

DR. LIZZY WANKA (Orcid ID : 0000-0002-5725-8227)

Article type : Letter to the Editor

Corresponding author mail id : ujappe@fz-borstel.de

Trained Immunity and Allergy: State of the Art and Future Perspectives

Lizzy Wanka¹ and Uta Jappe^{1,2}

¹ Division of Clinical and Molecular Allergology, Research Center Borstel - Leibniz Lung Center, Priority Area Asthma and Allergy, Airway Research Center North (ARCN), German Center for Lung Research (DZL), 23845 Borstel, Germany.

² Interdisciplinary Allergy Outpatient Clinic, MK III, University of Lübeck, Airway Research Center North (ARCN), German Center for Lung Research (DZL), 23538 Lübeck, Germany.

To the Editor,

Allergic diseases have become a global challenge during the last decades. Therefore, much effort has gone into understanding the mechanisms of allergy and improving diagnostic measures and treatment efficacy (precision medicine). Recently, the mechanistic understanding of immunity and its characteristics was considerably renewed by the upcoming research field of „trained immunity“, where the classical principle that only the adaptive immune system is able to build up a memory to reinfection with pathogens, was re-thought¹.

Netea *et al.* defined “trained immunity” as a reaction to a pathogenic insult (“first hit”), including environmental factors, microbial proteins and allergens, with subsequent epigenetic, metabolic

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14617](https://doi.org/10.1111/ALL.14617)

This article is protected by copyright. All rights reserved

and functional reprogramming of innate immune cells, resulting in a non-specific, modulated response to secondary stimuli ("second hit"). The concept of an innate immune memory explains why an „immunological memory“ is even observed in plants and invertebrates, organisms lacking adaptive immunity^{1,2}. As described several times for the tuberculosis vaccine *bacillus Calmette-Guérin* (BCG), trained immunity also explains cross-protection, a heightened response to a second infection, whereby it is independent whether this occurs to the same pathogen or a different one^{1,2}. This non-specific immune response seems unlikely for the classical highly specific allergic response, however, helminth³ as well as virus infections⁴ have been shown to affect both, tolerance or the increased risk of reactions to allergens.

Figure 1 displays an overview on the different aspects of trained immunity and where this concept is linked to allergy. Both, a systemic as well as a local trained immunity exist: Systemic trained immunity is induced at the level of bone marrow progenitor cells due to stimulation of these cells with BCG or the microbial β -glucan. The trained progenitor cells mature to monocytes and differentiate to trained effector cells such as macrophages or NK cells at their respective place of action². In contrast, local training of differentiated effector cells takes place in the peripheral tissue. Here, epithelial cells form the first line of defense, but this barrier can be overcome/activated by allergens and microbial products and is key to allergenic sensitization. Several allergens possess proteolytic activity and are able to cleave tight junctions and consequently provide a way through the epithelial layer⁵. Der p 2 mimics the myeloid differentiation protein-2 by binding LPS, which stimulates the Toll-like receptor 4 at the surface of epithelial cells and induces an T_H2 -like inflammation⁵. The paradigm that an allergen alone cannot overcome the epithelial barrier without enzymatic function or adjuvants was overthrown by the demonstration that grass pollen allergens were taken up by airway epithelial cells and were transported as intact allergens through the epithelium⁵. Besides allergens also microbial products can overcome/activate the epithelium, for example β -glucan for which trained immunity effects have explicitly been observed^{1,2}. Whether this activation of epithelial cells already fits the trained immunity characteristic of a change in cell function will be part of future research. Finally, environmental factors or respiratory diseases can increase the permeability of the epithelial barrier for allergens⁵.

The presence of a broad range of cytokines, chemokines, allergens, and microbial products mediates complex cellular processes with innate and adaptive immune cells. The cytokines thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 were shown to induce trained immunity⁶ and are also involved in the development of allergic responses. TSLP and IL-33 are important for the activation of group 2 innate lymphoid cells (ILC2s) which secrete IL-4, IL-5, and IL-13. IL-4 triggers the T_H2 immune response, and IL-5 is involved in the activation of B cells and mediates eosinophilia, whereas IL-13 induces mucus secretion and airway hyperreactivity. ILC2s were found to be sufficient to induce asthma-like pathological changes even in the absence of adaptive immune cells, and trained ILC2s show enhanced secretion of T_H2-type cytokines after re-stimulation⁷. Thus, ILC2s may have an enormous impact on the development of allergy, and T_H2-type allergic airway inflammation can develop independently of adaptive immunity. A second example therefore is the activation of an invariant NKT cell subpopulation after viral infection, subsequently recruiting and activating lung macrophages, expressing IL-13 and its receptor. This creates a positive feedback loop which results in a persistent expression of IL-13, causing chronic mucous cell metaplasia and airway hyperreactivity⁸. The persistent expression of cytokines displays no trained immunity effect by definition but leads to chronification of the inflammation process.

