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Effects of non-steroidal anti-inflammatory drugs and other eicosanoid pathway modifiers on antiviral and allergic responses. EAACI task force on eicosanoids consensus report in times of COVID-19

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) and other eicosanoid pathway modifiers are among the most ubiquitously used medications in the general population. Their broad anti-inflammatory, antipyretic and analgesic effects are applied against symptoms of respiratory infections, including SARS-CoV-2, as well as in other acute and chronic inflammatory diseases that often coexist with allergy and asthma. However, the current pandemic of COVID-19 also revealed the gaps in our understanding of their mechanism of action, selectivity and interactions not only during viral infections and inflammation, but also in asthma exacerbations, uncontrolled allergic inflammation, and NSAIDs-exacerbated respiratory disease (NERD). In this context, the consensus report summarises currently available knowledge, novel discoveries and controversies regarding the use of NSAIDs in COVID-19, and the role of NSAIDs in asthma and viral asthma exacerbations. We also describe here novel mechanisms of action of leukotriene receptor antagonists (LTRAs), outline how to predict responses to LTRA therapy and discuss a potential role of LTRA therapy in COVID-19 treatment. Moreover, we discuss interactions of novel T2 biologicals and other eicosanoid pathway modifiers on the horizon, such as prostaglandin D2 antagonists and cannabinoids, with eicosanoid pathways, in context of viral infections and exacerbations of asthma and allergic diseases. Finally, we identify and summarise the major knowledge gaps and unmet needs in current eicosanoid research.

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) and other eicosanoid pathway modifiers are among the most ubiquitously used medications in the general population. Their broad anti-inflammatory, antipyretic and analgesic effects are applied against symptoms of respiratory infections, including SARS-CoV-2, as well as in other acute and chronic inflammatory diseases that often coexist with allergy and asthma. However, the current pandemic of COVID-19 also revealed the gaps in our understanding of their mechanism of action, selectivity and interactions not only during viral infections and inflammation, but also in asthma exacerbations, uncontrolled allergic inflammation, and NSAIDs-exacerbated respiratory disease (NERD). In this context, the consensus report summarises currently available knowledge, novel discoveries and controversies regarding the use of NSAIDs in COVID-19, and the role of NSAIDs in asthma and viral asthma exacerbations. We also describe here novel mechanisms of action of leukotriene receptor antagonists (LTRAs), outline how to predict responses to LTRA therapy and discuss a potential role of LTRA therapy in COVID-19 treatment. Moreover, we discuss interactions of novel T2 biologicals and other eicosanoid pathway modifiers on the horizon, such as prostaglandin D2 antagonists and cannabinoids, with eicosanoid pathways, in context of viral infections and exacerbations of asthma and allergic diseases. Finally, we identify and summarise the major knowledge gaps and unmet needs in current eicosanoid research.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) and other eicosanoid pathway modifiers are one of the most frequently used anti-inflammatory medications worldwide against infections, other acute and chronic inflammatory diseases and pain. Eicosanoids, including prostaglandins (PGs), leukotrienes (LTs), thromboxanes (TXs), hydroxyeicosatetraenoic acids (HETEs), lipoxins (LXs), and many recently proposed pro-resolving mediators constitute a wide range of active lipid mediators possessing pro- and anti-inflammatory, as well as pro-resolution properties.[1] They are products of the major unsaturated fatty acids: arachidonic acid (AA), dihomo-γ-linolenic acid (DHGLA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), metabolized in three main pathways: cyclooxygenase (COX), lipoxygenase (LO or LOX) and cytochrome P450 **(Fig. 1)** . Those active lipid mediators play substantial roles in the development and resolution of

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inflammation, including allergic and viral inflammation, which we have reviewed extensively in the previous report.[1] Even though NSAIDs and other eicosanoid pathway modifiers are so commonly consumed and are relatively safe for the majority of people, the current pandemic of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) revealed substantial knowledge gaps in understanding their modes of action, benefits and risks related to their use in patients with respiratory and allergic diseases. Unfortunately, this resulted in the conflicting messages sent to the public from the scientific community. Therefore, we, the European Academy of Allergy and Clinical Immunology Task Force (EAACI TF) on Eicosanoids, here critically review the most recent findings on the roles of NSAIDs, leukotriene antagonists (LTRAs), prostaglandin D_2 (PGD_2) receptor antagonists and cannabinoids, as well as we summarize their selectivity, and additional modes of actions in allergic airway diseases, drug allergy and respiratory virus infections. In addition, we also describe here the effects of novel T2 biologicals used in allergic diseases on eicosanoid pathways.

