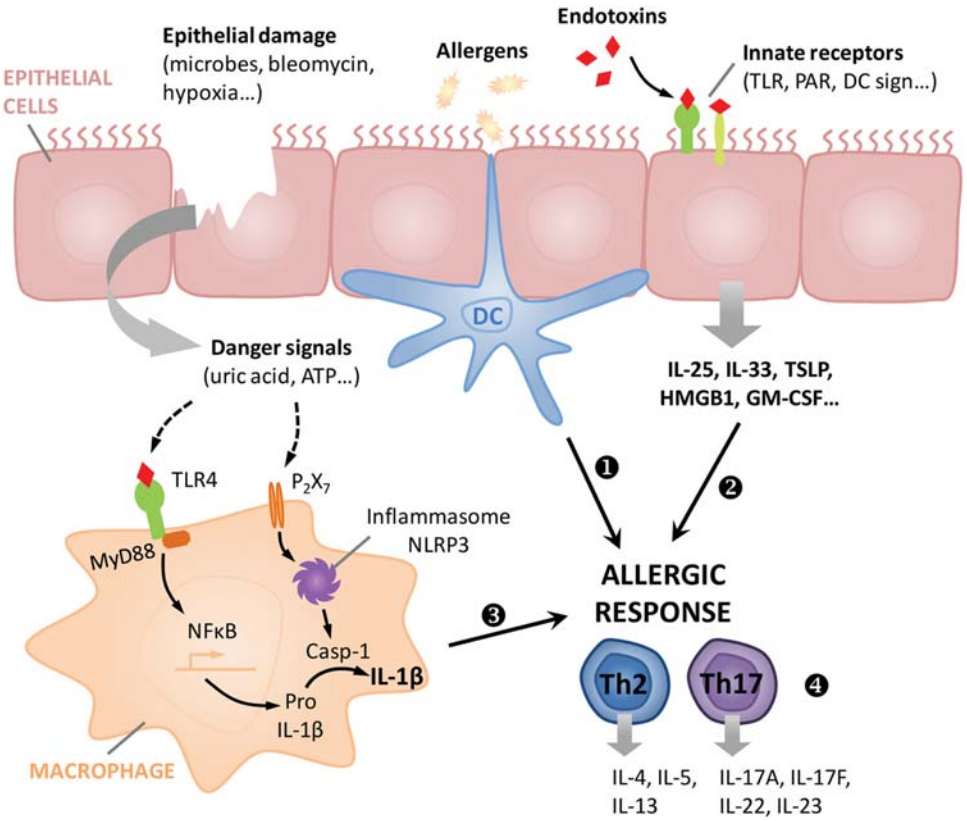

Figure 1 Role of innate receptors in allergic airway inflammation. DCs underneath the airway epithelial cells of the conducting airway sample inhaled antigens and migrate to draining lymph nodes to polarize naïve and memory T cells to Th2 cell subset (❶). Endotoxins from the environment or contained in experimental allergens are recognized by innate receptors expressed by lung epithelial cells, which release pro-inflammatory cytokines such as IL-25, IL-33, TSLP, and GM-CSF that promote Th2 allergic response (❷). Alveolar macrophages express TLRs and NLRs that sense danger signals (PAMPs and DAMPs) released by injured cells upon hypoxia or microbial infections. TLR activation by PAMPs leads to pro-IL-1β accumulation in the cytoplasm, which can be matured by caspase-1 upon NLRP3 inflammasome activation (❸). The NLRP3 inflammasome can be activated in response to a wide array of stimuli including virus, bacteria, and fungi or endogenous ligand such as extracellular ATP, uric acid crystals, and others. NLRP3 inflammasome, as well as the IL-1β signaling has been shown to be critical to developing experimental allergic inflammation. This crosstalk leads to the development of a specific adaptive response, characterized by Th2 and Th17 cell recruitment into the airways, which in turn orchestrate eosinophilic inflammation (❹).