A new link between the two immune systems where the adaptive immune system activates the innate immune memory, was described after a viral infection, inducing trained alveolar macrophages with changed metabolism and anti-microbial responsiveness⁹. The education of these macrophages required activated CD8⁺ T-cells and the release of interferon γ . This and other described effects of trained immunity are mediated through modulation of transcription factors and metabolic as well as epigenetic reprogramming of cells in contrast to gene rearrangement and proliferation of antigen-specific lymphocyte clones, forming the base for adaptive immune memory¹.

Altogether, figure 1 illustrates that there are innate immune cells which developed a memory effect without having changed their original function or which modulate/are modulated by the adaptive immune system and thus are not part of the trained immunity concept even when they differ considerably from the classical understanding of innate immune responses. Little is known about the existence or mechanisms of allergic trained immunity but pathological outcomes of

trained immunity were already shown for inflammatory and neurodegenerative diseases², and there is some evidence that this research field will reveal several well-guarded secrets about allergenic processes. Most likely, the allergic response is a highly regulated and complex mechanism with members of both, the innate and adaptive immune system, and this link is maybe also the key feature of very potent allergens. However, since an association between infections and allergy has been known for quite some time, it is most plausible that phenomena of innate immune memory observed for infections are also active in the development of allergy. First, *in vitro* studies could show how different innate immune cells react to allergen stimulation after training with pathogens and *in vivo* experiments with allergic mouse models after stimulation with pathogens/vaccines might support these investigations.

Figure 1: Impact of pathogens and foreign proteins/allergens on the development of allergy with emphasis on links to trained immunity¹⁻⁹. The immune stimulation with environmental factors, pathogens and proteins can lead to an enhanced immune response or even to a diminished immune reaction after re-stimulation as result of trained immunity. The training of immune cells can take place systemically within the bone marrow or locally in tissue. Here, diverse pathways are activated and linked to each other, and an orchestra of cytokines and chemokines mediates the induction trained immunity (shown in violet). More detailed description in the online supplement.

Abbreviations:

AM- alveolar macrophage, BCG- *bacillus Calmette-Guérin*, DC- dendritic cell, IL- interleukin, ILC2- group 2 innate lymphoid cells, IFN- γ - Interferon γ , LPS- lipopolysaccharide, M- macrophage, MO- monocyte, NK- natural killer cell, PRR- pattern recognition receptors, TLR4- toll-like receptor 4, TSLP- thymic stromal lymphopoietin

Authors and Affiliation:

Lizzy Wanka¹ and Uta Jappe^{1,2}

¹ Division of Clinical and Molecular Allergology, Research Center Borstel - Leibniz Lung Center, Priority Area Asthma and Allergy, Airway Research Center North (ARCN), German Center for Lung Research (DZL), 23845 Borstel, Germany.

² Interdisciplinary Allergy Outpatient Clinic, MK III, University of Lübeck, Airway Research Center North (ARCN), German Center for Lung Research (DZL), 23538 Lübeck, Germany.

Funding and Acknowledgement:

The authors gratefully acknowledge the funding of the Federal Ministry of Education and Research [German Center for Lung Research (DZL)]

