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IL-17A inhibits airway reactivity induced by respiratory syncytial virus infection during allergic airway inflammation
TH2, allergy and group 2 innate lymphoid cells

Authors: Licona-Limón P et al.
URL: http://www.ncbi.nlm.nih.gov/pubmed/23685824

Comment: Extensive research has shown that epithelial cells can initiate type 2 immune responses by releasing IL-25, IL-33 and TSLP. Further studies have identified a new innate lymphoid subset that produces the canonical type 2 cytokines IL-5, IL-9 and IL-13 in response to IL-25 and IL-33 and is called type 2 innate lymphoid cells (ILC2 cells). ILC2 cells produce large amounts of IL-5 and IL-13 in the tissues during an allergic response, even in cases in which T cells were thought to be the main mediators of the allergic response because those concentrations are equal to or greater than the amounts of IL-5 and IL-13 made by T cells. ILC2 cells specifically required the TH2-defining transcription factor GATA-3 and the transcription factor RO-Ra. So far, a unique transcriptional regulator that distinguishes ILC2 cells from classic TH2 cells has not been discovered, and transcriptional profiles of these cells are needed for identification of the molecular differences between them. Further characterization of ILC2 cell biology will enhance the understanding of type 2 responses and may identify new treatments for asthma. Interactions between ILC2 cells and the adaptive immune system, as well as examination of potential roles for ILC2 cells in the maintenance of homeostasis, promise to be particularly fruitful areas of future research.

IL-4 confers resistance to IL-27-mediated suppression on CD4+ T cells by impairing signal transducer and activator of transcription 1 signaling

Authors: Chen Z et al.
URL: http://dx.doi.org/10.1016/j.jaci.2013.06.035

Comment: Established Th2 cells resists to reprogramming into Th1 cells. The differentiation of Th2 cells downregulates both the IL-12 receptor b2 subunit and STAT4 expression, rendering these Th2 cells unresponsive to IL-12. IL-27, a cytokine member of the IL-12 family can also inhibit Th2 differentiation. This study sheds light on the mechanism by which committed Th2 cells are resistant to IL-27. The main results of this study demonstrated CD4+ T cells from patients with asthma resisted IL-27-mediated inhibition of IL-4 production through defective STAT1 signaling. IL-27-mediated suppression can also be induced in CD4+ T cells from healthy subjects by repeated or high-dose IL-4 stimulation that resulted in the upregulation of suppressor of cytokine signaling 3 (Socs3) mRNA expression, culminating in impaired IL-27-induced STAT1 phosphorylation. The knockdown of Socs3 mRNA expression restored IL-27-induced STAT1 phosphorylation and IL-27-mediated suppression of IL-4 production.
The effects of airway microbiome on corticosteroid responsiveness in asthma

Authors: Goleva E et al.
Reference: Am J Respir Crit Care Med 2013; 188: 1193-1201
URL: http://www.ncbi.nlm.nih.gov/pubmed/24024497

Comment: This study demonstrated that airway microbiome in corticosteroid-resistant (CR) asthmatic patients contributes to the underlying mechanism of cellular responsiveness to corticosteroids. The distinct bacteria expanded were mainly gram-negative organisms in association with high levels of LPS detected in the airways of CR asthmatics. In response to Hemophilus parainfluenzae it caused the activation of p38 mitogen-activated protein kinase (p38 MAPK) and subsequent significant upregulation of IL-8 mRNA in BAL macrophages. The authors further investigated cellular response to corticosteroids in the presence of H. parainfluenzae using monocyte-macrophage activation model and proposed the mechanisms of downregulated corticosteroid responsiveness. As known, LPS interacts with Toll-like receptor (TLR) 4 and activates transforming growth factor-b–associated kinase-1 (TAK1) by MyD88 pathway, resulting in p38 MAPK phosphorylation and nuclear factor-kB (NF-kB) activation, which activate transcription of the proinflammatory cytokines like IL-8. Corticosteroid-induced suppression of p38 MAPK activation primarily requires the induction of mitogen-activated kinase phosphatase 1 (MKP-1) that dephosphorylates activated p38 MAPK. Monocyte-macrophage activation by H. parainfluenzae results in reduced cellular responses to corticosteroids by the activation of TAK1 that results in the inhibition of GR-mediated MKP-1 production and suppresses GR inhibition of NF-kB-induced IL-8 production.

