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NOD-like receptors in human airways

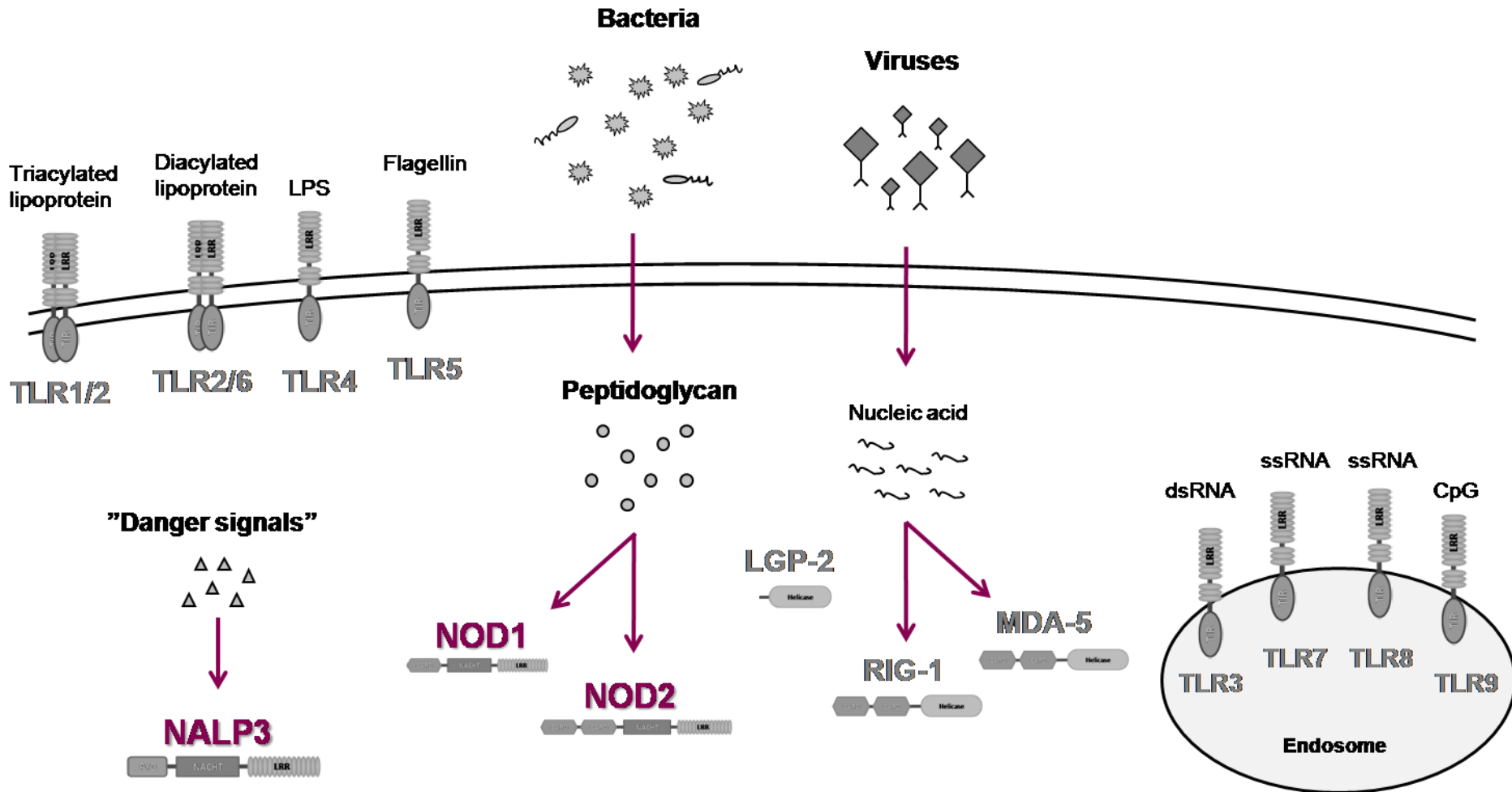
Lars Olaf Cardell

Division of ENT diseases

Department of Clinical Sciences, Intervention and Technology (CLINTEC)

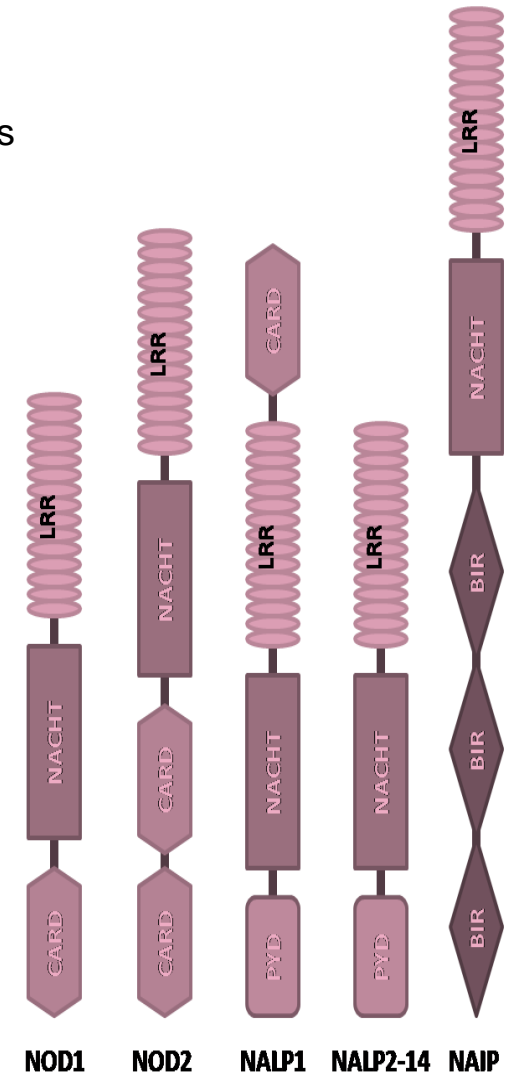
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Pattern-recognition receptors (PRRs)