NSAIDs in asthma and viral asthma exacerbations

Aside from NSAIDs-exacerbated respiratory disease (NERD), NSAIDs are usually well tolerated by patients with asthma and therefore they are often used in real life during asthma exacerbations together with intensified asthma treatment in children and adults.[2]Current Global Initiative for Asthma (GINA) guidelines are stating with evidence level A, that aspirin and other NSAIDs are generally not contraindicated in patients with asthma, unless there is a history of previous reactions to those medications. Nevertheless, it is still not very well studied whether NSAIDs facilitate or inhibit achievement of asthma control following exacerbations, and if they affect the speed of resolution of airway inflammation. Exacerbations of asthma are most often induced by common respiratory viruses including rhinovirus (RV), respiratory syncytial virus (RSV), bocavirus, influenza viruses, adenovirus and others.[3-5] RV is responsible for up to 76% of exacerbations of wheeze in children and up to 83% of asthma attacks in adults.[3-5] Recurrent viral infections do not only cause acute disease and exacerbations of established disease, but they also contribute to the pathophysiology of early wheezing in children and the development of asthma. Prophylaxis of RSV-induced bronchiolitis with palivizumab, an anti-RSV monoclonal antibody, in late pre-term infants decreased the risk of recurrent infant wheeze and the rate of parent reported asthma symptoms at 6 years of age, however without any effect on lung function or doctor-diagnosed asthma.[6,7] The majority of respiratory viruses are known to modify several major eicosanoid pathways, including the COX and the LOX pathways[8] **(Fig. 2)** . RV infection increases expression of 5-lipoxygenase (5-LOX), 5-lipoxygenase activating protein (FLAP), and cyclooxygenase-2 (COX-2), as well as the production of prostaglandins E_2 (PGE_2) and PGD_2 by the respective isomerases in human bronchial epithelial cells, with higher levels in asthmatic patients than in controls.[9] In addition, cysteinyl leukotriene (cysteinyl-LT) levels, 5-LOX positive cells and FLAP-positive cells in bronchoalveolar lavage fluid are increased in humans upon RV infection and correlate with the emergence of upper respiratory symptoms.[10] Infection with RV affects airway mucosal barriers and also the peripheral blood and distant tissues. PGE_2 plays an important role in optimal antibody synthesis, as COX inhibitors reduce antibody release by plasma cells, also in case of viral infections.[11,12] Healthy individuals experimentally infected with RV showed a suppressed serum neutralizing antibody response when treated with aspirin or acetaminophen.[13] Significant increase in COX-2 (PTGS2) expression and in COX-derived metabolites is a hallmark of RSV[14] and influenza virus infection.[15] Pharmacologic inhibition of the COX pathway decreased RSV-induced lung pathology, although this was not linked to a specific metabolite.[14,16] At a later stage of RSV infection there is an increase in LOX metabolites, which might promote appropriate resolution of infection-induced inflammation.[17] This resolution is impaired in 5-LOX and 15-LOX knockout mice upon RSV or pathogenic influenza strain infection. Moreover, in mice lacking 5-LOX there is an upregulation of COX2 expression and aggravation of infection-induced lung pathology.[14,16] During influenza A infection, newly generated PGE_2 leads to the inhibition of type I interferon (IFN) production, inhibition of macrophage apoptosis and subsequent increase in virus replication. *Ptges* $^{-/-}$ knockout mice, which do not produce PGE_2, or wild type mice treated with PGE_2 type 2 (EP2) and type 4 receptor (EP4) antagonists demonstrated enhanced protection against lethal influenza infection.[18] PGE_2 also inhibits activation of the Nod like receptor family pyrin domain containing 3 (NLRP3) inflammasome in human monocytes and macrophages, and COX pathway blocking increases inflammasome activation and mature Il-1β release.

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NLRP3 inflammasome activation can contribute to limiting viral replication at the early stages of infection, but in some instances, it may also lead to harmful hyperinflammation during late-stage infection.[19] Much less is known about PGD_2 and antiviral responses. However, it was shown that in aging mice there is an increase in PGD_2 in the lungs which correlates with the impaired migration of respiratory dendritic cells (DC) to lymph nodes, diminished T cell responses and more severe clinical disease in older mice infected with respiratory viruses, such SARS-CoV-1 and influenza.[20] Blocking PGD_2 function enhances DC migration, T cell responses, and survival in the infected animals.[20] In summary, prostaglandins and other COX-dependent metabolites are involved in a complex way in the pathogenesis of respiratory viral infections and thus in virus-induced exacerbation of asthma. Therefore, the use of NSAIDs to alleviate symptoms of viral infections in general population and in patients with asthma should be re-evaluated with assessment of the effects of the timing of the administration, their selectivity and the long-term effects.

NSAIDs in COVID-19

NSAIDs are used worldwide to alleviate symptoms of viral infections and inflammation, such as fever, cough and pain. Since NSAIDs inhibit COX-1 and COX-2 and thus decrease the release of many downstream lipid mediators, such as various PGs, prostacyclin and TXs, they have very broad effects on inflammation and immune responses, ranging from anti-inflammatory, immunosuppressive, anti-thrombotic to pro-resolving **(Fig. 2)** .[1,21] Therefore, at the beginning of the COVID-19 pandemic, there were several concerns and uncertainties about the effects of NSAIDs on SARS-CoV-2 infection and the course of COVID-19.[22] They were suspected to alter the expression of angiotensin-converting enzyme 2 (ACE2), the main entry receptor for SARS-CoV-2 and/or modify viral replication.[23-26] In addition, they could be either harmful by impairing anti-viral response and delaying resolution of inflammation[15,18,27,28] or be beneficial by dampening of hyperinflammation and cytokine storm[29,30] and preventing thrombosis[31,32] **(Fig. 3)** . Some of these concerns have now been addressed experimentally and epidemiologically and several clinical trials have been initiated. Indeed, SARS-CoV-2 increases *PTGS2* (COX-2) gene expression in variety of cell lines, in mouse lungs and in primary human bronchial epithelial cells as well many eicosanoids and docosanoids are increased in the lungs of severe COVID-19 patients.[33-35] However inhibition of the COX pathway by either ibuprofen (non-selective COX1/COX2 inhibitor) or meloxicam (more selective COX-2 inhibitor) did not change the expression of ACE2 in human cell lines (Calu-3 or Huh7.5)*in vitro* or in lungs, kidney, heart or ileum of mice *in vivo.* [33] Similarly, both NSAIDs did not affect SARS-CoV-2 entry or its replication in the same human cell lines.[33] Aspirin also did not affect ACE2 or transmembrane serine protease 2 (TMPRSS2) expression in human nasal epithelium.[36] Meloxicam also did not prevent SARS-CoV-2-infection-induced weight loss in mice and did not change frequencies or activations status of alveolar macrophages, neutrophils, NK cells, Ly6C+ Mo/Mϑ, $CD4^+$ T cells, $CD8^+$ T cells, γδ T cells. However, meloxicam treatment decreased the amount of spike-specific IgM and IgG antibodies and their neutralizing capacities as well as decreased infection-induced levels of IL-6, CCL2, GM-CSF, CXCL10, IL-2, and TNF-α, suggesting that while meloxicam can impair humoral immune response against SARS-CoV-2 to some extent, it might also limit levels of proinflammatory cytokines.[33] In contrast, naproxen, which is a non-selective COX-1/COX-2 inhibitor, has been shown to bind to the nucleocapsid protein N of SARS-CoV-2, which led to inhibition of SARS-CoV-2 replication in VeroE6 cells and primary human bronchial epithelial cells and protected epithelium against SARS-CoV-2-induced barrier damage.[37] There were no analogous effects in similar experiments with paracetamol (acetaminophen, which may affect PG production in the brain or may act via its metabolite on the cannabinoid receptors),[38,39] or celecoxib (selective COX-2 inhibitor).[37] Naproxen is currently examined in the clinical trial in COVID-19 (eudract_number:2020-001301-23; accessed 11.06.2021). So far, in various patient groups, it has been shown that usage of NSAIDs does not lead to the worse COVID-19 outcomes, however others still claim such associations.[40] In a retrospective study of 403 confirmed cases of COVID-19 there were no differences in terms of mortality rate or need for respiratory support between patients who were taking ibuprofen or those who did not take any NSAIDs.[41] It was also confirmed in the large prospective cohorts that either acute or chronic use of NSAIDs was not associated with worse COVID-19 outcomes.[42-44] It was even shown that in patients, who were treated with aspirin or other NSAIDs due to the cardiovascular diseases, positive aspects of such therapies have been noted, including reduction of COVID-19 mortality.[31] This clinical observation

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is further supported by a study on COX-2 induction and PGE_2overproduction in the human lung infected by SARS-CoV-2.[45] However, further basic in vitro, in vivo and large clinical studies assessing the influence of NSAIDs on the pathogenesis and treatment of COVID-19 are still greatly needed.