Dupilumab in persistent asthma with elevated eosinophil levels

Authors: Wenzel S et al.
URL: http://www.ncbi.nlm.nih.gov/pubmed/23688323

Comment: This study evaluated the efficacy and safety of dupilumab, a fully human monoclonal antibody to the alpha subunit of the interleukin-4 receptor, in patients with persistent, moderate-to-severe asthma and elevated eosinophil levels. Dupilumab therapy could reduce asthma exacerbations when LABA and inhaled corticosteroids were withdrawn. Significant improvements in lung function and asthma control were observed, with reduced levels of Th2-associated inflammatory markers. Injection-site reactions, nasopharyngitis, nausea, and headache occurred more frequently with dupilumab than with placebo.

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Randomized placebo-controlled trial to evaluate chronic dosing effects of propranolol in asthma

Authors: Short PM et al.
URL: http://www.ncbi.nlm.nih.gov/pubmed/23593932
Comment: The use of b-blockers, regardless of selectivity in asthma remains controversial issue. This double-blind randomized placebo control trial addressed the effect of chronic nonselective b-blockade propranolol as added to inhaled corticosteroids in patients with mild-to-moderated asthma. This study reported that chronic propranolol had no significant effect on either methacholine or histamine airway hyperresponsiveness (AHR), although there was significant partial attenuation of the post-challenge recovery response to acute albuterol. In addition, chronic propranolol treatment was not associated with any significant worsening of asthma control or quality of life.

Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma

Authors: Desai D et al.
Comment: Sputum IL-5 and submucosal eosinophils, but not sputum eosinophils, are elevated in obese individuals with severe asthma. The submucosal eosinophil number was increased in severe asthma compared with healthy control subjects and was correlated with body mass index (BMI) whereas sputum eosinophil count was also increased in severe asthma compared with healthy controls but was not associated with BMI. This study suggested that eosinophilic inflammation may play an important role in a group of obese severe asthmatics that hitherto have been labeled as noneosinophilic. The interesting issue was the explanation why the increase in IL-5 levels did not result in sputum eosinophilia in obese subjects with severe asthma. This may be due to either eosinophil function is altered in obesity, such that response to CCR3 chemokines and Th2 cytokines is impaired, or that eosinophils are retained in the airway wall and possibly have an altered survival or adhesion within the airway wall. The persistence of eosinophilic inflammation in the tissue dissociated with a sputum eosinophilia is an intriguing observation. One possibility is that the eosinophils in the tissue are undergoing apoptosis and necrosis and thus have impaired clearance. However, this study leaves some questions needed to be further investigated that is whether submucosal eosinophils are activated in obese individuals with severe asthma and contribute to disease and whether specific antieosinophilic therapy is beneficial, or improved diet and lifestyle in obese asthma has antiinflammatory effects beyond weight reduction.
Use of continuous positive airway pressure reduces airway reactivity in adults with asthma

Authors: Busk M et al.

Comment: The mechanical strain imposed on the lungs during breathing is an important modulator of airway responsiveness. Deep inspirations and tidal breathing decrease airway responsiveness in healthy adults and animals, while the absence of a deep inspiration or tidal breathing increases airway responsiveness. The bronchoprotective effect of acute mechanical strain in patients with asthma is less effective. This study was designed to apply nocturnal CPAP (8-10 cmH₂O) treatment to adult patients with stable asthma for 7 days. It demonstrated that short-term use of nocturnal CPAP in asthmatic patients can reduce airway hyperresponsiveness (AHR), as assessed by methacholine bronchial challenge. The authors proposed the mechanism of CPAP therapy in improving AHR was that CPAP therapy improved the detrimental plasticity of the contractile properties of ASM, as well as the airway wall by decreasing mechanical load that imposed on mechanosensitive protein complexes that localise to smooth muscle cell cytoskeletal/extracellular matrix junctions, possibly similar to deep inspiration-induced bronchodilatation.

A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma

Authors: Piper E et al.

Comment: Interleukin (IL)-13 is an important mediator in the development and maintenance of the asthma phenotype through its role in key underlying mechanisms including inflammation, airway hyperresponsiveness, fibrosis and increased mucus production. This study assessed the effects of tralokinumab, human IL-13-neutralising immunoglobulin G4 monoclonal antibody, in adults with moderate-to-severe uncontrolled asthma despite controller therapies. The results showed that treatment with tralokinumab did not significantly improve ACQ-6 score as primary end point but did increase prebronchodilator FEV₁ and reduce the use of short-acting b₂ agonists.
**Cyclooxygenase-2 inhibits T Helper cell type 9 differentiation during allergic lung inflammation via down-regulation of IL-17RB**

Authors: Li H et al.