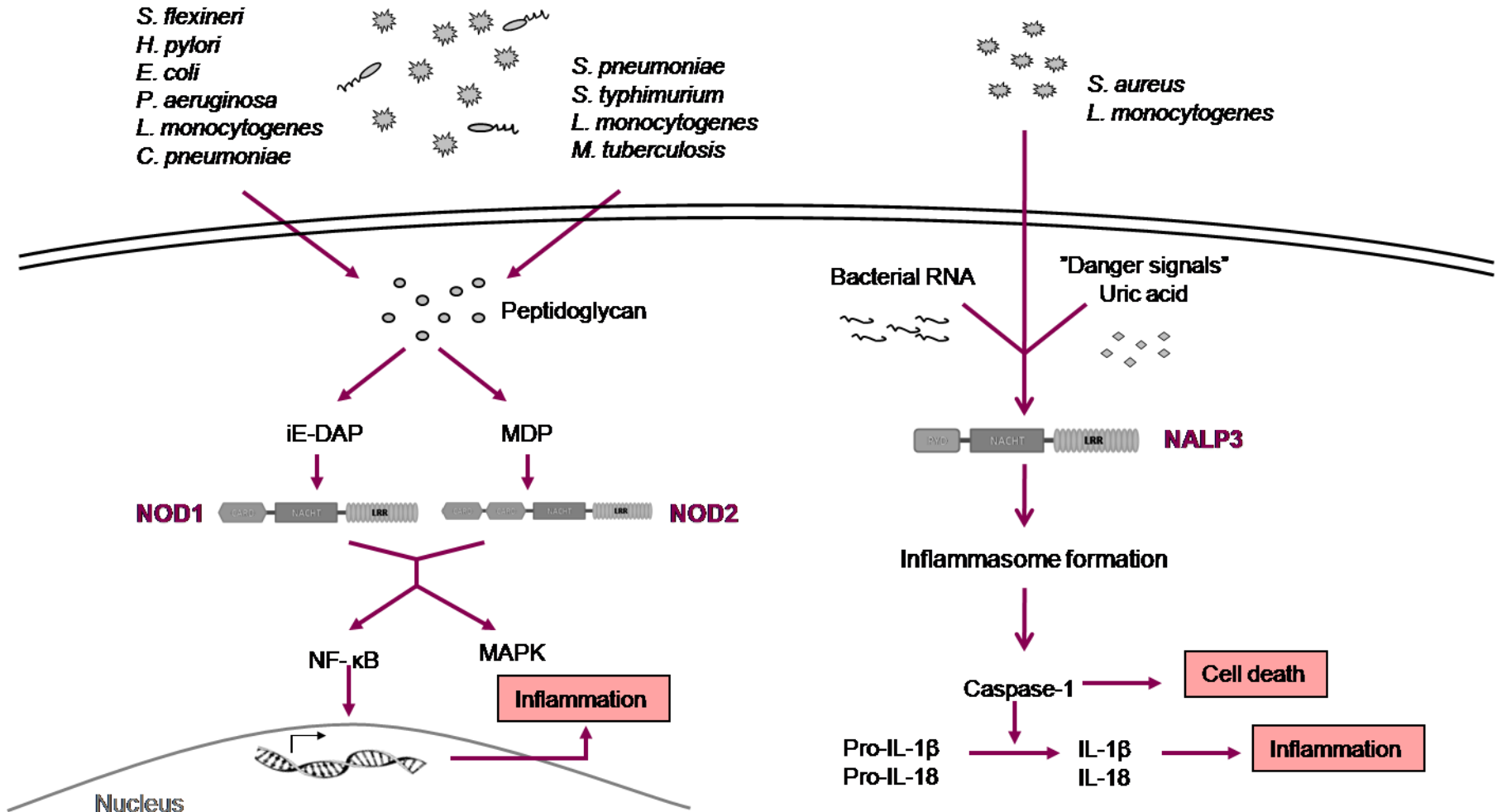


NOD-like receptors (NLRs)

- Also known as CATERPILLERS, NOD-LRR or NACHT-LRR proteins
- First identified in plants
- Cytosolic receptors
- 23 human members
- Tripartite structure
 - C-terminal leucine-rich repeat (LRR) domain
 - Central nucleotide-binding NACHT domain
 - N-terminal protein-protein interaction domain (variable)
- 3 subfamilies
 - NODs
 - NOD1 and NOD2
 - NALPs
 - NALP1-14
 - NAIPs



Signalling pathways



Expression of NLRs

■ Dendritic cells

- **Tada, H *et al.*** Synergistic effect of Nod1 and Nod2 agonists with toll-like receptor agonists on human dendritic cells to generate interleukin-12 and T helper type 1 cells. *Infect Immun* 2005. **73**: 7967-7976.
- **Fritz, J. H *et al.*** Synergistic stimulation of human monocytes and dendritic cells by Toll-like receptor 4 and NOD1- and NOD2-activating agonists. *Eur J Immunol* 2005. **35**: 2459-2470.

■ Monocytes

- **Uehara, A *et al.*** Muramyl dipeptide and diaminopimelic acid-containing desmuramylpeptides in combination with chemically synthesized Toll-like receptor agonists synergistically induced production of interleukin-8 in a NOD2- and NOD1-dependent manner, respectively, in human monocytic cells in culture. *Cell Microbiol* 2005. **7**: 53-61.

■ Epithelial cells

- **Uehara, A *et al.*** Various human epithelial cells express functional Toll-like receptors, NOD1 and NOD2 to produce anti-microbial peptides, but not proinflammatory cytokines. *Mol Immunol* 2007. **44**: 3100-3111.
- **Berube, J *et al.*** Distinct intracellular signaling pathways control the synthesis of IL-8 and RANTES in TLR1/TLR2, TLR3 or NOD1 activated human airway epithelial cells. *Cell Signal* 2009. **21**: 448-456.