Leukotriene receptor antagonists – novel mechanisms of action

All clinically available LTRAs (montelukast, zafirlukast and pranlukast) act on the cysteinyl leukotriene type 1 receptor ($CysLT_1$) and by competitive antagonism at this receptor are believed to be responsible for the control of airway inflammation, bronchoconstriction, and remodeling.[46-48] However, anti-inflammatory activity of LTRAs independent of $CysLT_1$ antagonism has been suggested. LTRAs reduced the eosinophil protease activity,[49] and inhibited TNFα-[50], or UDP-mediated[51,52]cytokine expression, as well as NF-κB activation in human mononuclear[53] or epithelial cells[54]through processes that appear to be distinct from $CysLT_1$antagonism. Although, mechanisms of these non-$CysLT_1$-related LTRA activities are not fully understood, concentration dependent inhibition of distinct receptors such as P2Y1, P2Y2, P2Y6 and GPR17 by LTRAs have been reported,[51,52,55] suggesting, at least for P2Y receptor, a non-competitive mechanism of action. Interestingly, it was also shown that LTRAs may have a potent inhibitory effect on 5-LOX activity (i.e. LT production)[52,56] and transport of LTs by the multidrug resistance protein ABCC4,[57]suggesting a much broader mechanism of action for these drugs than previously suspected. Indeed, non–$CysLT_1$-related mechanisms of LTRA might represent another level of variability in the response to treatment in patients with asthma and allergy. Some of these activities may be compound-specific or may depend on drug concentration (most non-$CysLT_1$-related effects required micromolar drug concentrations[51-53] in contrast to nanomolar levels needed for $CysLT_1$antagonism[58-60]) or may depend on the presence of a particular inflammatory pathway in patients with asthma (allergy), and therefore, clinically significant effects of treatment may be observed in some, but not all, treated patients. It should be emphasized that initial clinical interventional studies of montelukast in asthma used doses up to 200 mg a day[61,62] showing greater lung function improvement than in subsequent studies using recommended dose of 10 mg,[63] suggesting that higher doses of currently known LTRAs or new compounds derived from this class of drugs may represent a novel strategy for finding more efficient therapy. The demonstration that the bronchoconstrictive actions of LTE_4 in asthma are solely mediated by the $CysLT_1$ receptor further supports that effects on other targets than the CysLT receptors may take place[64]

Predicting responses to LTRA therapy

Heterogeneous effects of LTRA therapy in asthma and allergic diseases have been reported in many studies. Although some genetic[65,66] and acquired factors have been suggested,[67] other reasons for this heterogeneity remain unclear. While currently no clinical characteristics or laboratory assay can reliably predict responses to LTRAs, the most plausible biomarker that could potentially serve as response predictor to LTRAs seems LTE_4 production. Urinary LTE_4 ($uLTE_4$) is a biomarker of total body cysteinyl-LT production,[1] associated with Type 2 asthma, asthma severity, exacerbations and NERD.[68,69]Increased $uLTE_4$ to fractional exhaled nitric oxide (LTE_4: Fe_{NO}) ratio has been suggested to predict favourable response to LTRA therapy (montelukast) in asthmatic children,[70,71] but these observations have not been confirmed in adult patients. There is a considerable amount of evidence supporting the concept that some patients or clinical phenotypes seem sensitive to LTRAs, especially in a real-life setting, due to enhanced cysteinyl-LT production, better adherence to oral therapy or oral drug delivery. LTRAs have proven to be particularly effective in exercise-induced asthma,[72] asthma associated with allergic rhinitis,[73] NERD,[74] viral induced wheezing episodes,[75] and patients having difficulties with inhaled therapy such as children and elderly.[76,77] Cigarette smoking while inhibiting steroid anti-inflammatory responses,[78] increases cysteinyl-LT production,[79] leading to a greater response to montelukast in smokers with asthma, suggesting that LTRA could be more effective in treating such individuals.[80] In fact, asthmatic patients with smoking history above 11 pack-years showed more benefit with montelukast treatment than inhaled steroids.[81] Obesity is another potential risk factor for asthma development and efficacy of treatment. Interestingly, higher body mass index (BMI) is associated with increased LT production in asthmatics[82] and as therapeutic response to inhaled corticosteroids decreases with increasing BMI, response to montelukast remains unaffected,[83]suggesting LTRA therapy to be more effective

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in obese patients. The response to LTRA may also be associated with sex differences. The existence of a sex bias in LT biology is already suggested by the fact that many LT-related diseases including asthma, allergic rhinitis, rheumatoid arthritis or NERD have a higher occurrence in women compared to men, pointing to more pronounced pathophysiological roles of LTs in females.[84,85] Furthermore, several observations suggest that female sex is associated with higher LT biosynthesis, while androgens seem to exert a suppressing role on LT formation both in vitro and in vivo.[86-90] Although the clinical significance of these data is still to be confirmed, in a small prospective cohort study, montelukast showed superior effects on symptoms and lung function in women compared to men,[91] while a tendency for a better response to montelukast was evident in girls exposed to tobacco smoke.[92]

