APSR RESPIRATORY UPDATES

Volume 9 Issue 5 Newsletter Date: May 2017

APSR EDUCATION PUBLICATION

Inside this issue: Asthma

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Nicotinic acetylcholine receptor agonist attenuates ILC2-dependent airway hyperreactivity

Authors: Galle-Treger L et al

Reference: Nat Commun. 2016 18; 7: 13202

URL https://www.ncbi.nlm.nih.gov/pubmed/27752043

Comment: Type 2 innate lymphoid cells (ILC2s) are involved in allergic asthma by releasing large amounts of Th2 cytokines, particularly IL-5 and IL-13, and causing the development of airway hyperresponsiveness (AHR). Therefore, inhibition of ILC2 function might be potential therapeutic target for the treatment ILC2-mediated asthma. This study have demonstrated that ILC2s express the a7-nicotinic acetylcholine receptor (a7nAChR), which plays an anti-inflammatory role in several inflammatory diseases. Induction of a7nAChR on ILC2s by a specific agonist results in suppression of IL-5 and IL-13 production and ILC2-dependent AHR. This results from downregulation of GATA-3 and NF-kB. The specific a7nAChR agonist also downregulates Th2 cytokine production in a humanized ILC2 mouse model. The authors conclude that a7nAChR is a potential therapeutic target for the treatment of ILC2-perpetuated asthma.

Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation

Authors: Fujimura KE et al.

Reference: Nat Med. 2016; 22: 1187-1191.

URL https://www.ncbi.nlm.nih.gov/pubmed/27618652

Comment: This study has demonstrated a link between neonatal gut microbiota and the risk of development of asthma and atopy on the ground of previous report that gut microbiota bacterial depletions and altered metabolic activity at 3 months is associated with childhood atopy and asthma. It found that neonates with high risk of having multisensitized atopy at age 2 years and doctor-diagnosed asthma at age 4 years had distinct pattern of gut microbiome (lower relative abundance of certain bacteria, i.e. *Bifidobacterium*, *Akkermansia* and *Faecalibacterium*) with fecal pro-inflammatory metabolites. $CD4^+$T cells response to this gut microbiome dysbiosis showed increased IL-4 production with lower relative abundance of $CD4^+CD25^+FOXP3^+$ cells. The authors conclude neonatal gut dysbiosis might enhance $CD4^+$T cell dysfunction favoring Th2 response and therefore associates childhood atopy.

An asthma-associated IL4R variant exacerbates airway inflammation by promoting conversion of regulatory T cells to TH17-like cells

Authors: Massoud AH et al.

Reference: Nat Med. 2016 ; 22: 1013-22.

URL https://www.ncbi.nlm.nih.gov/pubmed/27479084

Comment: This study investigated the mechanism by which regulatory T cells failed to control inflammation in severe asthma that is associated with polymorphism in the gene coding the interleukin (IL)-4 receptor alpha chain (Il4ra(R576)). There is an increase in conversion of induced Treg (iTreg) cells toward a T helper 17 (TH17) cell bias that is mediated by IL-4Ra(R576)-induced recruitment of the growth-factor-receptor-bound protein 2 (GRB2) adaptor protein, which drives IL-17 expression. GRB2 adaptor protein activates a downstream pathway that contains extracellular-signal-regulated kinase, IL-6 and STAT3. The deletion of genes (IL6ra and RAR-related orphan receptor gamma) in Treg cells that regulate Th17 cell differentiation protected Il4ra (R576) mice against severe airway inflammation, which was comparable to the effects of neutralization of IL-6 with a specific antibody. Therefore, the stabilization of iTreg cells not reprogramming towards Th17 cell fate may be potentially effective therapeutic strategy in genetically prone severe asthmatics.

Increased mitochondrial arginine metabolism supports bioenergetics in asthma

Authors: Xu W et al.

Reference: J Clin Invest 2016; 126: 2465-81

URL https://www.ncbi.nlm.nih.gov/pubmed/27214549

Comment: This study sheds light on the mechanism(s) by which mitochondrial metabolism of arginine modulate gene expression, transcription factors, cell function, and inflammation that is associated with asthma pathogenesis. Greater arginine flux through arginase 2 (ARG2) into the mitochondria increases oxidative metabolism, dampens proinflammatory signal transduction events that are central to asthma origins, and serves as a brake on Th2 inflammation. The present study clearly showed that increased arginase activity in asthma resulted in greater mitochondrial arginine metabolism that is linked to changes in mitochondrial endotype and a shift toward oxidative bioenergetic pathways. The loss of mitochondrial arginine metabolism caused reduced production of nitric oxide (NO), lower mitochondrial membrane potential, greater activation of hypoxia sensing and Th2 signaling pathways, and more severe allergen-induced asthma. This was supported by the evidence that ARG2 overexpression in a human bronchial epithelial cell line enhanced oxidative bioenergetic pathways and suppressed hypoxia

inducible factors (HIFs) and phosphorylation of STAT6. In contrast, the lack of ARG2 in mice was associated with greater Th2 inflammation as shown by higher levels of pSTAT6, IL-13 and eosinophils, and more mucus metaplasia.