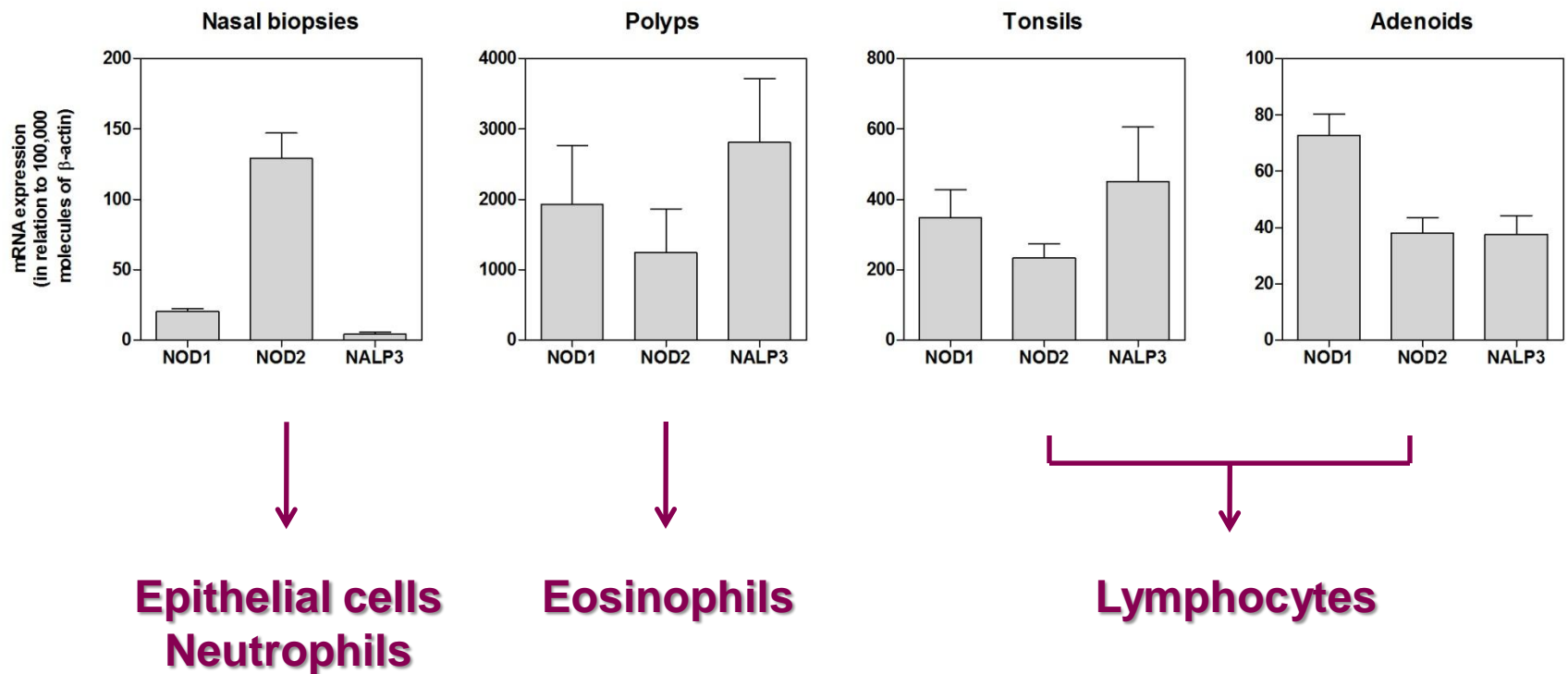
NLRs in human disorders

- Genetic variations in NOD1 (*CARD4*) and NOD2 (*CARD15*) are linked to allergic disorders
- Allergic asthma
- Elevated levels of allergen-specific IgE
- Atopic eczema
 - **Hysi, P. et al.** NOD1 variation, immunoglobulin E, and asthma. *Hum. Mol. Genet.* 14, 935–941 (2005).
 - **Eder, W. et al.** Association between exposure to farming, allergies and genetic variation in *CARD4/NOD1*. *Allergy* 2006;61(9):1117-1124.
 - **Weidinger S. et al.** Association of NOD1 polymorphisms with atopic eczema and related phenotypes. *J Allergy Clin Immunol* 2005;116(1):177-184.

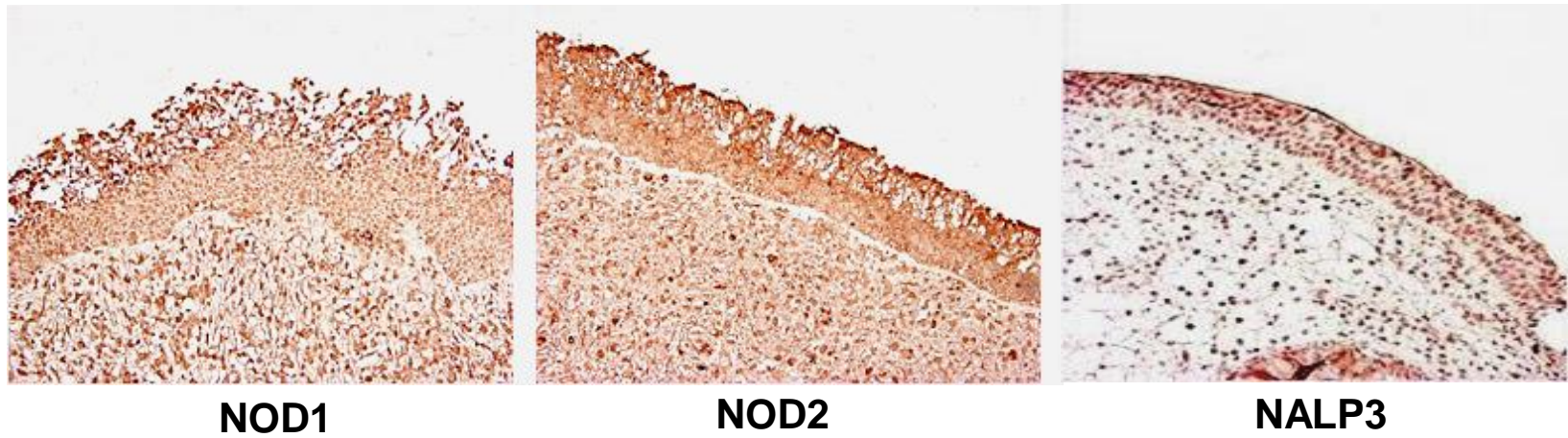
PRRs in allergic diseases

- The hygiene hypothesis
 - Reduced microbial exposure during childhood increases susceptibility to allergic diseases
 - Th1 → Th2
 - LPS and TLR4
- Role of NLRs?

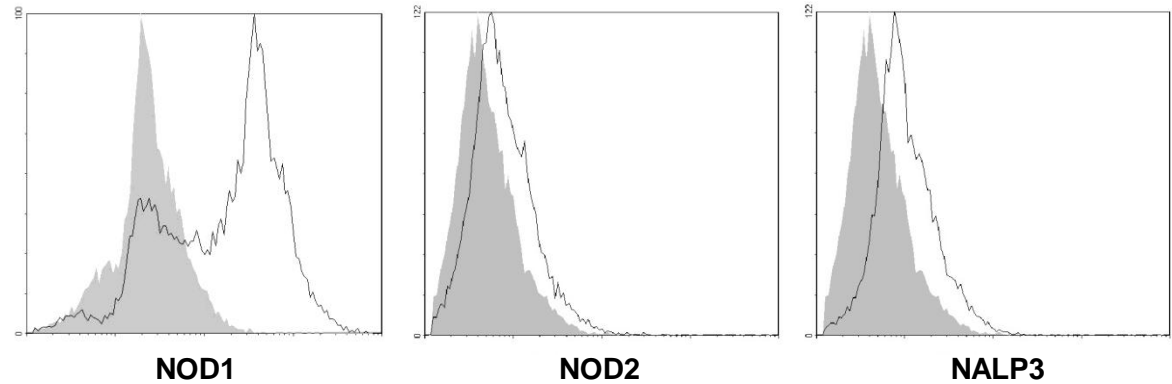
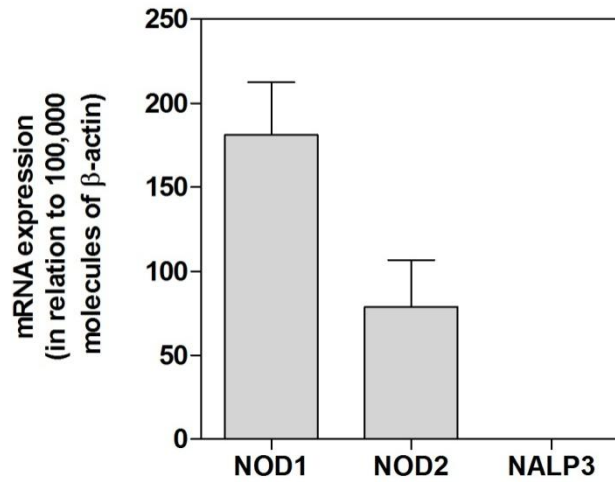
Presence of NLRs in human airways