Pulmonary exposure to bacterial and fungal products including endotoxin or lipopolysaccharide (LPS) plays an important role in the development and progression of chronic respiratory diseases including asthma (Kennedy et al., 1987; Schwartz et al., 1995; Michel et al., 1996). In the experimental situation, intranasal exposure to endotoxin from Gram-negative bacteria provokes acute pulmonary inflammation with neutrophil recruitment into the alveolar space and lung, epithelial damage, alveolar-capillary leak, and bronchoconstriction in normal C57BL/6 mice (Lefort et al., 2001; Schnyder-Candrian et al., 2005). Endotoxin-induced bronchoconstriction and neutrophil recruitment in the lung are abrogated in mice deficient for TLR4, CD14, or the TLR adaptor MyD88 (Togbe et al., 2006a, b). MyD88 is at the crossroad of multiple TLR-dependent and TLR-independent signaling pathways, including IL-1R and IL-18R, or the focal adhesion kinase (FAK) (Zeisel et al., 2005). TLR4 activation is critical for allergic lung inflammation and low levels of LPS enhance Th2-type response to inhaled allergens (Figure 1) (Eisenbarth et al., 2002). It has been reported that TLR4 expression by lung epithelial cells, but not DCs, is necessary and sufficient for house dust mite allergen-mediated DC activation and Th2 cell differentiation (Hammad et al., 2009; Trompette et al., 2009).

Indeed, airway epithelial cells are able to recognize endotoxins contained in allergens and to release innate cytokines such as TSLP, IL-25, and IL-33 that create a pro-allergic environment (Hammad et al., 2009). Using an ovalbumin (OVA)-induced model of allergic inflammation, we reported that IL-33 directly activates DCs to prime Th2 cells, which in turn enhanced allergic airway inflammation (Besnard et al., 2011c).

In addition to the microbe derived TLR agonists, endogenous products have been identified which engage TLR. Hyaluronic acid, heat shock protein such as hsp70, high mobility group box 1 (HMGB1) and other tissue components are released upon tissue injury and may activate TLR4 (Andersson and Tracey, 2011). These data suggest that injury or stress resulting in the release of endogenous TLR agonists may contribute to lung inflammation.

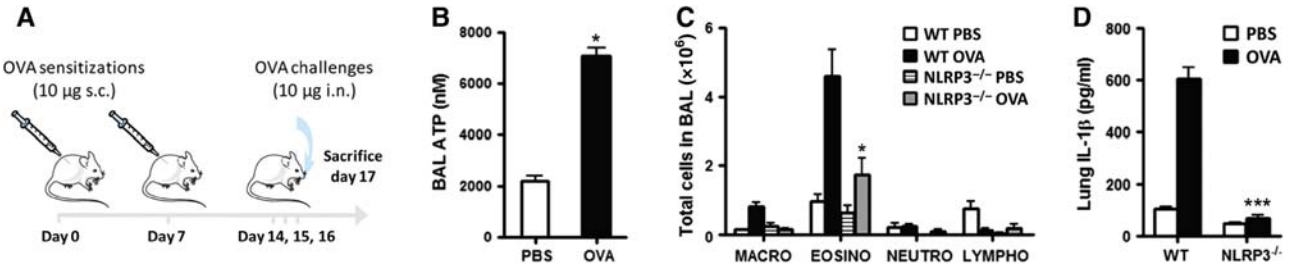

Figure 2 ATP release activates NLRP3 inflammasome during allergic airway inflammation. (**A**) Alum-free model of ovalbumin-induced allergic airway inflammation. Briefly, mice are sensitized subcutaneously twice with OVA without adjuvant at day 0 and 7. Animals are challenged intranasally at day 14, 15, and 16 with OVA. The extent of allergic inflammation is evaluated 24 h after the last challenge. (**B**) Extracellular ATP is measured by the luminescence assay in BAL fluid after 30 min heating at 55°C to avoid contamination of intracellular ATP. *$P < 0.05$ vs PBS control. (**C**) Differential cell counts are performed on BAL cells from wild-type (WT) and NLRP3$^{-/-}$ mice after May Grunewald Giemsa staining. *$P < 0.05$ vs WT OVA control. (**D**) ELISA detection of IL-1β levels in the lung of WT and NLRP3$^{-/-}$ mice sensitized and challenged with OVA or PBS (Besnard et al., 2011a). ***$P < 0.001$ vs OVA WT control.