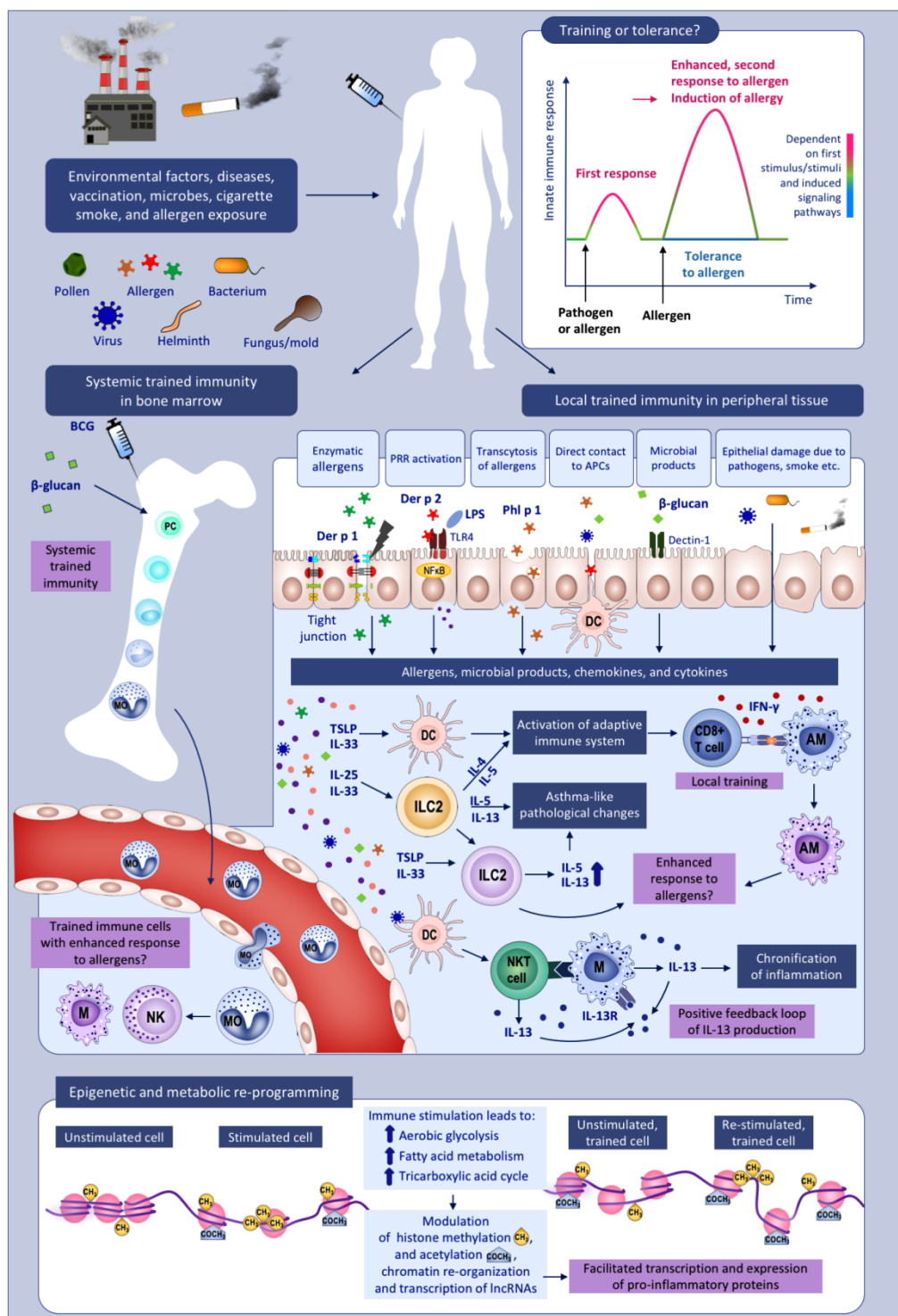
Conflict of interest:

Prof. Jappe reports grants and personal fees from Federal Ministry of Education and Science, German Center for Lung Research, during the conduct of the study.

References:

1. Netea MG, Joosten LA, Latz E, et al. Trained immunity: A program of innate immune memory in health and disease. *Science*. 2016;352(6284):aaf1098.
2. Netea MG, Dominguez-Andres J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol*. 2020.
3. Maizels RM. Regulation of Immunity and allergy by helminth parasites. *Allergy*. 2019.
4. Malinczak CA, Lukacs NW, Fonseca W. Early-Life Respiratory Syncytial Virus Infection, Trained Immunity and Subsequent Pulmonary Diseases. *Viruses*. 2020;12(5).
5. Golebski K, Roschmann KI, Toppila-Salmi S, et al. The multi-faceted role of allergen exposure to the local airway mucosa. *Allergy*. 2013;68(2):152-160.
6. Corren J, Ziegler SF. TSLP: from allergy to cancer. *Nat Immunol*. 2019;20(12):1603-1609.
7. Helfrich S, Mindt BC, Fritz JH, Duerr CU. Group 2 Innate Lymphoid Cells in Respiratory Allergic Inflammation. *Front Immunol*. 2019;10:930.