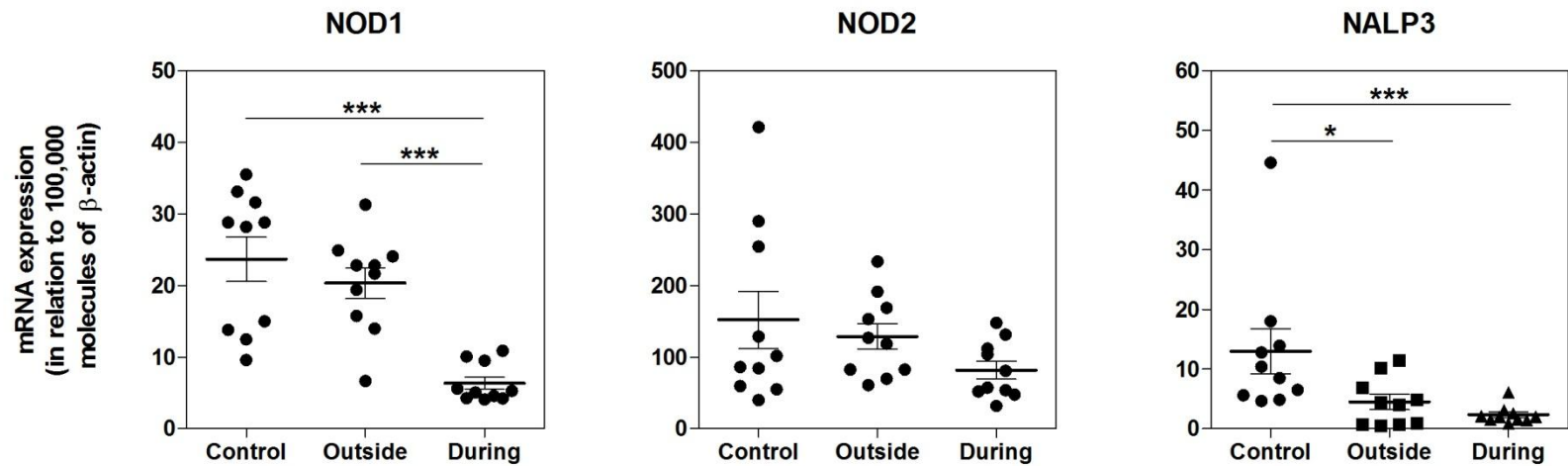
NLRs in nasal biopsies



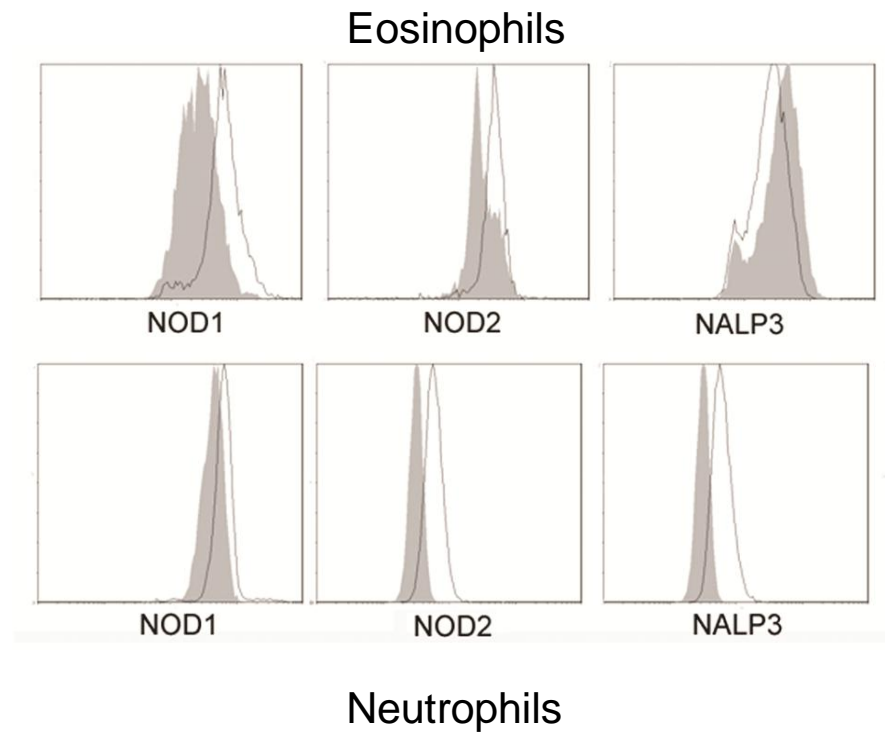
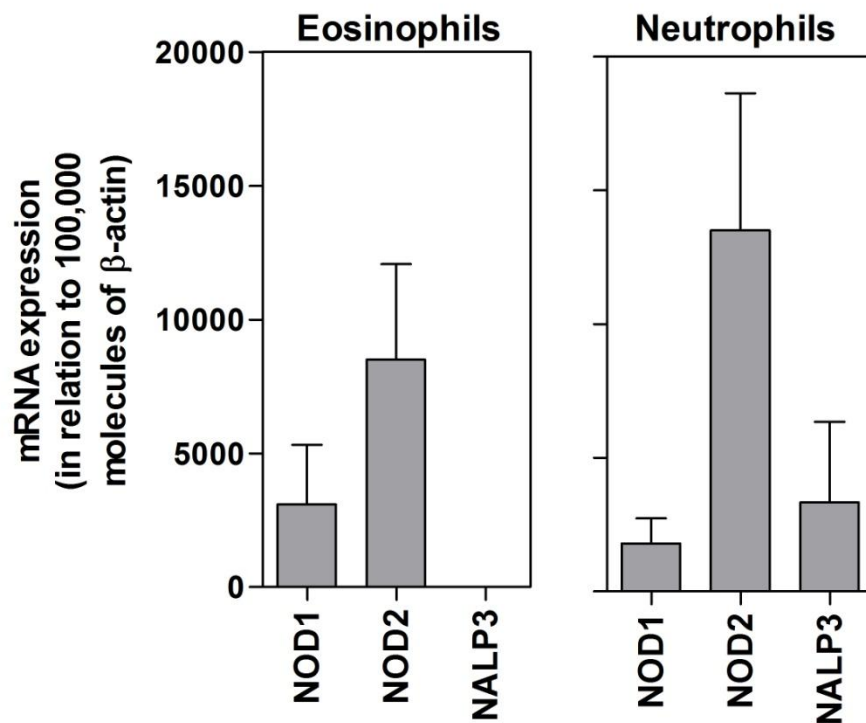
NLRs in nasal epithelial cells