Leukotriene modifying drugs in COVID-19 treatment

Due to the involvement of complement, coagulation and inflammation in COVID-19,[32,93,94] anti-inflammatory drugs have gained great interest as disease modifiers **(Fig. 3)** .[95] Already at the beginning of the COVID-19 pandemic, researchers suggested the use of the LTRA montelukast for treatment of COVID-19.[96-98] The reason for this early interest in LT modifying drugs was on the one hand related to the viral cell entry via ACE2 receptors and the known inhibitory effect of montelukast on bradykinin-related airway response[99]and, on the other hand to the fact that patients with severe COVID-19 develop an overwhelming state of inflammation that has been labelled COVID-19 cytokine storm syndrome (CSS).[32,100,101]Moreover, the most important cause of death in COVID-19 was recognized as the progressive respiratory failure with limited response to treatment together with hyperinflammation and hypoxia, quite similar to a severe Acute Respiratory Distress Syndrome (ARDS), which has been demonstrated to be characterized by an elevated level of LTs.[102] Of note, high levels of LTE_4have been detected in bronchoalveolar lavage (BAL) of hospitalized patients with severe COVID-19,[34] as well as there is a shift in serum eicosanoids into the increase of 5-LOX products in such patients.[35] Indeed, specific benefits of montelukast, or other LTRAs, have been suggested in the situation of hyperinflammation and massive cytokine release[103] to reduce elevated levels of LPS-induced IL-6, TNF-α, and MCP-1 production in the peripheral blood MNCs of patients with asthma,[104] as well as to reduce levels of many cytokines and chemokines (IL-4, IL-5, IL-1β, TNF-α, RANTES, and IL-8) in nasal mucosa[105] possibly due to modulation of TNF-α-stimulated IL-8 expression through changes in NF-κB p65-associated histone acetyltransferase activity.[50] In addition to its anti-inflammatory properties in humans, *in silico* studies also suggested, but still to be demonstrated, a direct anti-viral effect by showing a high affinity binding of montelukast to the terminal end of the virus' main protease enzyme needed for viral protein assembly.[106]

Thus, with increasing understanding of disease mechanisms, LTRAs have been also considered for treatment of COVID-19. Indeed, in a small retrospective study on COVID-19 hospitalized subjects, patients receiving montelukast had fewer episodes of confirmed COVID-19 or experienced significantly fewer events of clinical deterioration compared to patients not receiving montelukast.[107,108]These lipid mediators might not only contribute to inflammation and lung pathologies associated with COVID-19, but can also be involved in thrombosis, fibrosis, neuronal damage and cardiovascular disease.[97,109,110] Accordingly, since May 2020 a series of clinical trials involving montelukast have been registered (https://clinicaltrials.gov). However, not only antagonism of the CysLT receptors could be beneficial for patients with COVID-19, but interventions targeting LT biosynthesis, using eg. Zileuton, might represent promising targets, specifically at the turning point from a mild to critical disease course.[111]

PGD_2 receptor antagonists

In sensitized subjects, PGD_2 is initially released by allergen-triggered mast cells and plays a key role in the sequelae of the allergic response. Its pro-inflammatory effects are mediated through the interaction with G-protein-coupled receptors (GPCR): DP1, thromboxane (TP) and chemoattractant-homologous receptors (CRTH2 or DP2).[112] Apart from its broncho- and vaso-active properties in allergic airway disease, PGD_2 also acts as an important link between the allergen-induced early (EAR) and late phase allergic response (LAR) through the interaction with the DP2-receptors on key effector cells. DP2-receptors are expressed on immune (ILCs, Th2), inflammatory (eosinophils, basophils) and structural (epithelial) cells and involved in

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the recruitment and activation of these cells as well as the subsequent release of Th2-cytokines during the LAR.[112] [113-115] Therefore, DP2 (CRTH2) antagonists have been initially aimed for the treatment of allergic airway disease (allergic rhinitis, asthma).[116,117]

In two proof-of-concept studies in (unphenotyped) allergic asthmatics, DP2 (CRTH2) antagonists (timapiprant and setipiprant, respectively) showed only modest reduction (approx. 25%) in the allergen-induced LAR[118,119] while no convincing effects were observed on the allergen-induced changes in T2 biomarkers (blood eosinophils, FeNO)[119] with only a minimal reduction in sputum eosinophils post-allergen.[118] In addition, there was no decrease in the EAR in either study. The (relative) lack of protection against allergen-induced airway responses may (partly) consist with the fact that even with effective DP2-blockade, an allergen-triggered mast-cell (lacking DP2)[120] mediator release (histamine, PGD_2, cysteinyl-LTs) may still occur which is capable of causing an EAR and/or an LAR[121122] and therefore, especially in allergic asthma, a combined blockade of e.g. DP2 ± DP1 ± TP ± cysteinyl-LT-R might provide a superior protection.

In line with this reasoning - and despite prior evidence of superior efficacy in phase 2B studies of patients with an allergic (T2-) profile (atopy ± eosinophils [?]250/mcL)[123,124]- several DP2 (CRTH2) antagonists (e.g., setipiprant, fevipiprant) failed in phase 3 clinical trials of allergic airway disease.[124] More recently, DP2-blockade has been associated with the reduction in airway smooth muscle mass by decreasing airway eosinophilia and the recruitment of myofibroblasts and fibrocytes.[125] Therefore, with several clinical trials still ongoing, (add-on) DP2-blockade may show efficacy in more severe T2 asthma[126] and related conditions based on its anti-inflammatory and disease modifying potential.[125,127]

Respiratory viruses (e.g. RSV) represent other important triggers of chronic inflammatory airway disease capable of activating the PGD_2/DP2 receptor-mediated pathway, thereby eliciting a "non-allergen-induced" T2-immune response through airway epithelial cells and innate immune cells.[128] Indeed, RSV has been associated with upregulation of the PGD_2/DP2 pathway and increased PGD_2 levels both in experimental and clinical studies, while (combined) DP1/DP2-blockade showed protective potential in preclinical studies.[129] Therefore, blocking PGD_2 through (combined) DP1/DP2 blockade has been postulated to protect against respiratory viral infections, and more recently, including SARS-CoV-2.[130] Presently, this hypothesis awaits clinical evidence. In addition, the potent bronchoconstrictive actions of PGD_2 and other constrictive prostanoids in human airways, call for trials with TP receptor antagonists in patients with asthma[131]