Comment: Cyclooxygenase (COX) enzymes are known to be regulators of T helper cell type 1 (Th1), Th2, and Th17 cells in allergic lung disease. This study elucidated how COX-derived eicosanoids regulate Th9 cells during allergic lung inflammation by studying in a mouse model. It identified that COX-2 as a key negative regulator of Th9 cell differentiation and function in allergic lung inflammation via an autocrine loop that involves prostaglandin (PG) D2 and PGE2 suppression of IL-17RB through protein kinase A signaling. COX-2−/− mice enhanced lung Th9 cell responses to allergen exposure. In vitro experiments also conducted and showed that COX2−/− naïve CD4+ T cells differentiated into Th9 cells compared with wild type naïve CD4+ T cells and this finding was reproducible when the selective COX-2 inhibitor was used. The molecular mechanism by which COX-2 negatively regulated Th9 cell differentiation was further explored. They found that COX-2-derived PGD2 and PGE2 inhibited Th9 cell differentiation in vitro and in the allergic lung in vivo through downregulation of IL-17RB, signaling of which enhances IL-9 expression through a mechanism that is independent of endogenous IL-4 production from differentiating T cells, but dependent upon endogenous TGF-b. The mechanism of COX-2-derived PGD2–suppressed IL-17RB expression was further explored and found to be mediated through CREB-dependent, PKA-independent mechanism.

**Transcriptome analysis reveals upregulation of bitter taste receptors in severe asthmatics**

Authors: Ormark-Pietras C et al.


Comment: This study used genomics-based approach to identified novel pathway responsible for severe therapy-resistant asthma phenotype in particular children. It demonstrated that there was the upregulation of bitter taste transduction receptors (TAS2Rs) expression severe asthmatics which was replicated in leukocytes from adult asthmatics regardless of FEV1 value. However, this study did not provide the mechanisms underlying the connection between the high expression of TAS2Rs and severe asthma. The authors has just proposed that the activation of TAS2Rs may have anti-inflammatory actions other than bronchodilatory actions.
Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459

Authors: Singh D et al.
Reference: Eur Respir J 2013; 41: 46–52
URL: http://www.ncbi.nlm.nih.gov/pubmed/22496329
Comment: Prostaglandin (PG) D$_2$ is primarily produced by mast cells and by T helper type 2 (Th2) lymphocytes. PGD$_2$ levels are elevated in the airways of asthmatic patients after allergen challenge. PGD$_2$ induced Th2-mediated allergic airway inflammation by binding to CRTH2 (chemoattractant receptor expressed on Th2 cells) expressed by Th2 cells, eosinophils and basophils, resulting in chemotaxis and activation of these responsive cells. Therefore, inhibition of CRTH2 may suppress allergic airway inflammation in asthma. This study investigated the effect of OC000459, a potent and selective CRTH2 antagonist on allergic response in patients with steroid-naïve asthma. The results demonstrated that OC000459 treatment did inhibit late allergic response and post-allergen rising in sputum eosinophils, indicating its ability to inhibit the Th2 inflammatory response after allergen challenge in asthma.

Statins enhance the effects of corticosteroids on the balance between regulatory T cells and Th17 cells

Authors: Maneechotesuwan K et al.
URL: http://www.ncbi.nlm.nih.gov/pubmed/23331562
Comment: Plasticity of CD4$^{+}$Th17/regulatory T cell (Treg) subset is involved in the pathogenesis of chronic airway inflammation in asthma. Reversal of Th17/Treg cell balance towards Treg cells may be beneficial for suppression of chronic airway inflammation in particular neutrophilic predominance. As currently known, corticosteroids could not directly suppress Th17 cells as a result of defective GR nuclear translocation. However, it was unknown whether corticosteroids and statins could tip Th17/Treg balance towards Treg cells. Therefore, this study demonstrated that corticosteroids suppressed Th17 polarizing cytokine (IL-6 and IL-23) expression in monocyte-derived dendritic cells and enhanced indoleamine 2, 3-dioxygenase (IDO), resulting in promoting Treg differentiation at the expense of Th17 cells. Interestingly, simvastatin also enhanced this effect of corticosteroids and therefore this paves the way for further investigation of the clinical implication of the combination therapy with corticosteroids and statins in suppression of airway inflammation, the control of asthma symptoms, impact on systemic comorbidities in asthma.
Endoplasmic reticulum stress influences bronchial asthma pathogenesis by modulating nuclear factor κB activation