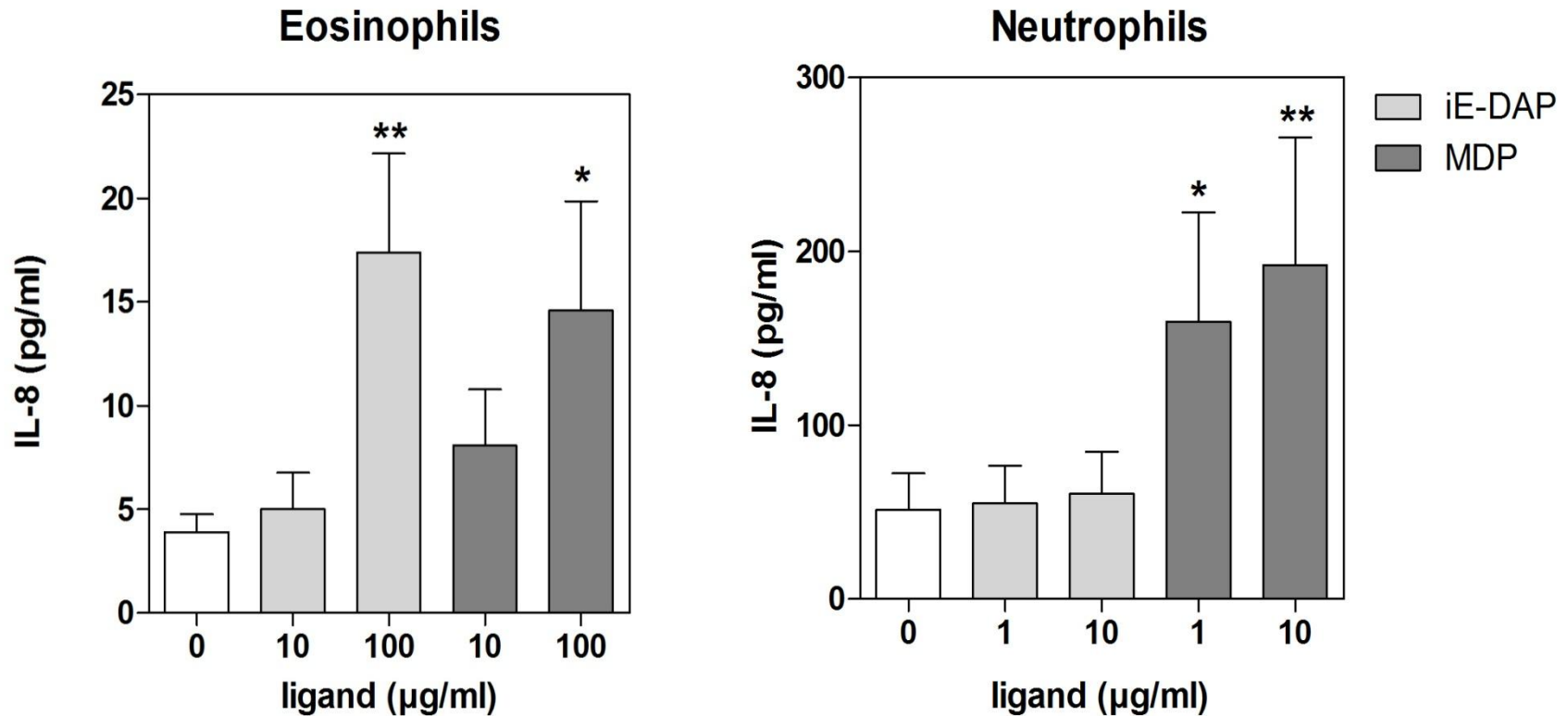
NLRs in nasal biopsies



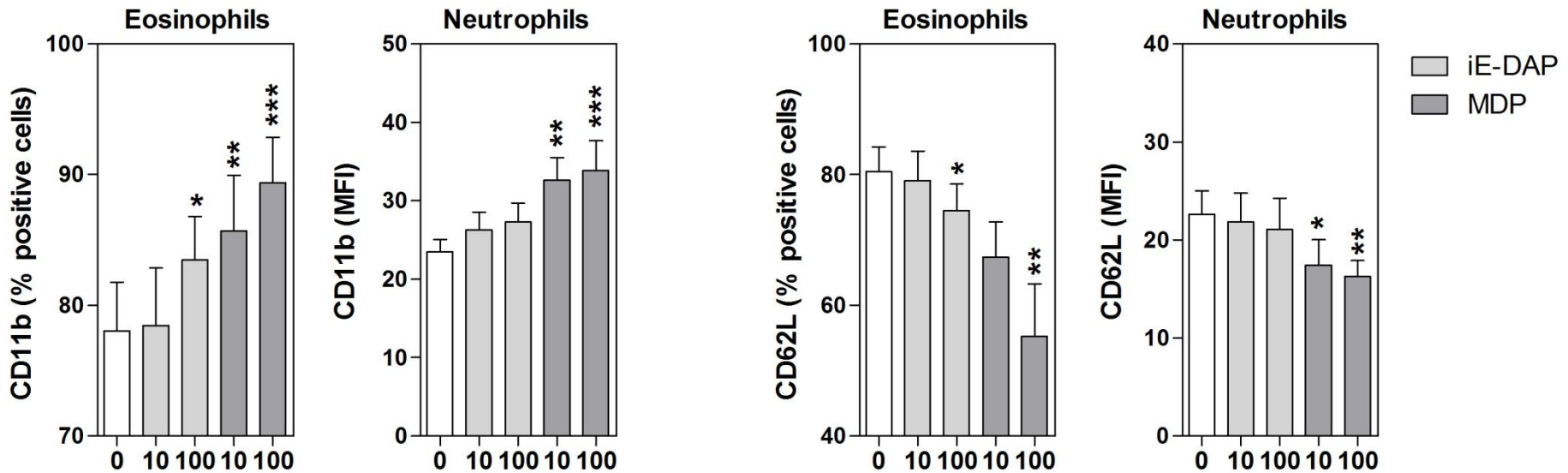
NLRs in eosinophils and neutrophils



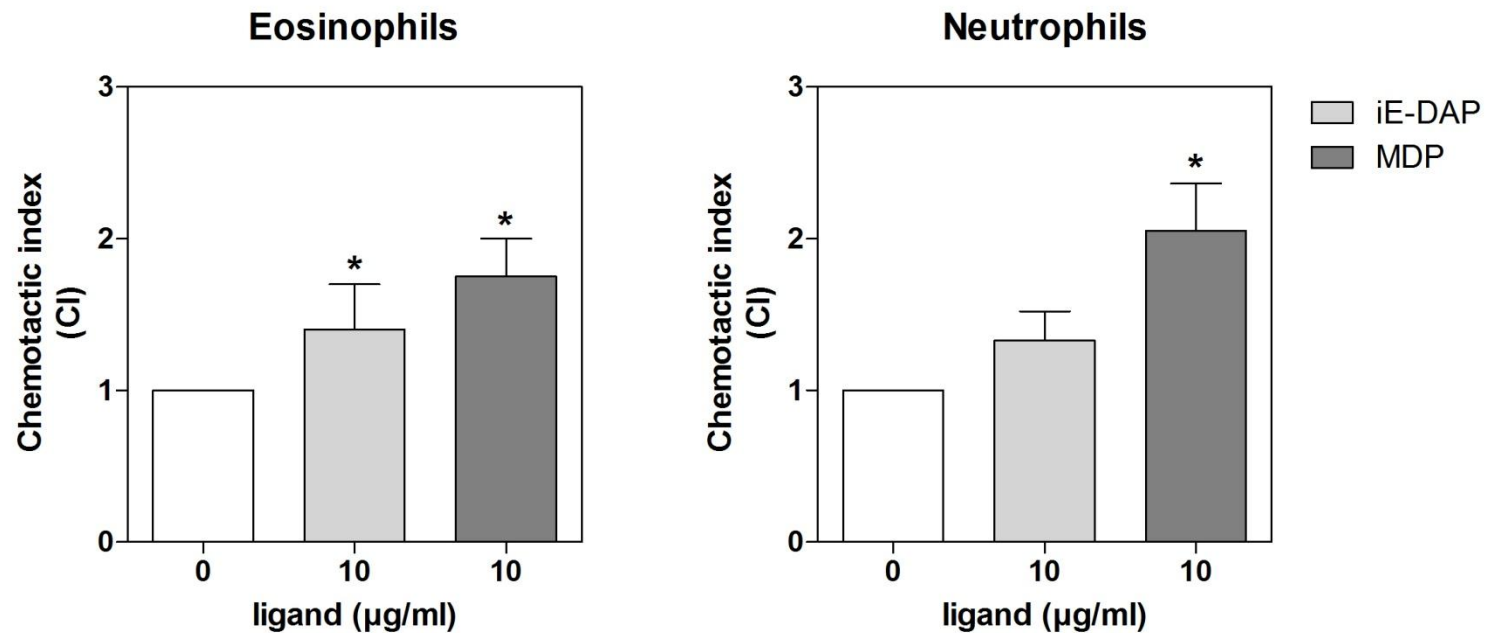