Cannabinoids in asthma, allergic diseases and viral infections

The human endogenous cannabinoid system (ECS) is involved in many physiological processes. It consists of the cannabinoid receptors (CBRs), the endogenous ligands (anandamide and 2-arachidonoylglycerol) and the proteins related to their synthesis and degradation.[132] Cannabinoid receptor 1 (CB1) and 2 (CB2) are the main CBRs. CB1 is largely expressed in the central nervous system but also in peripheral tissues and immune cells. CB2 is mainly expressed in immune cells but also in other cell types such as progenitor neurons. The biosynthesis and inactivation of endocannabinoids involve five main enzymes: N-acyl-phosphatidylethanolamine-hydrolysing phospholipase D (NAPE-PLD),*sn* -1-specific diacylglycerol lipase-α (DGLα), DGLβ, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL). The main product of endocannabinoids inactivation is the AA **(Fig. 1)** .[133,134] The role of cannabinoids in allergic diseases is still a bit controversial.[135] Sukawara*et al* demonstrated that endocannabinoids limited mast cell maturation and activation in human airway mucosa and skin through CB1.[136,137] Tetrahydrocannabinol (THC) and cannabidiol (CBD) attenuated airway allergic inflammation, decreased cytokine production, cell infiltration, mucus secretion and bronchial hyperresponsiveness in mice.[138-140] Similarly, the synthetic agonist CP55,940 induced lung protection in ovalbumine (OVA)-induced asthma guinea pig models via CB1 and CB2.[141] In keratinocytes, CB1 prevented transepithelial water loss and skin inflammation, cell infiltration and cytokine production in atopic dermatitis mouse model.[142] Anandamide and different CB1 agonists also accelerated skin barrier recovery and reduced pro-inflammatory cytokine production and cell recruitment.[143,144] Several cannabinoids have also shown a protective role in allergic contact dermatitis by reducing inflammatory responses.[145-147]CB1 activation may also induce bronchodilation in the airways.[141,148] In human bronchial epithelial cells, the synthetic agonist WIN55212-2 restored the epithelial barrier disruption induced by RV.[149]

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In addition, WIN55212-2 decreased the immediate anaphylactic reaction in a mouse model of peanut allergy, and promoted the generation of allergen-specific regulatory T cells.[150] Currently, different studies suggest the therapeutic potential of cannabinoids in COVID-19 pandemic.[151-153] In contrast, Frei *et al* showed that CB2 activation enhanced migratory responsiveness of eosinophils in an OVA-asthma mouse models.[154] Accordingly, the lack of CB2 decreased allergic inflammation in asthma and dermatitis mouse model.[155] This result correlated with increased number of NK cells and reduced number of ILC2s in the lung of CB2 knockout mice, demonstrating that NK cells are negative regulators of ILC2s.[156] Interestingly, it has been described that mRNA expression levels of CB1 are upregulated in tonsils and peripheral blood of patients with allergic rhinitis, atopic dermatitis, and food allergy, but the functional relevance remains unknown.[157] These studies suggest that the ECS could be explored as a potential therapeutic target in the treatment of asthma, allergic and skin diseases and viral infections.

The effect of T2-targeted biologicals on eicosanoids

Ample evidence from clinical trials showing effectiveness of drugs targeting T2-inflammation (targets include IgE and the cytokines IL5, IL4, and IL13) on asthma exacerbations, as well as improvements in symptoms and disease severity in chronic rhinosinusitis with nasal polyps (CRSwNP),[158,159] underscored the involvement of T2-inflammation in these conditions.[160,161] As mentioned above, the majority of asthma exacerbations are precipitated by respiratory viruses (esp. RSV and RV),[162] while in sensitized subjects, allergen exposure may enhance virally-triggered exacerbations due to synergistic interaction through joint mechanisms including the T2-inflammatory pathway.[162-165] Both viral and allergen-triggered pathways include several inflammatory and immune (effector) cells, such as mast cells, basophils, Th2 cells, ILCs, macrophages, neutrophils and eosinophils. Many of these cells are capable of releasing eicosanoids upon activation and/or possess one or more eicosanoid receptors,[166] thus contributing to the exacerbation and its sequelae (e.g. bronchoconstriction, airway inflammation, bronchial hyperresponsiveness).[167] In CRSwNP the T2-inflammatory pathway is also triggered by several stimuli such as viruses, bacteria and allergens, which stimulate inflammatory cell- and cytokine-mediated pathomechanisms in the nasal and paranasal mucosa.[161]

Although *in vitro* data indicate that biologicals may influence eicosanoid pathways in mast cells and basophils,[168] so far there are no published data on direct effects of T2-targeted biologicals on the synthesis or release of eicosanoids in humans*in vivo* **(Fig. 4)** . However, it makes sense that, by blocking pathways and cells (esp. mast cells, basophils, eosinophils and neutrophils) responsible for the release of these pro-inflammatory mediators, may consequently also reduce eicosanoid levels. In addition, previous evidence from clinical studies in asthma showed (partial) reduction of both allergen- and virus-induced airway responses and asthma exacerbations by selective eicosanoid antagonists.[48,118,119,169,170,171] Besides, clinical studies on biologicals in CRSwNP also included a representative cohort of patients with NERD and also found a good clinical response[158] as well as a reduced T2-biomarker profile in this subpopulation.[172] However, so far there are no data on the direct effect of T2-biologicals on the individual eicosanoids nor head-to-head studies comparing biologicals with selective eicosanoid blockers or combinations.

NSAID-exacerbated respiratory disease (NERD). Selectivity of NSAIDs

NERD, also called AERD-aspirin exacerbated respiratory disease or AIA-aspirin-intolerant asthma, is a phenotype of asthma recognized in 5 to 25% asthmatics. It is characterized by a non-immunological hypersensitivity to low doses of NSAIDs and a cross-reactivity (a multi-responder phenotype). Profound changes in biosynthesis of eicosanoids comprise overproduction of cysteinyl-LTs, excreted in urine as LTE_4.[173,174] Some patients have higher excretion of LTE_4 also during a stable period of NERD.[74,175-177] It is debatable, which cells produce cysteinyl-LTs in NERD. Since overproduction of PGD_2 and increase of histamine concentration accompanies symptoms of NERD, these could be mast cells. However, eosinophils in NERD overexpress leukotriene C4 synthase (LTC4S), thus can contribute to the symptoms and concurrent release of eosinophils cationic protein was observed. PGE_2 plays a key role in NERD, where both decreased production of PGE_2 and reduced EP_2expression were observed.[174,178] When PGE_2 is further decreased, it leads to mast cell activation and bronchoconstriction because it removes the stabilising effect of PGE_2 on mast cell mediator release[131]. Accordingly, inhalation of PGE_2 before aspirin challenge prevented reduction in