8. Kim EY, Battaile JT, Patel AC, et al. Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease. *Nat Med.* 2008;14(6):633-640.
9. Yao Y, Jeyanathan M, Haddadi S, et al. Induction of Autonomous Memory Alveolar Macrophages Requires T Cell Help and Is Critical to Trained Immunity. *Cell.* 2018;175(6):1634-1650 e1617.



all_14617_f1.png

Supplement – Description of Figure 1

The diversity of factors which influences the induction of trained immunity reaches from environmental factors to different classes of pathogens such as viruses¹, bacteria² and fungi³. Nevertheless, the infection with a pathogen does not always result in an inflammatory response and a development of allergy but it can modulate the immune responses in several ways. This modulation of inflammation was described for helminth infections and allergy. Quinn *et al.* described a trained immunity after helminth infection with anti-inflammatory effect⁴, and in line with the hygiene-hypothesis a decrease in allergic diseases was observed in areas with a high prevalence of chronic helminth infections^{5,6}. In contrast, the most common soil-transmitted nematode *Ascaris lumbricoides* is very allergenic, and the IgE responses to this helminth are a risk factor for asthma at all ages⁷. It was found that acute helminth infections enhance the allergic inflammation which can be directed against parasites and non-parasites⁸. Chronic infections in areas with strong helminth infections can suppress the allergic inflammation by immune modulation⁸. Thus, the stimulation of human innate immune cells with helminths can result in **tolerance or training** of the innate immune cells. Similar results were observed for virus infections (Figure part “Training or Tolerance?”). It was found that infections with murine herpesvirus 4 can inhibit the development of house dust mite-induced asthma in mice⁹. In contrast, respiratory syncytial virus (RSV) infections are able to train innate immune cells, especially macrophages and dendritic cells to an enhanced response to unrelated exposures such as allergen stimulation¹. Only little is known about the determinants being responsible for the decision between training or tolerance. It was shown that the pattern recognition receptors (PRR) which are engaged in the mediation of the immunological response may have an impact on the immunological effect¹⁰. The activation of Nod-like receptors induces trained immunity whereas the activation of Toll-like receptors (TLRs) with high doses of TLR ligand induces tolerance¹⁰. In contrast, low doses of TLR ligands were found to train the monocytes¹⁰. The itaconate pathway was identified as mediator of the LPS induced immune tolerance and was inhibited by β -glucan inducing the trained immunity effect¹¹. Thus, the induction of training or tolerance depends on the stimuli and the activated signaling pathways.

If there is an induction of training within the innate immune cells, there are two possible concepts. First, the **systemic trained immunity**, being observed in hematopoietic stem cells and multipotent progenitors within the bone marrow of mice after intravenous vaccination with bacillus Calmette-Guérin (BCG)² (Figure part “Systemic trained immunity in bone marrow”). The vaccination led to an enhanced myelopoiesis and local cell expansion. The trained hematopoietic stem cells generated epigenetically modified macrophages with improved protection against tuberculosis infection compared to naïve macrophages². This training effect was also reported for hematopoietic progenitors upon β -glucan stimulation¹². A second vaccine with protective impact is the whole-cell pertussis vaccination which results in a decreased risk of IgE-mediated food allergy but the molecular mechanism remains unclear¹³.

The second concept of trained immunity is the **local immune memory** in peripheral tissue, which is observable in different cell types, the epithelial barrier being the starting point for these various processes (Figure part: “local trained immunity in peripheral tissue”). Several allergens possess proteolytic activity, such as the house dust mite (*Dermatophagoides pteronyssinus*) major allergen Der p 1, which is able to cleave the tight junctions’ molecules occludin and claudin between epithelial cells

