Breakfast Seminar

Inflammasome and Allergic Diseases

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A Trinity of Pathogen Sensors: Team work in Innate Immunity

**Sensor**

- Bacteria
- Viruses
- Fungi
- Protozoa

**Signal**

- TLRs
- NLRs
- RLRs

**Response**

- NF-κB
- MAPKs
- IRFs
- Caspase-1
- NF-κB
- IRFs

- Cytokines, chemokines, anti-viral proteins, pro-IL-1, pro-IL-18
- IL-1 and IL-18
- Anti-viral proteins

**Adaptor**

- MyD88
- Mal
- Trif
- TRAM
- MyD88 (IL-1R, IL-18R)
- IPS-1

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*TRENDS in Immunology*

Creagh & O’Neil 27:352
TLR signaling pathways

• Ligand induced dimerization of TLR--> induced assembly with TIR-domain containing adaptors
• MyD88 pathway and TRIF pathway;
• Activate Transcription factors and MAP kinases
• NFKb upregulates ~350 proinflammatory genes.

<table>
<thead>
<tr>
<th>Inflammatory cytokines</th>
<th>Chemokines</th>
<th>Adhesion molecules</th>
<th>Immune effector molecules</th>
<th>Pro-survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>IL-8, MIP-1a, MCP, RANTES, Eotaxin</td>
<td>ICAM-1, VCAM-1, E-selectin</td>
<td>FasL, iNOS, COX-2, β-defensins, c-IAP1, 2</td>
<td>Bcl-XL, A1</td>
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</table>
NOD1 & NOD2 recognize peptidoglycan substructures and promote innate immune responses

NOD1 and NOD2 are intracellular molecules and resemble some plant disease resistance proteins; best understood of the “NOD-like receptors” or NLRs.
Endocytosed crystals
Bacterial pore-forming toxins
Efflux of K+
Other insults/stresses

• TLRs or NOD1/NOD2 induce synthesis of pro-IL-1
• Inflammasome processes it to generate active IL-1

• Periodic fever synd., Crohns
• Gout, atherosclerosis, diabetes-2, alzheimer’s
Crosstalk between TLR and NLR pathways
Newly Identified Cells and Cytokines f the Innate Immune System in Asthma

Kim et al. nature immunology 11: 7july 2010
NLRP3 inflammasome is required in murine asthma in the absence of aluminum adjuvant

• Used an adjuvant-free model of allergic lung inflammation induced by ovalbumin (OVA) to investigate the role of NLRP3 inflammasome and related it to IL-1R1 signaling pathway.
• Employed mice deficient in NLRP3 inflammasome, and examined IL-1R1, IL-1β or IL-1α. Eosinophil recruitment, Th2 cytokine, and chemokine levels were determined in bronchoalveolar lavage fluid, lung homogenates, and mediastinal lymph node cells ex vivo.
• Allergic airway inflammation depends on NLRP3 inflammasome activation. Dendritic cell recruitment into lymph nodes, Th2 lymphocyte activation in the lung and secretion of Th2 cytokines and chemokines are reduced in the absence of NLRP3.
• Absence of NLRP3 and IL-1β is associated with reduced expression of other proinflammatory cytokines such as IL-5, IL-13, IL-33, and thymic stromal lymphopoietin. Furthermore, the critical role of IL-1R1 signaling in allergic inflammation is confirmed in IL-1R1-, IL-1β-, and IL-1α-deficient mice.
• NLRP3 inflammasome activation leading to IL-1 production is critical for the induction of a Th2 inflammatory allergic response.
Mite allergen is a danger signal for the skin via activation of inflammasome in keratinocytes

- Investigated whether HDM allergens activate the inflammasome in epidermal keratinocytes.
- Keratinocytes were stimulated with Dermatophagoides pteronyssinus (Dp), and examined the activation of caspase-1 and secretion of IL-1β and IL-18 and analyzed the subcellular distributions of inflammasome proteins.
- Dp activated caspase-1 and induced caspase-1-dependent release of IL-1β and IL-18 from keratinocytes.
- Dp stimulated assembly of the inflammasome by recruiting apoptosis-associated specklike protein containing a caspase-recruitment domain (ASC), caspase-1, and nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin-domain containing 3 (NLRP3) to the perinuclear region.
- Infection with lentiviral particles carrying ASC, caspase-1, or NLRP3 shRNAs suppressed the release of IL-1β and IL-18 from the keratinocytes. Activation of the NLRP3 inflammasome by Dp was dependent on cysteine protease activity.
- Thus, house dust mite allergens are danger signals for the skin. In addition, HDM-induced activation of the NLRP3 inflammasome may play a pivotal role in the pathogenesis of atopic dermatitis.