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pulmonary function and mast cell activation.[179]However, inhibition of PGE_2 biosynthesis by NSAIDs is difficult to measure, since this prostaglandin is produced by most cells of the body. Interestingly, patients with NERD have also an imbalance in pro-resolving lipoxin A_4 (LXA_4) that may contribute to the increased severity of this particular asthma endotype.[180] The minimal dose triggering bronchial constriction and extra bronchial symptoms (cutaneous flush, nasal obstruction, irritations of conjunctiva) varies across patients, but generally it reflects NSAID potency to inhibit cyclooxygenase-1 isoenzyme (COX-1).[181,182] Highly selective inhibitors of COX-2 like coxibs (e.g. celecoxib, etoricoxib)[183]are well tolerated in most NERD patients, whereas preferential COX-2 inhibitors (nimesulide, meloxicam) can trigger symptoms at high doses[184] **(Table 1)** . Diclophenac, ketorolac, ibuprofen, naproxen, indomethacin or pyrazolone derivatives inhibits both COX-2 and COX-1,[185] therefore are contraindicated in NERD. Acetylsalicylic acid is more potent inhibitor of COX-1 than COX-2.[183,186] This was the first NSAID ever reported to trigger symptoms in asthmatics. Paracetamol (acetaminophen), with an unclear effects on prostanoids biosynthesis including possible inactivation of brain cyclooxygenases by a non-substrate mechanism, is tolerated by the vast majority of NERD patients unless given in very high doses.[39]

Eicosanoids in drug allergy

Most of the information available on the role of eicosanoids in allergy and related diseases concerns NERD.[187,188] This fact can be explained because it was the first clinical phenotype in which a link between NSAIDs pharmacological activity and the inhibition of PGE_2 synthesis by blocking COX-1 and the subsequent increase in cysteinyl-LTs release was established.[189]Nevertheless, some data are also available for cutaneous NSAID-induced cross-hypersensitivity. Thus, increased LTE_4 and $9\alpha,11\beta\text{-}PGF_2$ urinary levels have been described for NERD[190-193] and for NSAID-induced acute urticaria/angioedema (NIUA).[193]

For NSAID-exacerbated cutaneous disease (NECD), contrasting results have been found regarding eicosanoids levels at basal state. Thus, Di Lorenzo*et al* . did not report baseline differences for LTE_4 in patients with chronic urticaria and hypersensitivity to acetylsalicylic acid (ASA, aspirin) or food additives,[194] and no variations at basal state were reported for LTE_4 and $9\alpha,11\beta\text{-}PGF_2$ by two other independent studies.[191,193] However, Mastalerz*et al* . reported increased LTE_4 levels in NECD patients with a positive aspirin challenge with respect to those with a negative aspirin challenge, and with no changes found for $9\alpha,11\beta\text{-}PGF_2$.[195] It has been recently published that NIUA and NECD showed similar increased levels in both LTE_4 and $9a,11b\text{-}PGF_2$ within the first 3 hours following a positive aspirin challenge; however, after this time interval these mediators showed different behaviours, being such levels long-lasting in NECD.[193] In spite of these differences being not statistically significant, the reasons explaining the existence of these particular profiles are at present unknown although they may be due to the presence of additional factors in NECD, which could include sensitization to autoantibodies or the existence of histamine-releasing factors.[193]

Data on the role of eicosanoids beyond NSAIDs-hypersensitivity are scarce. However, a potential role for cysteinyl-LTs was proposed in adverse reactions to non-ionic contrast media. Thus, iopromide and iotrolan induced a significant increase of cysteinyl-LTs *in vivo* , with no changes in preformed mediators levels.[196]However, a previous study showed the heterogeneity of the effects of contrast media on mediator release, showing an increase in histamine and tryptase release from different human cells without changes in LTE_4 or PGD_2levels.[197]

Conclusions and unmet needs

NSAIDs, LT modifiers and biologicals are used every day in clinical practice in treatment of viral infections and common respiratory or allergic diseases. Although a significant progress has been made in our understanding how these medications act and how they affect eicosanoid pathways, there are still no sufficient data available to fully address all issues important for prediction of their activities affecting immune response and estimation of their clinical efficacy. This consensus report summarises up to date knowledge in this complex area and identifies major knowledge gaps and unmet needs to be addressed in the future.

Unmet needs

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- Assessment of NSAIDs role in alleviating symptoms of viral infections in general population and in patients with asthma/ allergy with the strong emphasis on the timing of its administration, their selectivity and long-term effects.
- Further basic in vitro, in vivo and large clinical studies assessing NSAIDs influence on the pathogenesis and treatment of COVID-19 are greatly needed.
- Understanding molecular and cellular mechanisms of eicosanoids activity in immune response with focus on balance between pro- and anti-inflammatory properties.
- Characterization of emerging sub-phenotypes, and sub-endotypes of allergic diseases (asthma, rhinitis, NERD) and potential biomarkers for the more effective therapy using eicosanoid pathway modifying drugs (NSAIDs, LTRA, CRTH2 antagonists)
- Evaluation of how the effectiveness of new biologicals for the treatment of allergic diseases relates to the eicosanoids.
- Re-assessment of the effects of prostanoids in allergic and asthmatic reactions in humans by targeted intervention studies with selective inhibitors of receptors or tissue specific synthases.
- Development and testing of novel treatment modalities targeting lipid mediators (eicosanoids) and their receptors.

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Figure legends

Figure 1 . Eicosanoid biosynthesis and signalling pathways are therapeutic targets of medications used in the treatment of infections, acute and chronic inflammatory diseases (including asthma and allergy) and pain. Glucocorticosteroids (GCs), non-steroidal anti-inflammatory drugs (NSAIDs), leukotriene receptor antagonists (LTRAs; eg. montelukast, zafirlukast, pranlukast), 5-lipoxygenase (5-LOX) inhibitor, zileuton, as well as still clinically tested, timapiprant and setitpiprant act directly on the

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synthesis of eicosanoid mediators or their signalling molecules and receptors. Biosynthesis of endocannabinoids (2-AG, AEA) interfere with eicosanoids metabolic pathways.2-AG- 2-Arachidonoyl-glycerol (endocannabinoid); AEA-arachidonyl- ethanolamide (endocannabinoid); COX– cyclooxygenase; Cyt-cytochrome; EET-epoxyeicosatrienoic acid; GC- glucocorticoids; HETE- hydroxyeicosatetraenoic acid; HPETE- hydroperoxyeicosatetraenoic acid; LOX – lipoxygenase; LTE_4 – leukotriene; LTRA - leukotriene receptor antagonists; LX – lipoxin; PLA – phospholipase; PG – prostaglandin; TX-thromboxane