and consequently provides a way through the epithelium layer¹⁴. Other allergens, like Der p 2, are lipophilic proteins, able to bind lipids. The effect of such complexes in the allergen-barrier-interaction is a receptor-mediated activation of epithelial cells via mimicry: Der p 2 mimics the myeloid differentiation *protein-2* (MD-2) by binding lipopolysaccharide (LPS), which stimulates the TLR 4 at the surface of epithelial cells. Thus, the epithelial cells are stimulated and release mediators of the innate immune response¹⁵. The paradigm that an allergen/protein alone cannot activate the epithelial barrier without enzymatic function or adjuvant lipids was overthrown by several further studies. Röschmann et al. demonstrated that purified timothy grass pollen (*Phleum pratense*) major allergen Phl p 1 stimulated airway epithelial cells and induced the modulation and release of a broad range of mediators (e.g. IL-6, IL-8 and TGF- β) through a non-proteolytic activity¹⁶. Moreover, the uptake of Phl p 1 and Phl p 6 by bronchial epithelial cells and alveolar epithelial cells was observed. The intact allergens were transported through the epithelial barrier and were released rapidly by exocytosis¹⁷. These allergens may also directly interact with dendritic cells within the epithelial cell layer and thus, induce further immune processes¹⁸.

Allergens are often part of a mixture of proteins besides spores from fungi or microbial products from resident bacteria or viruses^{19,20}, and also these microbial products can overcome or activate the epithelium. β -glucan, a cell wall component of fungi and an element of house dust²¹, is described to bind the C-type lectin dectin-1²², which was shown to be among others expressed on human bronchial epithelial cells²³. Here, dectin-1 induces phagocytosis and prepares an immune response in collaboration with Toll-like receptors (reviewed in²⁴).

Another class of microbial products, which is associated with allergic inflammation, are bacterial superantigens. One prominent example is staphylococcal enterotoxin B (SEB), a soluble exotoxin from *Staphylococcus aureus*²⁵. *Staphylococcus aureus* is for about 25 % of the population a permanent part of the microflora of the skin, the upper respiratory tract as well as the intestinal tract²⁶. The staphylococcal superantigens are released within the airway epithelium and act on B lymphocytes where they induce an antibody class switch to the production of polyclonal IgE and IgE against the superantigen itself, showing that the superantigen becomes a superallergen. Superallergens are able to activate human basophils and mast cells to release proinflammatory mediators and cytokines^{27,28}.

Environmental factors like cigarette smoke or respiratory diseases such as COPD, infections, and asthma can also increase the permeability of the epithelial barrier²⁹⁻³¹ thus, there is a broad variation of possibilities to overcome or activate the epithelium, and the allergens and microbial products are together with mediator molecules now accessible behind the epithelial barrier and activate and modulate diverse pathways and cell types. Important mediators of inflammation are the thymic stromal lymphopoietin (TSLP), an interleukin 7 (IL-7)-like cytokine, being among others produced by epithelial lung cells³² and IL-33, a member of the IL-1 family, which is released by damaged epithelial cells, dendritic cells, and macrophages³³ and is a modulator of type 2 innate and adaptive immunity and inflammation³⁴. This was shown for a specific subset of lymphoid cells in the lung of mice which was found to produce the T_H2-type cytokines IL-5 and IL-13 in response to IL-33 and TSLP during allergic airway inflammation and in murine models of allergic asthma³⁵⁻³⁷. These cells are necessary and sufficient to induce airway eosinophilia and asthma-like pathological changes to fungal allergens (*Alternaria alternata*) even in the absence of cells of the adaptive immune system³⁵. The authors

conclude that T_H2-type allergic airway inflammation can develop independently of adaptive immunity^{35,36}. These results were confirmed by *Kim et al.*, who described the development of airway hyperreactivity by innate lymphoid cells in the absence of T_H2 cells and adaptive immunity³⁸. Here, a pathway including IL-13 and IL-33, cytokines of the innate immune system, leads to the pathological lung reaction^{35,38,39}. These cytokines play also a role in the development of chronic lung diseases which was shown in a synchronized analysis of a mouse model and human samples⁴⁰. After a viral infection, an invariant NKT cell subpopulation is activated and recruits and activates lung macrophages, which express IL-13 and the IL-13 receptor, creating a positive feedback loop. This results in a persistent expression of IL-13, causing chronic mucous cell metaplasia and airway hyperreactivity, characteristics of chronic inflammatory lung diseases⁴⁰. Further studies with NKT-deficient mice report that the NKT cells are necessary to develop allergen-induced airway hyperreactivity even when the T_H2 helper cells are present^{41,42}.