Authors: Kim SR et al.
URL: http://www.ncbi.nlm.nih.gov/pubmed/24161747

Comment: Endoplasmic reticulum (ER) stress occurs when there is the accumulation of unfolded and misfolded proteins in the ER lumen during the process of protein synthesis. This results in cellular initiation of an adaptive response called the unfolded protein response (UPR) to maintain homeostasis of ER function against an excess of ER stress. The UPR is mediated by ER membrane proteins, which are reflected by increased expression of glucose-regulated protein 78 (GRP78) (ER-resident chaperone) and CCAAT/enhancer-binding protein-homologous protein (CHOP). Excess ER stress interferes protein synthesis and secretion, induces reactive oxygen species production, enhances inflammation through nuclear factor κB (NF-κB) activation, and mediates apoptotic cell death. This study demonstrated ER stress could be induced in mice sensitized with ovalbumin (OVA) and LPS and challenged with OVA, resulting in neutrophilic airway inflammation and airway hyperresponsiveness. In addition, ER stress markers were dramatically increased in bronchoalveolar lavage cells and PBMCs from patients with asthma. Enhanced ER stress and ER stress-induced airway inflammation could not be suppressed by dexamethasone. Induction of UPR by a chemical chaperon 4-phenylbutyric acid (4-PBA) significantly reduced the increases in ER stress and NF-κB activation.

Production of serotonin by tryptophan hydroxylase 1 and release via platelets contribute to allergic airway inflammation

Authors: Dürk T et al.
URL: http://www.ncbi.nlm.nih.gov/pubmed/23328530

Comment: 5-Hydroxytryptamine (5-HT) is involved in the pathogenesis of allergic airway inflammation. However, how 5-HT contributes to allergic airway inflammation. This study first demonstrated increased 5-HT levels in bronchoalveolar lavage fluid (BALF) of patients with allergic asthma who underwent allergic challenge. 5-HT expression was regulated by tryptophan hydroxylase (TPH) 1 as supported by the evidence that TPH1 deficient mice was deprived of endogenous 5-HT in BALF and blood in association with significant reduction in BALF eosinophilia and bronchial hyperresponsiveness. The role of TPH1 deficiency in allergic airway inflammation was validated in OVA-sensitized wild type mice treated with TPH1 inhibitor that bore the resultant similarity to genetic inhibition of TPH1. The pivotal role of 5-HT production by structural cells was corroborated by bone marrow chimera experiments. Platelets were the main source of 5-HT that enhanced allergic airway inflammation. This was corroborated by transfusion of platelets from wild-type and TPH1-deficient mice demonstrating that only platelets containing 5-HT from wild-type mice potentiated allergic airway inflammation. The lack of 5-HT resulting from TPH1 deficiency led to an impaired Th2-priming capacity of BMDCs and an impairment in their full maturation. This study casts light on role of TPH1 that may be novel therapeutic target for asthma.
Diesel exhaust particle induction of IL-17A contributes to severe asthma

Authors: Brandt EB et al.
URL: http://dx.doi.org/10.1016/j.jaci.2013.06.048

Comment: Particulate matter has been shown to induce IL-17A in the lungs of exposed mice. Diesel exhaust particles (DEPs), a major component of particulate matter in traffic-related air pollution, can exacerbate allergic airway responses. Coexposure to allergen and DEPs can enhance local and systemic TH2 cytokine release compared with allergen alone. This study demonstrated that coexposure of DEPs and house dust mite induced a mixed Th2/Th17 response and increased asthma severity shown by more severe inflammation, mucus production and AHR. Neutralization of IL-17A with a neutralizing antibody reduced DEP-induced enhancement of AHR. This study also evaluated the role of Th17 response in the context of DEP exposure in children patients with allergic asthma and found that DEP exposure was associated with more frequent asthma symptoms and increased IL-17A serum levels.

Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma

Authors: Wechsler ME et al.
URL: http://dx.doi.org/10.1016/j.jaci.2013.08.009

Comment: This study assessed the effectiveness and long-term safety of bronchial thermoplasty (BT) in asthmatic patients 5 years after therapy. The outcomes assessed included severe exacerbations, adverse events, health care use, spirometric data, and high-resolution computed scans. Persistent reduction in the proportion of subjects experiencing severe exacerbations was maintained. Persistent reduction in ED visits for respiratory symptoms, with an average decrease in the proportion of subjects with ED visits over 5 years was also observed. Respiratory adverse events remained unchanged in years 2 through 5.