NLRs in eosinophils and neutrophils



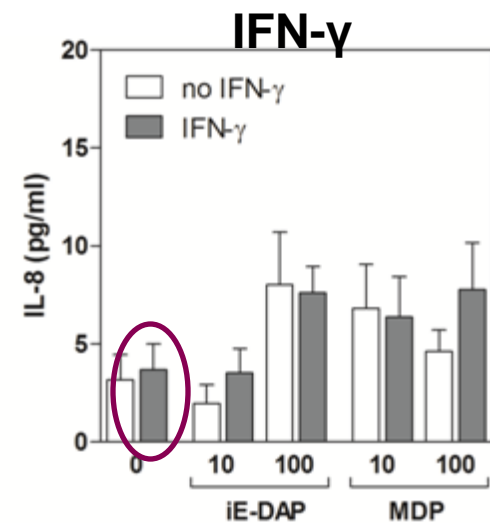
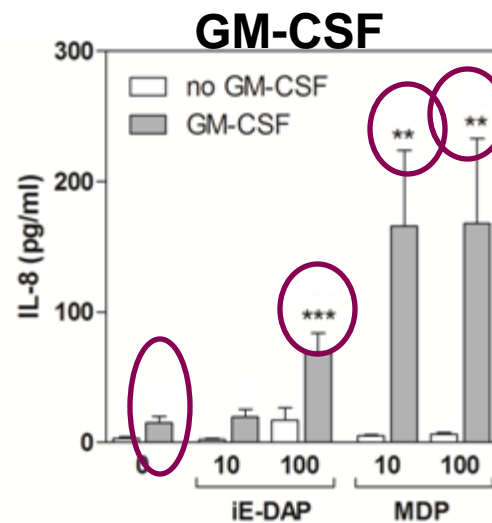
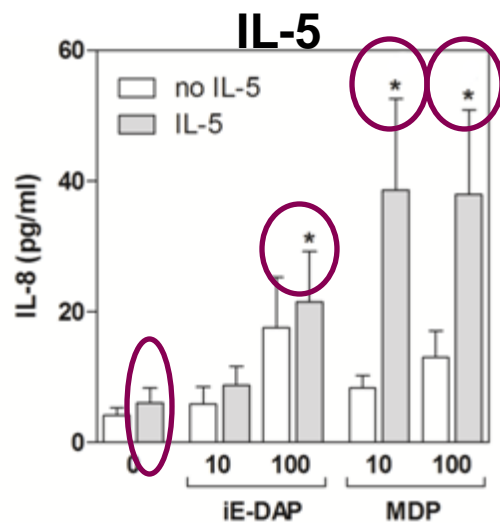
NLRs in eosinophils and neutrophils