Previous studies by Martinez-Gonzalez *et al.* describe a training effect also in group 2 innate lymphoid cells (ILCs) and show simultaneously the enormous impact on allergy⁴³. Intranasal injections of IL-33 stimulated ILCs in mice. A second stimulation with the allergen papain led to an enhanced secondary response of ILCs as well as increased cell proliferation and production of type 2 cytokines⁴³. This heightened response to re-stimulation shows a training effect, but the definition of „trained immunity“ is only partly fulfilled because the ILCs do not acquire a new function⁴³.

Finally, Yao *et al.* described in recent studies a new link between the two immune systems where the adaptive immune system activates the unspecific innate immune memory and thus, a new way to educate innate immune cells³. Here, an acute respiratory viral infection induced trained alveolar macrophages with changed surface marker and gene expression, metabolism and an anti-microbial responsiveness³. The education of these macrophages required activated CD8⁺ T-cells and the release of interferon γ . Interferon γ seems to be a key mediator in trained immunity, because it is not only elementary for the local induction of innate immune memory in the respiratory tract but also for the systemic trained immunity in the education of myeloid progenitor cells within the bone marrow².

The basis of these training effects in innate immune cells is the **epigenetic reprogramming** of transcriptional pathways which enables these cells to react with a faster, increased response to different stimuli and modulates the cellular metabolism (figure part: “epigenetic and metabolic reprogramming”). The complex molecular basis of these reprogramming processes is subject of ongoing studies and has only partly been elucidated but includes changes in chromatin organization at the level of the topologically associated domains (TADs), transcription of long non-coding RNAs (lncRNAs), DNA methylation and reprogramming of cellular metabolisms like the mTOR and HIF-1 α mediated aerobic glycolysis⁴⁴⁻⁴⁶. Interestingly, the different stimuli such as BCG vaccine or β -glucan can induce different trained immunity programmes, reviewed in detail by *Netea et al.*⁴⁶, and demonstrating the complexity of this new concept.

References:

1. Malinczak CA, Lukacs NW, Fonseca W. Early-Life Respiratory Syncytial Virus Infection, Trained Immunity and Subsequent Pulmonary Diseases. *Viruses*. 2020;12(5).