Deficient glucocorticoid induction of anti-inflammatory genes in nasal polyp fibroblasts of asthmatic patients with and without aspirin intolerance

Authors: Fernández-Bertolín L et al.
URL: http://dx.doi.org/10.1016/j.jaci.2013.07.010

Comment: This study results elucidated the mechanism that might explain the relative glucocorticoid insensitivity in patients with aspirin-intolerant asthma (AIA) by investigating glucocorti-
Rhinovirus infection causes steroid resistance in airway epithelium through nuclear factor κB and c-Jun N-terminal kinase activation

Authors: Papi A et al.
URL: http://dx.doi.org/10.1016/j.jaci.2013.05.028
Comment: Rhinoviruses are the most frequently identified viruses in patients with asthma exacerbations. High doses of ICSs or systemic corticosteroids has been shown to be ineffective in the treatment/prevention of virus-induced acute asthma exacerbations, particularly in children with unknown mechanisms. The key findings of this study were that rhinovirus infection induced steroid resistance by inhibiting its mechanisms of action at upstream aspect of GR activation. Rhinovirus-impaired GR nuclear translocation was dependent upon nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK) pathways as supported by the evidence that inhibition of both JNK and NF-κB activation fully restored all aspects of glucocorticoid responsiveness.

Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia

Authors: Laviolette M et al.
URL: http://dx.doi.org/10.1016/j.jaci.2013.05.020
Comment: Benralizumab is a humanized afucosylated mAb designed to target IL-5Ra expressed on eosinophils and basophils. Lack of a fucose sugar moiety on the oligosaccharide core enhances the binding affinity of benralizumab to FcγRIIia and augments antibody-dependent cell-mediated cytotoxicity (ADCC), inducing apoptosis of target cells. This phase I study evaluated the effects and safety of single-dose intravenous and multiple-dose subcutaneous benralizumab and found that it could reduce the number of eosinophils in airway mucosa/submucosa, sputum, bone marrow and peripheral blood with safety profile.
Viral and bacterial infection in acute asthma and chronic obstructive pulmonary disease increases the risk of readmission

Authors: Wark PA et al.
URL: http://www.ncbi.nlm.nih.gov/pubmed/23600594
Comment: This study determined the prevalence and nature of virus and bacterial infections over a period of 2 and half years to accurately characterize seasonal infection and the impact of these infections in adults with acute asthma and COPD. It showed that asthmatic and COPD patients with co-infection of virus infection and chronic bacterial infection were more likely to be readmitted to hospital following their exacerbation.

Poly (ADP-ribose) polymerase 14 and its enzyme activity regulates T(H)2 differentiation and allergic airway disease

Authors: Mehrotra P et al.
URL: http://dx.doi.org/10.1016/j.jaci.2012.06.015
Comment: Poly (ADP-ribose) polymerase 14 (PARP-14) acts as biological switch for IL-4-dependent STAT6-mediated transcription. This study showed that PARP-14 deficient mice were protected against allergic airway inflammation and inhibition of PARP-14 activity during allergen sensitization and challenge reduced airway hyperresponsiveness. The exploration of the underlying mechanism for this demonstrated that PARP-14 promoted Th2 differentiation by regulating the binding of STAT6 to the GATA-3 promoter.

Programmed cell death ligand 2 regulates TH9 differentiation and induction of chronic airway hyperreactivity

Authors: Kerzerho J et al.
URL: http://dx.doi.org/10.1016/j.jaci.2012.09.027
Comment: IL-9 plays a central role in the pathogenesis of chronic allergic asthma. The key findings of this study were that Th9 differentiation was induced in the lungs in a murine model of A fumigatus–induced chronic AHR and that the costimulatory molecule programme cell death ligand 2 (PD-L2) was a negative regulator of Th9 differentiation through suppression of TGF-b and IL-1α production.
IL-17A inhibits airway reactivity induced by respiratory syncytial virus infection during allergic airway inflammation

Authors: Newcomb DC et al.
URL: http://dx.doi.org/10.1136/thoraxjnl-2013-203307

Comment: IL-17A has been identified as a potential therapeutic target in asthma, and it is vital to understand the role of IL-17A in increased allergic airway inflammation and airway reactivity with viral infections during ongoing allergic airway inflammation. The key finding of this study was that IL-17A inhibited airway reactivity and airway inflammation induced by respiratory syncytial virus infection during ongoing allergic airway inflammation.