Targeting integrin alpha5beta1 ameliorates severe airway hyperresponsiveness in experimental asthma

Authors: Sundaram A et al.

Reference: J Clin Invest 2017; 127: 365-374

URL https://www.ncbi.nlm.nih.gov/pubmed/27918306

Comment: There are limited therapeutic options in severe asthma. Integrin has been previously shown to induce airway hyperresponsiveness in mice through downregulation of chymase. Chymase inhibits IL-13-augmented bronchoconstriction by cleaving fibronectin to disrupt tension transmission in airway smooth muscle (ASM), ASM adhesion, focal adhesion phosphorylation without alterations in calcium homeostasis or myosin light chain phosphorylation. This was the case for blockade of fibronectin-binding integrin $\alpha_5\beta_1$ in ASM via the same mechanisms of chymase, resulting in suppression of allergen-induced bronchoconstriction and enhancement of bronchodilator effect of isoproterenol. Therefore, $\alpha_5\beta_1$ is identified as potential therapeutic target to alleviate severe airway hyperresponsiveness.

Epithelial tethering of MUC5AC-rich mucus impairs mucociliary transport in asthma

Authors: Bonser LR et al.

Reference: J Clin Invest 2016; 126: 2367-71

URL https://www.ncbi.nlm.nih.gov/pubmed/27183390

Comment: Mucus plugging contributes to morbidity and mortality in asthma although development of this pathological mucus is not clear. The present study demonstrated that mucus plugs derived from fatal asthmatics are heterogeneous gels, whose compositions are the presence of distinct MUC5AC- and MUC5B-containing domains. IL-13 was able to induce formation of heterogeneous mucus gels that obviously disrupt mucociliary transport, despite normal ciliary function, through tethering of MUC5AC-containing mucus gel domains to mucus-producing cells in the epithelium. When tethered mucus was replaced with untethered mucus, this caused restoration of mucociliary transport. Authors draw the conclusion that tethering of MUC5AC-containing domains to the epithelium is likely to cause mucostasis and subsequent mucus plugging in asthma.

Regulation of T cell receptor signaling by DENND1B in TH2 cells and allergic disease

Authors: Yang CW et al.

Reference: Cell. 2016 Jan 14; 164: 141-55

URL https://www.ncbi.nlm.nih.gov/pubmed/26774822

Comment: The DENN domain is an evolutionary conserved protein module present in all eukaryotes functions enzymatically as Rab guanine nucleotide exchange factor by interacting with members of the Rab family of small GTPases. Variants in DENND1B contribute to development of childhood asthma and other immune disorders. To understand the mechanism of DENND1B involved in asthma and allergic disease, the present study was conducted to investigate this in Dennd1b$^{-/-}$ mice challenged with allergen. The results uncovered the mechanism of DENND1B that DENND1B is critical for downmodulation of the T cell receptor (TCR) in Th2 cells by promoting receptor internalization and subsequent destruction in endocytic vesicles. For this reason, providing that there is loss or mutations of DENND1B, this could enhance TCR signaling in Th2 cells and Th2 responses, and therefore puts individuals at extremely high risk for asthma.

Type I interferon restricts type 2 immunopathology through the regulation of group 2 innate lymphoid cells

Authors: Duerr CU et al.

Reference: Nat Immunol. 2016; 17: 65-75.

URL https://www.ncbi.nlm.nih.gov/pubmed/26595887

Comment: Viral respiratory tract infections archetypally induce the development of asthma and asthma exacerbations through the mechanisms that remain unexplained. This study highlighted the critical role of type I interferon (IFN) in negatively regulating group 2 innate lymphoid cells that express large amount of type 2 cytokines, including prominent IL-5 and IL-13. Type I IFN mediated this inhibition through the transcriptional activator ISGF3 that caused altered cytokine production, cell proliferation and increased cell death. In addition, IFN-γ and IL-27 suppressed ILC2 function in a STAT1-dependent manner. The mechanisms demonstrated in this study could explain why the deficiency in type I IFN, commonly seen in asthmatic airway epithelium, raised the susceptibility of asthmatics to viral infection-associated asthma exacerbations. In conclusion, type I and type II IFN, in concert with IL-27, modulate ILC2 cells to limit type 2 immunopathology in asthma.

DUOX1 mediates persistent epithelial EGFR activation, mucous cell metaplasia, and airway remodeling during allergic asthma

Authors: Habibovic A et al.