- 123 2. Kaufmann E, Sanz J, Dunn JL, et al. BCG Educates Hematopoietic Stem Cells to Generate
124 Protective Innate Immunity against Tuberculosis. *Cell*. 2018;172(1-2):176-190 e119.
- 125 3. Yao Y, Jeyanathan M, Haddadi S, et al. Induction of Autonomous Memory Alveolar Macrophages
126 Requires T Cell Help and Is Critical to Trained Immunity. *Cell*. 2018;175(6):1634-1650 e1617.
- 127 4. Quinn SM, Cunningham K, Raverdeau M, et al. Anti-inflammatory Trained Immunity Mediated by
128 Helminth Products Attenuates the Induction of T Cell-Mediated Autoimmune Disease. *Front*
129 *Immunol*. 2019;10:1109.
- 130 5. Maizels RM. Regulation of Immunity and allergy by helminth parasites. *Allergy*. 2019.
- 131 6. Weiss ST. Parasites and asthma/allergy: what is the relationship? *J Allergy Clin Immunol*.
132 2000;105(2 Pt 1):205-210.
- 133 7. Ahumada V, Garcia E, Dennis R, et al. IgE responses to Ascaris and mite tropomyosins are risk
134 factors for asthma. *Clin Exp Allergy*. 2015;45(7):1189-1200.
- 135 8. Cooper PJ. Can intestinal helminth infections (geohelminths) affect the development and
136 expression of asthma and allergic disease? *Clin Exp Immunol*. 2002;128(3):398-404.
- 137 9. Machiels B, Dourcy M, Xiao X, et al. A gammaherpesvirus provides protection against allergic
138 asthma by inducing the replacement of resident alveolar macrophages with regulatory
139 monocytes. *Nat Immunol*. 2017;18(12):1310-1320.
- 140 10. Ifrim DC, Quintin J, Joosten LA, et al. Trained immunity or tolerance: opposing functional
141 programs induced in human monocytes after engagement of various pattern recognition
142 receptors. *Clin Vaccine Immunol*. 2014;21(4):534-545.
- 143 11. Dominguez-Andres J, Novakovic B, Li Y, et al. The Itaconate Pathway Is a Central Regulatory Node
144 Linking Innate Immune Tolerance and Trained Immunity. *Cell Metab*. 2019;29(1):211-220 e215.
- 145 12. Mitroulis I, Ruppova K, Wang B, et al. Modulation of Myelopoiesis Progenitors Is an Integral
146 Component of Trained Immunity. *Cell*. 2018;172(1-2):147-161 e112.
- 147 13. Estcourt MJ, Campbell DE, Gold MS, et al. Whole-Cell Pertussis Vaccination and Decreased Risk of
148 IgE-Mediated Food Allergy: A Nested Case-Control Study. *J Allergy Clin Immunol Pract*.
149 2020;8(6):2004-2014.
- 150 14. Wan H, Winton HL, Soeller C, et al. Der p 1 facilitates transepithelial allergen delivery by
151 disruption of tight junctions. *J Clin Invest*. 1999;104(1):123-133.
- 152 15. Trompette A, Divanovic S, Visintin A, et al. Allergenicity resulting from functional mimicry of a
153 Toll-like receptor complex protein. *Nature*. 2009;457(7229):585-588.
- 154 16. Röschmann K, Farhat K, König P, Suck R, Ulmer AJ, Petersen A. Timothy grass pollen major
155 allergen Phl p 1 activates respiratory epithelial cells by a non-protease mechanism. *Clin Exp*
156 *Allergy*. 2009;39(9):1358-1369.
- 157 17. Blume C, Foerster S, Gilles S, et al. Human epithelial cells of the respiratory tract and the skin
158 differentially internalize grass pollen allergens. *J Invest Dermatol*. 2009;129(8):1935-1944.
- 159 18. Holt PG, Schon-Hegrad MA, Oliver J, Holt BJ, McMenemy PG. A contiguous network of dendritic
160 antigen-presenting cells within the respiratory epithelium. *Int Arch Allergy Appl Immunol*.
161 1990;91(2):155-159.
- 162 19. Golebski K, Röschmann KI, Toppila-Salmi S, et al. The multi-faceted role of allergen exposure to
163 the local airway mucosa. *Allergy*. 2013;68(2):152-160.
- 164 20. Gehring U, Heinrich J, Hoek G, et al. Bacteria and mould components in house dust and children's
165 allergic sensitisation. *Eur Respir J*. 2007;29(6):1144-1153.
- 166 21. Gehring U, Douwes J, Doekes G, et al. Beta(1-->3)-glucan in house dust of German homes:
167 housing characteristics, occupant behavior, and relations with endotoxins, allergens, and molds.
168 *Environ Health Perspect*. 2001;109(2):139-144.
- 169 22. Brown GD, Herre J, Williams DL, Willment JA, Marshall AS, Gordon S. Dectin-1 mediates the
170 biological effects of beta-glucans. *J Exp Med*. 2003;197(9):1119-1124.
- 171 23. Sun WK, Lu X, Li X, et al. Dectin-1 is inducible and plays a crucial role in *Aspergillus*-induced innate
172 immune responses in human bronchial epithelial cells. *Eur J Clin Microbiol Infect Dis*.
173 2012;31(10):2755-2764.
- 174 24. Underhill DM. Collaboration between the innate immune receptors dectin-1, TLRs, and Nods.
175 *Immunol Rev*. 2007;219:75-87.