Figure 2. Eicosanoid pathways in viral infections and allergic inflammation of the respiratory airways are affected by several groups of medications. Eicosanoids are important immune mediators coordinating the inflammatory response to viral infections and allergen challenges between bronchial epithelial cells, airway-resident and -infiltrating immune cells. Several groups of drugs used in the treatment of allergic diseases and respiratory tract infections interfere with eicosanoid production and signalling pathways. Glucocorticoids (GCs) reduce the activity of phospholipase A_2 (PLA_2) and COX-2, therefore restricting both the upstream substrate for eicosanoid production and subsequent enzyme. NSAIDs block COX-1 and COX-2 -mediated synthesis of prostaglandins by both bronchial epithelial cells and immune cells. This reduces tissue inflammation and alleviates the symptoms of infection, but at the same time affects the anti-viral response. LTRAs block eicosanoid leukotriene signalling at the receptor level, reducing activation of granulocytes. Biologicals used in the treatment of allergic diseases (anti-IL-5, anti-IL-5Rα, anti-IL-4Rα and anti-IgE) interfere with the eicosanoid signalling in a non-direct manner, by preventing undue activation of eosinophils and Th2 cells, as well as degranulation of basophils and mast cells. BAS – basophil; COX-1 – cyclooxygenase 1; CysLTs – cysteinyl leukotrienes; DC – dendritic cell; EOS – eosinophil; GCs – glucocorticoids; IFN – interferon; IL – interleukin; LOX – lipoxygenase; LTE_4– leukotriene E4; LTRA - leukotriene receptor antagonists; LXA_4 – lipoxin A4; MC – mast cell; MO – monocyte; Mϑ – macrophage; NEU – neutrophil; NSAIDs – non-steroidal anti-inflammatory drugs; PLA2 – phospholipase A2; PGD2 – prostaglandin D2; PGE2 – prostaglandin E2; PGD2-inh – prostaglandin D2 inhibitors; PUFA – polyunsaturated fatty acids; TSLP – thymic stromal lymphopoietin;

Figure 3. Non-steroidal anti-inflammatory drugs and leukotriene antagonists in SARS-CoV-2 infection. Increased levels of eicosanoids have been found in bronchoalveolar lavage fluid of patients with severe COVID-19, with predominance of prostaglandins and thromboxane. There are strong grounds to explore eicosanoid inhibition as a potential therapeutic target in SARS-CoV-2 infections. Prostaglandins amplify innate immune responses to pathogen- and damage-associated molecular patterns, enhance the cascade of proinflammatory cytokine release, activate Th1 and Th17 cells and contribute to recruitment of macrophages and T cells. Moreover, studies in mouse adapted to SARS-CoV-2 infection showed that PGD_2 inhibition protected from severe disease. Despite the initial mixed reports on the use of NSAIDs in COVID-19, it has been concluded that these medications can be safely used to alleviate the symptoms of SARS-CoV-2 infection. This effect is attributed to the disruption of inflammatory circuits. Other effects of NSAIDs in COVID-19 are being investigated and preliminary studies suggest that a non-selective NSAID naproxen could negatively influence SARS-CoV-2 replication. Furthermore, the efficacy of leukotriene antagonist montelukast is being evaluated in a series of clinical trials. The hypothesised mode of action in COVID-19 includes inhibition of leukotriene signalling, as well as direct anti-viral effect (damage to the viral lipid membrane and genome), as reported for other viruses.

Figure 4. The effect of biologicals used in the treatment of allergic diseases on eicosanoid pathways.

Biologicals have revolutionized therapeutic algorithms for patients with the most severe form of allergic diseases. Currently, 5 monoclonal antibodies have been approved for the treatment of severe asthma. Their use has been associated with a decrease in the concentration of proinflammatory lipid mediators. This is most probably an indirect effect of inhibition of immune cells which are the main eicosanoid producers in allergic inflammation.

Omalizumab (anti IgE) binds to free IgE and inhibits their binding to IgE receptors, which results in a downregulation of FcεRI expression on mast cells, basophils and dendritic cells. This leads to a significant

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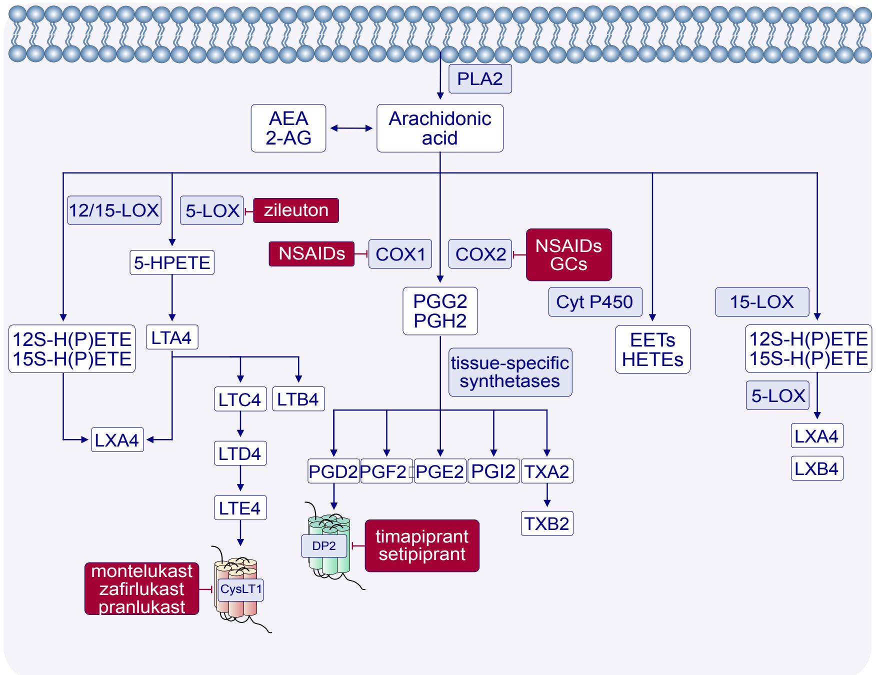
decrease in biosynthesis and release of proinflammatory eicosanoids from these cells, and prevents expansion of eosinophils and ILC2. Dupilumab (anti IL-4Rα) binds to the α subunit of the IL-4 receptor, which is shared by IL-4 and IL-13 receptor complexes. Therefore it blocks the effect of these cytokines on cells contributing to type 2 immune reaction. This results in an inhibition of IgE production, mast cell activation and eicosanoid production, goblet cell metaplasia and mucus production. Mepolizumab, reslizumab (anti-IL-5) and benralizumab (anti IL-5Rα) block IL-5 activity on different levels, therefore inhibiting the maturation, activation and proliferation of eosinophils, as well as basophil activation. Monoclonal antibodies targeting IL-5Rα moreover leads to antibody-dependent cell-mediated cytotoxicity of NK cells against eosinophils and basophils, vast producers of proinflammatory eicosanoids such as prostaglandin D_2 and cysteinyl leukotrienes. While no direct effect of biologicals on eicosanoid biosynthesis has been reported, these medicines disrupt the cascade of immune events leading to type 2 inflammatory responses and the concomitant overproduction of proinflammatory lipid mediators.