Inflammasome activation, IL-1β, and allergic lung inflammation

Another class of innate immune receptors has been shown to be critical in the initiation of inflammatory responses. These receptors, named nod-like receptors (NLRs), are located in the cytoplasm and have been implicated in the sensing of invading microbes, tissue damage, or stress (Chamaillard et al., 2003; Magalhaes et al., 2008). The most thoroughly characterized, the NLRP3 protein, forms a large signal-induced multiprotein complex, the inflammasome, resulting in pro-inflammatory caspase activation (Tschopp et al., 2003). Thus far, a broad range of exogenous and endogenous stimuli have been demonstrated to activate the NLRP3 inflammasome. In asthma and COPD, it has been suggested that hypoventilation and hypoperfusion lead to acidotic milieu in the lung which in turn induces danger associated molecular pattern (DAMP) release, IL-1β secretion, and eosinophilic inflammation (Hoffman and Wanderer, 2010). These DAMPs include host-derived molecules released under stress or injury, such as extracellular ATP, hyaluronan, uric acid crystals, and cholesterol. Uric acid crystals engage the caspase-1 activating NLRP3 (or cryopyrin) inflammasome, resulting in the production of IL-1β (Figure 1). Macrophages from mice deficient in various components of the inflammasome such as caspase-1, ASC, and NLRP3 are defective in uric acid crystal-induced IL-1β activation (Martinon et al., 2006). Moreover, uric acid crystal-induced inflammation in the lung and the peritoneum is impaired in the absence of NLRP3 inflammasome or IL-1R1 signaling (Martinon et al., 2006; Gasse et al., 2009). These findings provide insight into the molecular mechanisms of the inflammatory diseases and support a pivotal role of the NLRP3 inflammasome in inflammatory diseases.

Lung-injury-induced inflammation and fibrosis provoked by the cancer chemotherapeutic drug bleomycin are reduced in ASC-deficient mice, which is a critical adapter of the NLRP3 inflammasome complex (Gasse et al., 2007) and we found that uric acid (Gasse et al., 2009) and ATP (Riteau et al., 2010) are released upon injury and contribute to NLRP3 inflammasome activation. Importantly, uricase administration diminished uric acid levels and apyrase reduced ATP levels and both attenuated lung inflammation upon bleomycin injury.

Based on these results, we searched whether in allergen-induced lung inflammation similar mechanisms may be involved as those following chemical tissue injury. Using an OVA-induced model of allergic lung inflammation without aluminum adjuvant, we found that extracellular ATP release in the lung activates NLRP3 inflammasome and IL-1β production (Figure 2). Importantly allergic lung inflammation was reduced in the absence of NLRP3 (Besnard et al., 2011a). Eosinophil recruitment in the airways, mucus hypersecretion, and IL-1β were dramatically reduced in NLRP3-deficient mice, as well as Th2 cytokine and chemokine production. Furthermore, allergic inflammation was similarly reduced in mice deficient for IL-1R1 and IL-1β. Reduced allergic inflammation was also found in the absence of IL-1α. Our data suggest that IL-1α and IL-1β are co-regulated (Besnard et al., 2011a). It should be emphasized again that a TLR4 signal provided by endotoxin contamination of allergen is required to induce NF-κB-dependent pro-IL-1β production, while the inflammasome is involved in IL-1β maturation and secretion. Therefore, NLRP3 inflammasome activation leading to IL-1 production is critical in allergic lung inflammation. Increased levels of ATP have been reported in patients with allergic asthma (Idzko et al., 2007) linking innate activation of the immune system through NLRP3, IL-1, and allergic inflammation as shown in our experimental model.