- 176 25. White J, Herman A, Pullen AM, Kubo R, Kappler JW, Marrack P. The V beta-specific superantigen
177 staphylococcal enterotoxin B: stimulation of mature T cells and clonal deletion in neonatal mice.
178 *Cell*. 1989;56(1):27-35.
- 179 26. Jappe U. Superantigens and their association with dermatological inflammatory diseases: facts
180 and hypotheses. *Acta Derm Venereol*. 2000;80(5):321-328.
- 181 27. Stow NW, Douglas R, Tantilipikorn P, Lacroix JS. Superantigens. *Otolaryngol Clin North Am*.
182 2010;43(3):489-502, vii.
- 183 28. Marone G, Rossi FW, Detoraki A, et al. Role of superallergens in allergic disorders. *Chem Immunol*
184 *Allergy*. 2007;93:195-213.
- 185 29. Coyne CB, Bergelson JM. Virus-induced Abl and Fyn kinase signals permit coxsackievirus entry
186 through epithelial tight junctions. *Cell*. 2006;124(1):119-131.
- 187 30. Xiao C, Puddicombe SM, Field S, et al. Defective epithelial barrier function in asthma. *J Allergy Clin*
188 *Immunol*. 2011;128(3):549-556 e541-512.
- 189 31. Aghapour M, Raee P, Moghaddam SJ, Hiemstra PS, Heijink IH. Airway Epithelial Barrier
190 Dysfunction in Chronic Obstructive Pulmonary Disease: Role of Cigarette Smoke Exposure. *Am J*
191 *Respir Cell Mol Biol*. 2018;58(2):157-169.
- 192 32. Corren J, Ziegler SF. TSLP: from allergy to cancer. *Nat Immunol*. 2019;20(12):1603-1609.
- 193 33. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1
194 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity*.
195 2005;23(5):479-490.
- 196 34. Enoksson M, Lyberg K, Moller-Westerberg C, Fallon PG, Nilsson G, Lunderius-Andersson C. Mast
197 cells as sensors of cell injury through IL-33 recognition. *J Immunol*. 2011;186(4):2523-2528.
- 198 35. Bartemes KR, Iijima K, Kobayashi T, Kephart GM, McKenzie AN, Kita H. IL-33-responsive lineage-
199 CD25+ CD44(hi) lymphoid cells mediate innate type 2 immunity and allergic inflammation in the
200 lungs. *J Immunol*. 2012;188(3):1503-1513.
- 201 36. Klein Wolterink RG, Kleinjan A, van Nimwegen M, et al. Pulmonary innate lymphoid cells are
202 major producers of IL-5 and IL-13 in murine models of allergic asthma. *Eur J Immunol*.
203 2012;42(5):1106-1116.
- 204 37. Toki S, Goleniewska K, Zhang J, et al. TSLP and IL-33 reciprocally promote each other's lung
205 protein expression and ILC2 receptor expression to enhance innate type-2 airway inflammation.
206 *Allergy*. 2020.
- 207 38. Kim HY, Chang YJ, Subramanian S, et al. Innate lymphoid cells responding to IL-33 mediate airway
208 hyperreactivity independently of adaptive immunity. *J Allergy Clin Immunol*. 2012;129(1):216-227
209 e211-216.
- 210 39. Chang YJ, Kim HY, Albacker LA, et al. Innate lymphoid cells mediate influenza-induced airway
211 hyper-reactivity independently of adaptive immunity. *Nat Immunol*. 2011;12(7):631-638.
- 212 40. Kim EY, Battaile JT, Patel AC, et al. Persistent activation of an innate immune response translates
213 respiratory viral infection into chronic lung disease. *Nat Med*. 2008;14(6):633-640.
- 214 41. Akbari O, Stock P, Meyer E, et al. Essential role of NKT cells producing IL-4 and IL-13 in the
215 development of allergen-induced airway hyperreactivity. *Nat Med*. 2003;9(5):582-588.
- 216 42. Lisbonne M, Diem S, de Castro Keller A, et al. Cutting edge: invariant V alpha 14 NKT cells are
217 required for allergen-induced airway inflammation and hyperreactivity in an experimental asthma
218 model. *J Immunol*. 2003;171(4):1637-1641.
- 219 43. Martinez-Gonzalez I, Matha L, Steer CA, Ghaedi M, Poon GF, Takei F. Allergen-Experienced Group
220 2 Innate Lymphoid Cells Acquire Memory-like Properties and Enhance Allergic Lung Inflammation.
221 *Immunity*. 2016;45(1):198-208.
- 222 44. Cheng SC, Quintin J, Cramer RA, et al. mTOR- and HIF-1alpha-mediated aerobic glycolysis as
223 metabolic basis for trained immunity. *Science*. 2014;345(6204):1250684.
- 224 45. Weichhart T, Hengstschlager M, Linke M. Regulation of innate immune cell function by mTOR.
225 *Nat Rev Immunol*. 2015;15(10):599-614.
- 226 46. Netea MG, Dominguez-Andres J, Barreiro LB, et al. Defining trained immunity and its role in
227 health and disease. *Nat Rev Immunol*. 2020.