Table 1. Molecular targets and selectivity of drugs affecting eicosanoid pathways

Drug	**Group**	**Target**	**Remarks**
Ketoprofen	NSAID	COX-1 >> COX-2	
Aspirin	NSAID	COX-1 >> COX-2	
Naproxen	NSAID	COX-1, COX-2	
Ibuprofen	NSAID	COX-1, COX-2	
Diclofenac	NSAID	COX-1, COX-2	
Ketorolac	NSAID	COX-1, COX-2	
Indomethacin	NSAID	COX-1, COX-2	
Dipyrone (metamizole)	NSAID	COX-1, COX-2	
Piroxicam	NSAID	COX-2 > COX-1	
Meloxicam	NSAID	COX-2 >> COX-1	
Nimesulide	NSAID	COX-2 >> COX-1	
Celecoxib	NSAID	COX-2 >> >COX-1	
Etoricoxib	NSAID	COX-2 >> >COX-1	
Paracetamol (acetaminophen)	Related to NSAIDs	COX-1, COX-2-non-substrate mechanism	
Montelukast	LTRA	CysLTR1	Additional
Zafirlukast	LTRA	CysLT1	
Pranlukast	LTRA	CysLT1	
Zileuton	Leukotriene synthesis inhibitor	5-LOX	
Fevipiprant	Prostaglandin receptor antagonist	DP2	Phase 3 cl
Asapiprant	Prostaglandin receptor antagonist	DP1	Phase 2 cl
Laropiprant	Prostaglandin receptor antagonist	DP1	Temporari
Vidupiprant	Prostaglandin receptor antagonist	DP2 > DP1	Phase 2 cl



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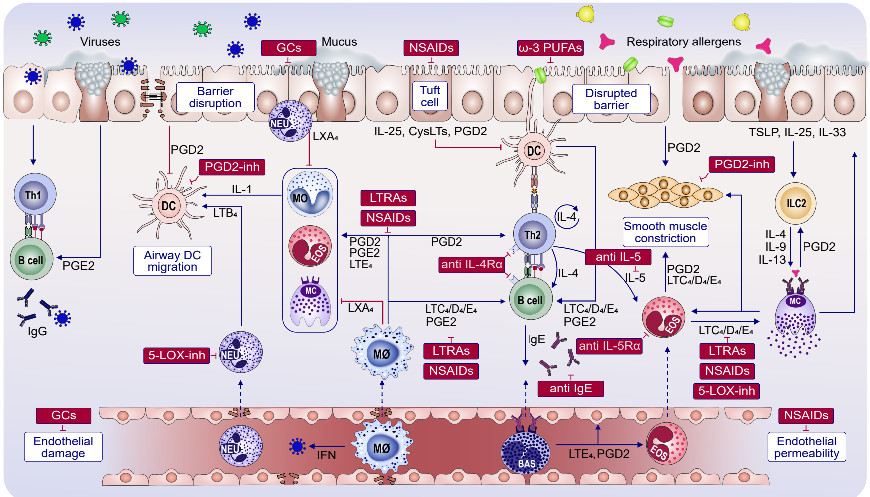

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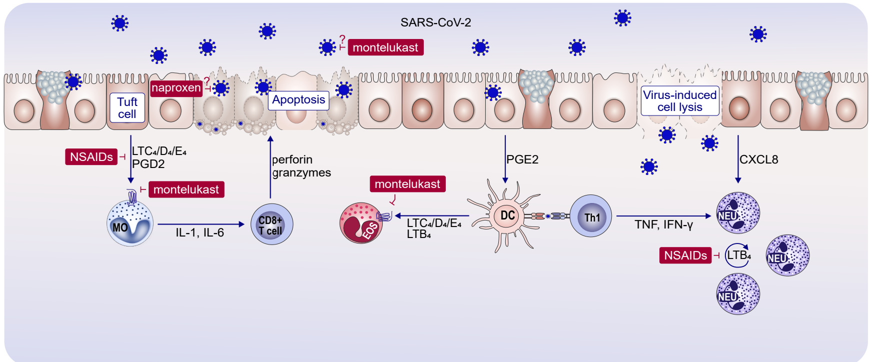

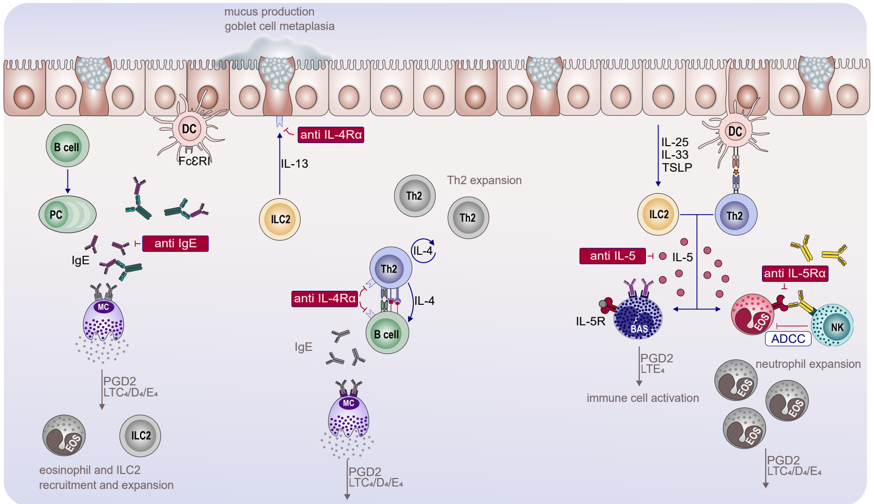

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