We extended this investigation and found that uric acid is also released upon allergen exposure in an alum-free model of allergic asthma (our unpublished data), and may participate in NLRP3 inflammasome activation. Uric acid involvement in allergic asthma was first demonstrated in a murine model of allergic inflammation using alum adjuvant which is known to activate NLRP3 inflammasome (Kool et al., 2008). A recent report suggests that uric acid could directly activate airway DCs in a TLR4, MyD88, and IL-1R-independent manner (Kool et al., 2011).

In conclusion, NLRP3 inflammasome activation is required together with a TLR4 signal to produce mature IL-1β and allergic lung inflammation. In addition to the role of the IL-1 axis, which has been shown previously (Nakae et al., 2003; Schmitz et al., 2003), we showed a crucial role of NLRP3 in an allergic Th2 response and suggest now an additional link to a Th17 response in the allergic response.

Th17 cell differentiation and function

The $CD4^+$ effector cells were initially separated into Th1 and Th2 cells. Another lineage of T cells that produce IL-17, Th17 cells, has been recently identified that is highly pro-inflammatory and induces autoimmunity (Bettelli et al., 2007a, b; Korn et al., 2007b, 2009; Sutton et al., 2009). While TGF-β induces the transcription factor Foxp3 and generates regulatory T cells, IL-6 inhibits Foxp3 expression and together with TGF-β and IL-1β promotes Th17 cell differentiation. IL-1β, especially in synergy with IL-23, plays an essential role in the induction or expansion of murine and human Th17 cells (Sutton et al., 2006; Acosta-Rodriguez et al., 2007; Wilson et al., 2007; Lee et al., 2010). It has been shown that Th17 cells express higher IL-1R1 levels than other T cell subsets (Lee et al., 2010), and that IL-1β regulates IRF4 and RORγt expression during Th17 cell polarization and maintains cytokine production in effector Th17 cells (Chung et al., 2009). Recent evidence suggests that the retinoic acid receptor-related orphan nuclear receptor RORγT is required for Th17 lineage differentiation (Stockinger and Veldhoen, 2007). In addition, arylhydrocarbon receptor activation may be required for IL-17 and IL-22 production (Bettelli et al., 2008; Quintana et al., 2008; Veldhoen et al., 2008; Yang et al., 2008), whereas the cardiac glycoside digoxin may inhibit RORγt transcriptional activity and suppress Th17 cell differentiation (Huh et al., 2011).

Th17 cells have taken an important place in autoimmunity, inflammation, and infection as reviewed recently (Quesniaux et al., 2009). $CD4^+$ Th17 cells often co-express IL-17A and IL-17F, which form either homo- or heterodimers. These cytokines signal mainly through IL-17RA receptors (Conti et al., 2009). Further, Th17 cells may co-express IL-22 and IL-23, which are responsible for the expansion and maintenance of Th17 cells (Korn et al., 2007a). IL-22 is structurally related to the IL-10 family (Dumoutier et al., 2000a, 2001) and exerts either inflammatory or cytoprotective effects depending on the inflammatory context (Sonnenberg et al., 2010).

IL-17 in lung inflammation

To explore a potential link between IL-1 and IL-17, we instilled recombinant IL-1β into the airways, which upregulated IL-17A and induced acute neutrophilic lung inflammation, which is diminished by IL-17 antibody neutralization or in IL-17RA-deficient mice (Gasse et al., 2011). Moreover, we showed that bleomycin-induced lung injury triggers the expression of early IL-23, IL-17A, and IL-17F in an IL-1-dependent manner. IL-23 and IL-17A expression as well as IL-17RA signaling are necessary for pulmonary TGF-β production, collagen deposition, and fibrosis. These findings demonstrate the existence of an early IL-1β/IL-23/IL-17A axis leading to pulmonary inflammation and fibrosis and identify innate IL-23 and IL-17A as interesting drug targets for IL-1β driven lung pathology (Gasse et al., 2011). Similarly, recombinant IL-17A causes rapid neutrophil recruitment and acute pulmonary inflammatory response (Hoshino et al., 2000; Kolls and Linden, 2004; Ivanov et al., 2005). Recombinant human IL-17 was shown to induce the production of IL-8 by human bronchial epithelial and endothelial cells, and the intratracheal instillation of IL-17 in rats elicited neutrophil recruitment and MIP-2