Reference: JCI Insight 2016; 1: e88811

URL https://www.ncbi.nlm.nih.gov/pubmed/27812543

Comment: Chronic epithelial EGFR expression and activation involved in chronic wound response has been implicated in the pathophysiology of asthma. However, the proximal mechanisms responsible for persistent EGFR activation are poorly understood. Oxidative stress in response to allergen challenge is the oxidative mechanism of airway EGFR activation in allergic asthma that requires the initial activation of the epithelial NADPH oxidase dual oxidase 1 (DUOX1). The activation of DUOX1 leads to the production of soluble EGFR ligands such as amphiregulin and enhanced EGFR tyrosine kinase activity. This study has demonstrated that DUOX1 mediates persistent EGFR activation, mucous cell metaplasia, and airway remodeling in allergic asthma. Pharmacologic and genetic inhibition of DUOX1 diminished oxidative EGFR activation and amphiregulin production. DUOX1 deficiency also suppressed multiple EGFR-dependent characteristics of HDM-induced allergic airway inflammation, including neutrophilic inflammation, both IL-13 and IL-33 production, mucous metaplasia, subepithelial fibrosis, and central airway resistance. Most importantly, direct inhibition of airway DUOX1 in previously established HDM-induced airway remodeling reversed most of these changes. Therefore, targeting DUOX1 may be an attractive target for novel pharmacotherapy in asthma.

Mitochondrial CaMKII inhibition in airway epithelium protects against allergic asthma

Authors: Sebag SC et al.

Reference: JCI Insight 2017; 2: e88297

URL https://www.ncbi.nlm.nih.gov/pubmed/28194433

Comment: Although excessive ROS generation promotes allergic asthma, the mechanisms underlying increased airway ROS and its association with disease phenotypes are poorly understood. The important source of cellular ROS production in mitochondria is regulated by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activated by oxidation. Targeted inhibition of mitochondrial ROS generation by antioxidant therapy could reduce the severity of allergic asthma. This study has demonstrated the effects of mitochondrial CaMKII inhibition in *Aspergillus fumigatus* challenged mice on several ROS-mediated immunopathological outcomes in airway epithelium. After this inhibition was introduced, there was the significant suppression of AHR, inflammation, and eosinophilia fol-

lowing lowering mitochondrial ROS. This was associated with downregulated induction of NF-κB, the NLRP3 inflammasome. The results provided clear insights into the mechanistic view how mitochondrial ROS establish pathological features of asthma.

Role for NLRP3 Inflammasome-mediated, IL-1beta-dependent Responses in Severe, Steroid-resistant Asthma

Authors: Kim RY et al.

Reference: Am J Respir Crit Care Med

URL https://www.ncbi.nlm.nih.gov/pubmed/28252317

Comment: Treatment for severe, steroid-resistant asthma is still ineffective and the major unmet need. This may be in part due to unclear pathogenic mechanisms driving perpetual airway inflammation. This study developed mouse models of respiratory infection-mediated, and ovalbumin-induced severe, steroid-resistant allergic airway disease, all of which share the hallmark features of human asthma, including airway neutrophilia, and both NLRP3 inflammasome and IL-1β activation. This study has demonstrated that NLRP3 inflammasome, caspase-1, and IL-1β drive steroid-resistant neutrophilic airway inflammation and hyperresponsiveness, whose expression correlates with severity, steroid resistance, and airway neutrophilia of human asthma. Simultaneous inhibition of NLRP3 inflammasome, caspase-1, and IL-1β could reverse steroid-resistant features of disease in mice, including IL-1β-induced steroid-resistant airway hyperresponsiveness.

More on this topic in Respirology:

Invited review series: Seeking Innovative Solutions for Severe Asthma,

Edited by Vanessa M McDonald, Peter G Gibson and Steven Maltby

- McDonald, V.M., Maltby, S. and Gibson, P.G. (2016) **Severe asthma: Can we fix it?.** Respirology, 22: 19–20. doi: 10.1111/resp.12956.
- McDonald, V.M., Maltby, S., Reddel, H.K., King, G.G., Wark, P.A.B., Smith, L., Upham, J.W., James, A.L., Marks, G.B. and Gibson, P.G. (2016) **Severe asthma: Current management, targeted therapies and future directions—A roundtable report.** Respirology, 22: 53–60. doi: 10.1111/resp.12957.
- Fricker, M., Heaney, L.G. and Upham, J.W. (2017) **Can biomarkers help us hit targets in difficult-to-treat asthma?**. Respirology, 22: 430–442. doi: 10.1111/resp.13014.
- Porsbjerg, C. and Menzies-Gow, A. (2017) **Co-morbidities in severe asthma: Clinical impact and management.** Respirology, doi: 10.1111/resp.13026.

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