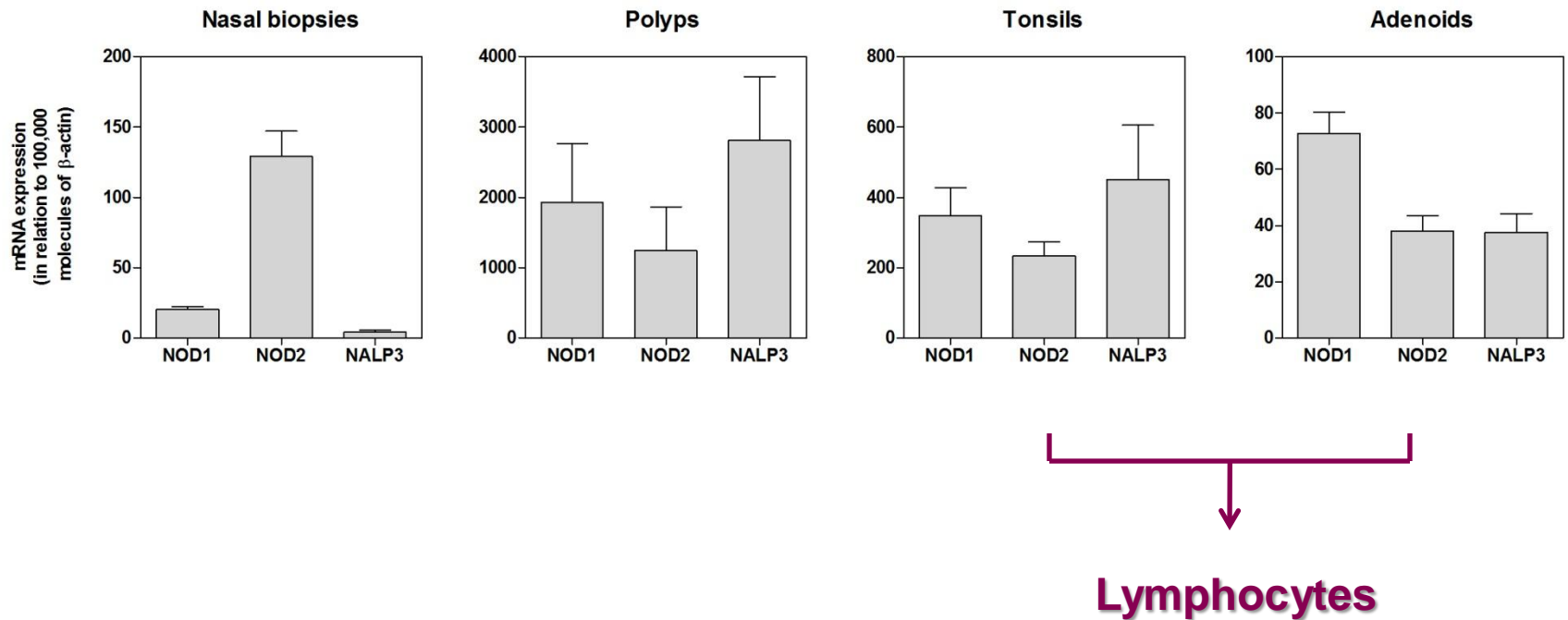
NLRs in eosinophils and neutrophils



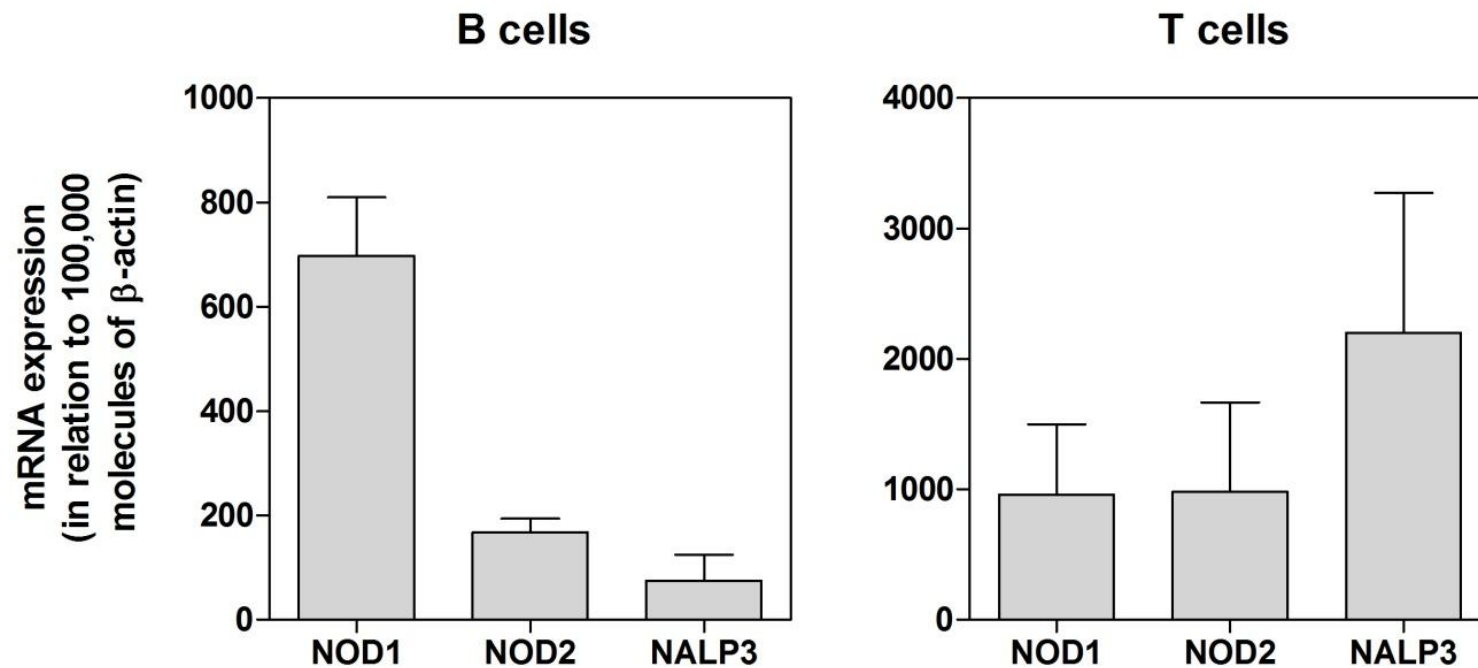
NLRs in eosinophils



Presence of NLRs in human airways

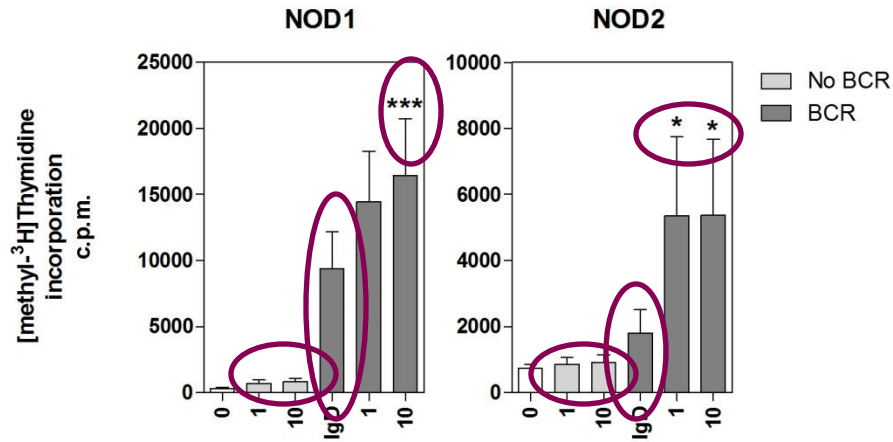


NLRs in lymphocytes

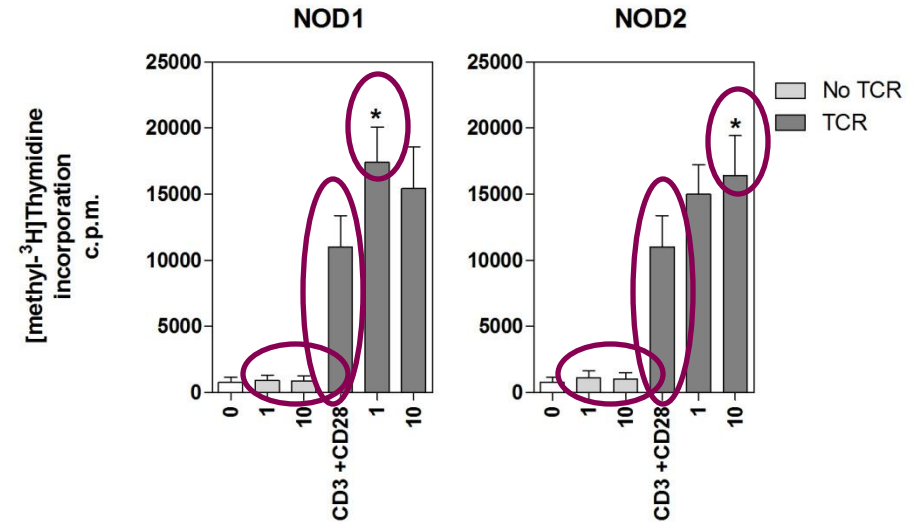


NLRs in lymphocytes

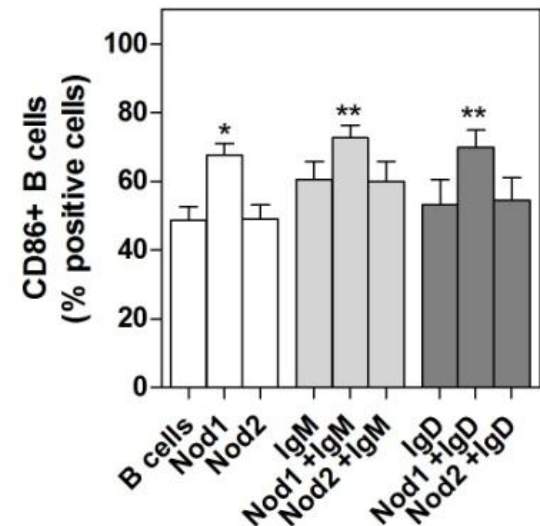
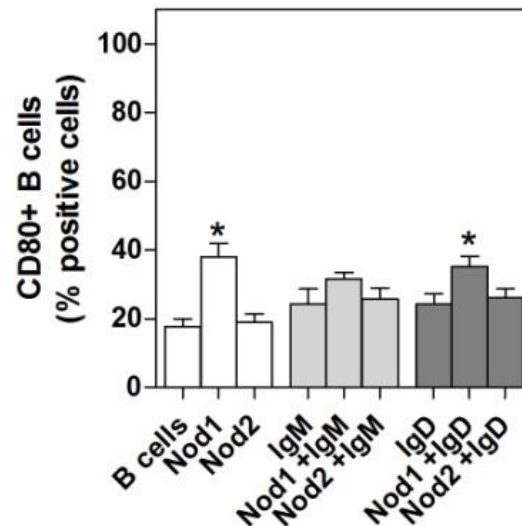
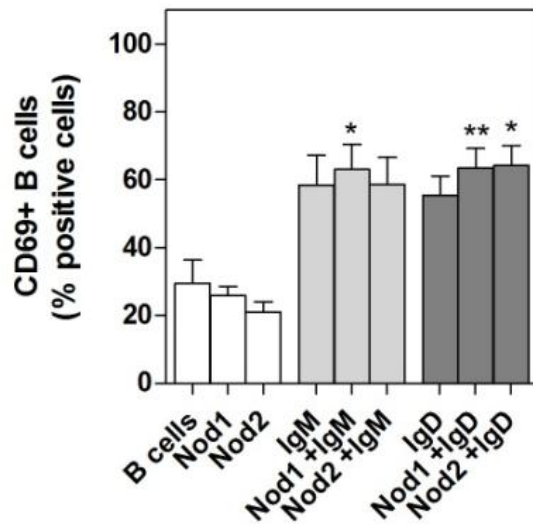
B cells



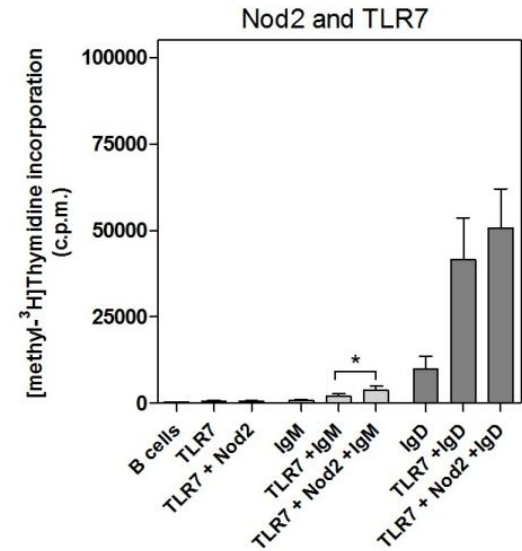
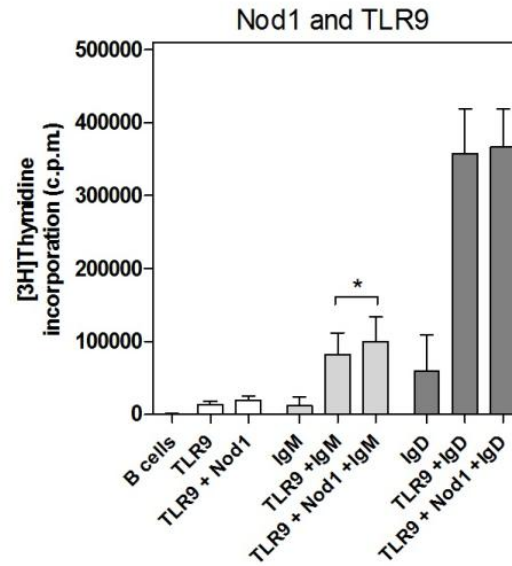
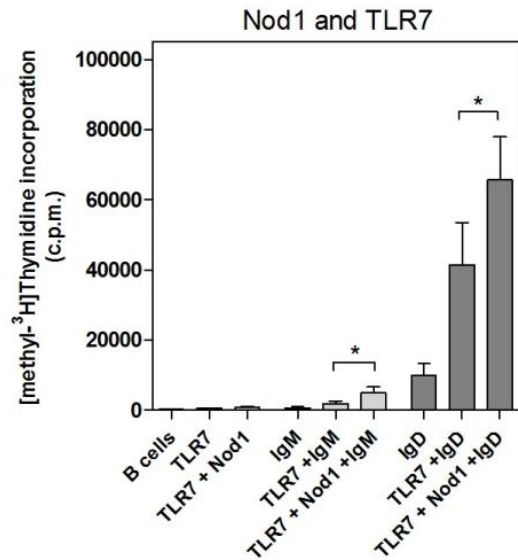
T cells



NLRs in lymphocytes



NLRs in lymphocytes



Summary

- NLRs are present in the human airways
 - Nasal biopsies, polyps, tonsils and adenoids
- NLRs are expressed in human cells
 - Epithelial cells, neutrophils, eosinophils and lymphocytes
- NLRs are linked to allergic disorders
 - NOD1 and NALP3 are down-regulated in allergic patients during pollen season
 - Th2 cytokines enhance NLR-induced responses of eosinophils

Future perspectives

- The PRR family keeps growing
- Alum mediates effect via the NALP3 inflammasome
- The discovery of more ligands will enable us to understand the complex roles of NLRs in host defence both in health and diseases