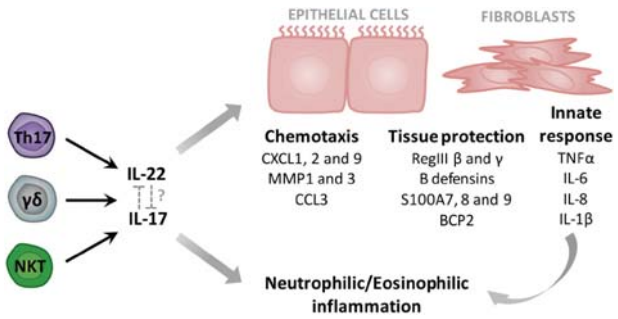

Figure 3 Origins and functions of IL-17 and IL-22 in the airways. The main producers of IL-17 and IL-22 in the lung are Th17, γδ T cells, and NKT cells (IL-22 production by NKT cells has to be confirmed in the lung). IL-17 orchestrates allergic airway inflammation by inducing the expression of various pro-inflammatory mediators such as cytokines, chemokines, and adhesion molecules, in turn leading to recruitment and activation of neutrophils and Th2-mediated eosinophils. IL-22 binds to its receptor expressed by structural cells such as epithelial cells or fibroblasts. It activates a number of signaling pathways including STAT1, 3 and 5, MEK, ERK, as well as the JNK and p38 kinase pathways. This induces the expression of genes of chemotaxis, tissue repair, or innate host defense. Recent studies in mice suggested that IL-17 and IL-22 may regulate each other but the exact molecular mechanism is unknown.

production in the BAL, which were both inhibited by neutralizing IL-17 antibodies (Laan et al., 1999). Importantly, endotoxin instilled intratracheally elicited the production of IL-17A within 24 h together with IL-6 and MIP-2 release in the airways (Ferretti et al., 2003; Laan et al., 2003). A recent finding showed that Derp2, the major allergen of HDM, has structural homology with the TLR complex protein MD-2, facilitating TLR4 activation in the absence of MD-2 (Hammad et al., 2009). These data have to be related to the study of Phipps et al. (2009), which showed that the development of allergic Th2 and Th17 responses to HDM are differentially regulated and the Th17 response may be dependent of MyD88 and TLR2 rather than TLR4.

In the airways, IL-17 is not only produced by adaptive Th17 cells but also in the early stages of inflammation by innate immune cells including NKT and γδ T cells (Figure 3). A functionally distinct peripheral invariant NKT (iNKT) cell subset that is implicated in airway neutrophilia has been reported to constitute an important source of IL-17 in the airways; these cells, lacking the NK1.1 marker, generated a high amount of IL-17, together with low IL-4 and IFNγ levels in response to several iNKT cell ligands, such as α-galactosylceramide or glycolipids derived from *Sphingomonas wittichii* and *Borrelia burgdorferi* (Michel et al., 2007).

Another source of innate IL-17 in the lung is γδ T cells which are located in the subepithelium of alveolar regions (Simonian et al., 2010). These cells are able to respond directly to inhaled particles such as microbial pathogens (Nanno et al., 2007). In an OVA-induced model of allergic asthma, we observed an increase of γδ T cells in the lung of sensitized and challenged mice and about 10% of these cells produce IL-17A after phorbol ester and ionomycin restimulation (our unpublished data).

