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NLRP3 Inflammasome in Severe Asthma

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Allergic asthma has increased dramatically in prevalence and severity over the last decades. Both clinical and experimental data support an important role of Th2 cell immune cells in the allergic response [1]. We reported that the NLRP3 expressed on T cells may function as transcriptional regulator of Th2 differentiation [2]. Innate cells producing rapidly large amounts of type 2 cytokines sparked the interest in type 2 innate lymphoid cells (ILC), which have diverse biological processes including allergic responses [3]. The contribution of myeloid cells and crucial role of epithelial cells activated by allergen is now well established in asthma [4].

Several recent investigations revealed that airway exposure to allergen in sensitized individuals causes the release of danger signals including ATP [5], uric acid and other crystals [6] activating the NLRP3 inflammasome complex [7,8]. NLRP3 triggers the caspase-1 cleaving pro-IL-1b to mature IL-1b, highly inflammatory cytokine [9,10]. The production of pro-IL-1b requires toll-like receptor (TLR) signal which is provided by endotoxin or other agonists [11]. IL-1b creates a pro-inflammatory milieu with the production of IL-6, IL-23 and chemokines which mobilize neutrophils and enhance Th17 cell differentiation in the lung which is blocked by neutralizing IL-17 antibody [12]. The cellular and molecular events of NLRP3 activation resulting in IL-1 and IL-18 dependent inflammation are depicted in (figure 1). Alternative pathways may also be of interest such cell stress and death induced free DNA activating the DNA sensing cGAS and STING pathway triggering type I interferon dependent inflammation [13]. A cross-talk of the NLRP3 and cGAS and STING pathways is also considered.

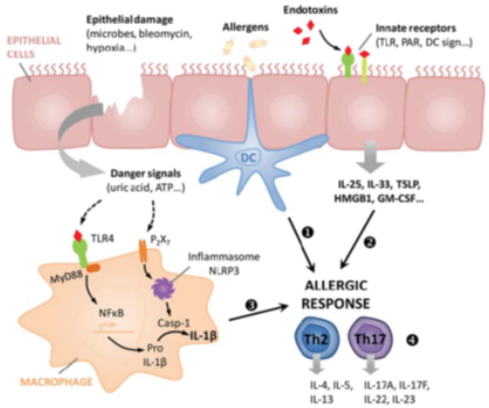

Figure 1 Role of innate receptors in allergic airway inflammation. DCs underneath the airway epithelial cells of the conducting airway sample inhaled antigens and migrate to draining lymph nodes to polarize naïve and memory T cells to Th2 cell subset (1). Endotoxins from the environment or contained 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 (2). 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 (3). 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 (4).

Severe asthma is a broad term of treatment resistant asthma Th2 dependent immune response with airways hyperreactivity and eosinophils, or Th17 response with neutrophils and is major therapeutic challenge [14]. Severe asthma is associated increased IL-1R family transcript in the sputum [15]. We used repeated house dust mite and birch pollen induced mouse models which mimic severe allergic asthma [16,17] and other experimental mouse models as reviewed [18]. An important feature of severe asthma is reactivation by environmental factors such as airway pollution including ozone [19,20]. Ozone causes airways hyperreactivity [21] and disruption of the respiratory barrier with neutrophilic inflammation, emphysema and fibrosis [22,23]. Bacterial infection with S. pneumoniae [24] and viral infection by rhinovirus, RSV and other viruses may aggravate allergic asthma [25]. In models of papain and alternaria proteases induced allergic inflammation we demonstrated a critical role of type 2 and 3 ILCs expressing acetylcholine, which is abrogated in cell specific deficient mice [26,27].

Therapeutic targeting of NLRP3 inflammasome

There is ample evidence that the NLRP3 inflammasome is activated and required to develop allergic airway inflammation and that IL-17 contributes to severe, neutrophilic asthma, which is glucocorticoid resistant [28,29]. Pharmacological inhibition of NLRP3 by the small molecules such as MCC950 related compounds may be an attractive choice to inhibit severe asthma [14,30].

Therefore, targeting the NLPR3 inflammasome complex is of tremendous therapeutic interest to inhibit severe asthma but needs further clinical confirmation. Cell death occurring upon allergen exposure liberates extracellular or cytosolic DNA, which is highly inflammatory strongly suggests that chemical blockade of the DNA sensing cGAS and STING pathway is a novel alternative to attenuate severe allergic asthma, which is under investigation in our laboratory [13].

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