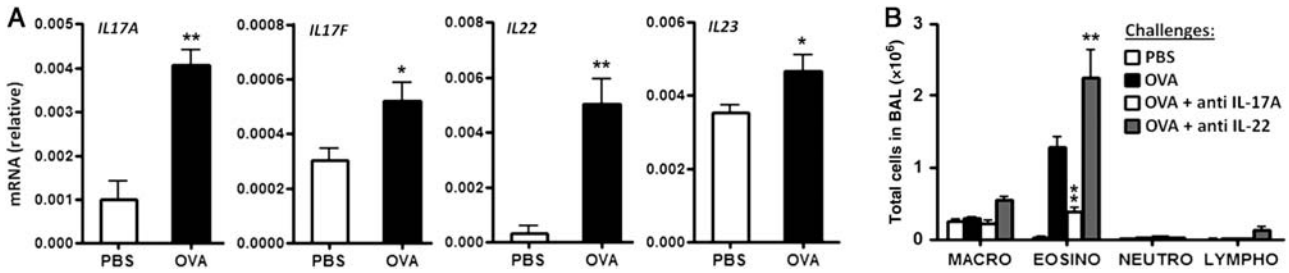

Figure 4 IL-17A and IL-22 have antagonist functions during the effector phase of asthma. (**A**) Quantitative PCR analysis of Th17 cytokine gene expression in lung tissues from OVA sensitized and challenged mice. Results are normalized to HPRT1 and β2-globulin mRNA levels. *$P < 0.05$ vs PBS control. (**B**) Differential cell counts are performed on BAL cells from OVA-sensitized mice challenged with PBS, OVA, OVA + anti IL-17A, or OVA + anti IL-22 (Besnard et al., 2011b). **$P < 0.01$ vs OVA control.

Investigations in immunodeficient SCID mice and transcriptional analysis of purified cells from BAL revealed that neutrophils, but not macrophages express IL-17 (Ferretti et al., 2003). The finding that non-T cells produce IL-17 is interesting and needs additional confirmation.

Role of IL-17 in allergic airway inflammation

Th17 responses as well as the levels of IL-17 in the airways and serum correlate with disease severity in asthmatic patients (Bullens et al., 2006). IL-17A has been found in sera and BAL fluids from asthmatic patients suggesting a role in allergic reactions (Molet et al., 2001). Recent investigations revealed that IL-17A contributes to Th2-cell-mediated and eosinophilic lung inflammation (Wakashin et al., 2008). Experimentally, IL-17 signaling has been shown to be necessary for antigen-induced allergic inflammation of the airways and T cell activation, since the response was ablated in IL-17-deficient mice (Nakae et al., 2002). IL-17 plays a critical role in neutrophil and eosinophil recruitment to the lung by regulating expression of various inflammatory mediators which include cytokines (IL-6, GM-CSF, and others), chemokines (CXCL1, 2, 5, and 6) and adhesion molecules (ICAM-1) (Figure 3) (Korn et al., 2007a). We extended this investigation and showed that IL-23 is increased in the lung of OVA sensitized and challenged mice, and IL-23 can enhance IL-17 production by cells from mediastinal lymph nodes of asthmatic mice; and we also confirmed that IL-17 is required during antigen sensitization to develop allergic asthma, as shown in IL-17RA-deficient mice (Schnyder-Candrian et al., 2006). A recent work showed that complement activation, occurring upon inflammation process, is linked with IL-17 production in allergic inflammatory response (Lajoie et al., 2010). This could explain the correlation between IL-17 expression levels and asthma severity.

Dual role of IL-22 in allergic airway inflammation

Recent investigations revealed that IL-22 is mainly produced by Th17 and γδ T cells in the lung (Martin et al., 2009; Siegemund et al., 2009; Sutton et al., 2009; Simonian et al., 2010). IL-22 receptor complex is composed of IL-22R and IL-10Rβ (Dumoutier et al., 2000b; Xie et al., 2000) and is only expressed by non-hematopoietic cells such as hepatocytes, keratinocytes, lung and intestinal epithelial cells and fibroblasts. IL-22 ligation to its receptor activates STAT3 signaling pathway leading to the expression of genes involved in inflammation, chemotaxis, host defense, and mucosal protection (Figure 3) (Wolk et al., 2004; Liang et al., 2006; Zenewicz et al., 2007; Aujla et al., 2008; Zheng et al., 2008). Biological effects of IL-22 depend on tissue location and cytokine environment (Sugimoto et al., 2008; Munoz et al., 2009; Sonnenberg et al., 2010). IL-22 is protective during acute inflammation in hepatitis model and in *Citrobacter rodentium* intestinal infection (Radaeva et al., 2004; Zenewicz et al., 2007; Zheng et al., 2008). In keratinocytes, IL-22 alone induced antibacterial proteins like β-defensins and S100A proteins (Wolk et al., 2004). However, in experimental dermal inflammation IL-22 amplifies inflammation (Zheng et al., 2007; Ma et al., 2008). The reason for this dual nature of IL-22 in the skin is probably due to the fact that IL-22 alone has only minimal inflammatory properties but it enhances the inflammatory effects of TNF-α, IL-1β, IL-17, and GM-CSF (Wolk et al., 2006, 2009a, b).

We previously found increased levels of IL-22 in the serum of asthmatic patients and in the lung during experimental asthma in mice (Besnard et al., 2011b). Therefore we hypothesized that IL-22 may be important in asthma pathogenesis. Using an OVA-induced model of allergic asthma, we reported that IL-22 can be either pro-inflammatory or tissue protective depending on the phase of the disease. Briefly, IL-22 is required to develop a robust allergic airway inflammation, as IL-22-deficient mice, or IL-22 antibody neutralization during allergen sensitization reduced eosinophil recruitment in the airways, as well as Th2 cytokine and chemokine production. By contrast, IL-22 is protective upon the effector phase since exogenous IL-22 treatment during the allergen challenges reduces lung inflammation, or in contrary IL-22 antibody blockade exacerbates the disease (Figure 4). This tissue protective property of IL-22 has been previously shown in different mouse models of inflammation such as hepatitis or inflammatory bowel diseases (Radaeva et al., 2004; Zenewicz et al., 2008; Zheng et al., 2008; Xu et al., 2011). Emerging data suggest that IL-22 may provide mucosal protection by accelerating epithelial repair, as well as maintaining epithelial integrity (Liang et al., 2006; Zheng et al., 2007; Aujla et al., 2008). Recently, it has been reported that IL-22 attenuates Th2 cell-mediated airway inflammation by inhibiting IL-25 production from lung epithelial cells (Takahashi et al., 2011). Our study also suggested that the protective effect of IL-22 is partially linked to IL-17 since IL-17A neutralization reverses the phenotype in IL-22-deficient

mice. In addition, we observed that IL-17 and IL-22 are reciprocally regulated in the lung during allergic airway inflammation, but the exact mechanism is unknown. Because of its restricted receptor expression, IL-22 acts strictly on structural cells, which in turn modulate the inflammatory response. This constitutes an example of how an inflammatory cytokine influences the microenvironment by activating structural cells.

Conclusions

Present knowledge about injury- or allergen-induced inflammasome activation and TLR4-dependent allergic inflammation is emerging. There is now evidence to suggest that tissue injury or allergen exposure leads to NLRP3 activation, with formation of the NLRP3 inflammasome complex and caspase-1 activation resulting in mature IL-1β release, which may elicit IL-17 production. Given the role of IL-1 signaling and Th17 cells in the development of allergic inflammation, therapeutic strategies inhibiting IL-1R1 signaling or Th17 cell differentiation could be considered as a novel approach for the treatment of allergic asthma. However, the role of IL-1α and other mediators needs to be further explored. Importantly, we demonstrated that IL-17 and IL-22 are expressed and required in experimental asthma, which needs to be further investigated in patients. Finally, the molecular mechanisms by which IL-22 protects from airway inflammation during the effector phase of experimental asthma are under intense investigation.

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Conflict of interest: none declared.

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