ANNUAL REVIEWS

Annual Review of Immunology

Emerging Paradigms in Type 2 Immunity

Hamida Hammad,[1,2] Nincy Debeuf,[1,2] Helena Aegerter,[1,2] Andrew S. Brown,[1,2] and Bart N. Lambrecht[1,2,3]

[1]Laboratory of Mucosal Immunology and Immunoregulation, VIB-UGent Center for Inflammation Research, Ghent, Belgium; email: hamida.hammad@ugent.be

[2]Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium

[3]Department of Pulmonary Medicine, Erasmus Medical Center, Rotterdam, the Netherlands

Annu. Rev. Immunol. 2022. 40:443–67

The *Annual Review of Immunology* is online at immunol.annualreviews.org

https://doi.org/10.1146/annurev-immunol-101320-030339

Keywords

type 2 immunity, neuroimmune interactions, respiratory viruses, cancer, metabolism

Abstract

A principal purpose of type 2 immunity was thought to be defense against large parasites, but it also functions in the restoration of homeostasis, such as toxin clearance following snake bites. In other cases, like allergy, the type 2 T helper (Th2) cytokines and cells present in the environment are detrimental and cause diseases. In recent years, the recognition of cell heterogeneity within Th2-associated cell populations has revealed specific functions of cells with a particular phenotype or gene signature. In addition, here we discuss the recent data regarding heterogeneity of type 2 immunity–related cells, as well as their newly identified role in a variety of processes ranging from involvement in respiratory viral infections [especially in the context of the recent COVID-19 (coronavirus disease 2019) pandemic] to control of cancer development or of metabolic homeostasis.

INTRODUCTION

Research over the last decades has provided deep insights into cellular immune responses and has elucidated how adaptive immunity is activated to support the functioning of innate immune cells, such as macrophages and granulocytes. Type 1 T helper (Th1) cells and natural killer (NK) cells are well-known to produce cytokines like IFN-γ so as to increase the capacity of phagocytes to engulf and kill pathogens. Whereas the evolutionary purpose of this so-called type 1 immune response is easily understood, less is known about the function of type 2 immunity, where adaptive $CD4^+$ Th lymphocytes (Th2 cells) and group 2 innate lymphoid cells (ILC2s) produce the cytokines IL-4, IL-5, IL-9, and IL-13 mainly to help innate eosinophils, basophils, and mast cells. This type 2 immune response is mainly known for its role in causing allergic diseases, but it is believed that type 2 immunity was primarily needed to provide defense against large parasites as vertebrates coevolved with nematodes (1). Symptoms induced by type 2 immunity include itching, swelling, sneezing, wheezing, diarrhea, and abdominal cramping. Such responses can contain or get rid of large parasites as they colonize the gut or pass through the lungs, but they have been proposed to also help expel or neutralize poisons or toxins after skin bites of ectoparasites and snakes, with mast cells and basophils being crucial for venom detoxification (2, 3). Therefore, the primary function of type 2 immune responses is detoxification and expulsion. If this is not sufficient and the parasite finds a way to persist, type 2 immune responses will strive to ignore or regulate the conflict, resolve inflammation, and restore tissue homeostasis. In an ultimate attempt to confine the infectious threat, type 2 immunity will also initiate a fibrotic program leading to encapsulation.

Most immunologists and clinicians know type 2 immunity mainly as a detrimental response to innocuous allergens, like those present in house dust mites (HDMs), cockroaches, pollen, animal dander, and certain foods. Much has been learned about initiation of adaptive type 2 immunity by studying these allergens in animal models. In contrast to type 1 immunity, where stimuli directly activate dendritic cells (DCs) to instruct Th1 immunity via production of IL-12, instruction of Th2 immunity via DCs is indirect, with an intermediate step often involving the barrier epithelial cells. Upon allergen exposure on the skin or other mucosal surfaces, keratinocytes or epithelial cells produce alarmins such as TSLP (thymic stromal lymphopoietin), IL-1α, IL-25, and IL-33. This epithelium-derived response is necessary for the activation of tissue-resident type 2 IRF4-dependent $SIRP\alpha^+$ conventional DCs (cDC2s). With the help of alarmin-activated, IL-13-producing ILC2s, $IFNAR^+$ cDC2s migrate to the draining lymph nodes, where they induce the differentiation of Th2 effector cells (4, 5). Effector Th2 cells produce the typical Th2-associated cytokines IL-4, IL-5, IL-9, and IL-13. Also, T follicular helper (Tfh) cells adopt a Th2 phenotype required for the differentiation of IgE-secreting cells (6). In the lung, for instance, Th2 cytokines contribute to the development of eosinophil-rich local inflammation, mucus production, bronchoconstriction, and tissue remodeling. In the case of chronic allergen exposure, type 2 immune responses can also lead to pathological airway fibrosis and thickening of the subepithelial basement membrane (7). Fibrosis is characterized by the deposition of extracellular matrix components caused by the proliferation of fibroblasts and immune cells. Th2-associated cells such as eosinophils, ILC2s, and a subset of amphiregulin-producing pathogenic Th2 cells are involved in this process (7, 8).

While the roles of type 2 immunity in the fight against parasites and in responses to allergens have been extensively studied, it has become increasingly clear over the last years that type 2 immunity is also closely related to tissue repair processes after injury (9) and maintenance of homeostasis. Cutting-edge technologies have allowed better characterization of type 2 immune cells and identification of functions specific to cells with a particular phenotype or gene signature. In this review, we discuss recent data showing that Th2-associated cells are more heterogeneous than initially

believed and that these cells and related factors are central to a variety of processes contributing to respiratory viral infections [especially in the context of the recent COVID-19 (coronavirus disease 2019) pandemic], to control of cancer development, and to metabolic homeostasis.

HETEROGENEITY IN CELLS ASSOCIATED WITH TYPE 2 IMMUNITY

Th2 Cells

Since the original description of the Th1/Th2 paradigm, Th2 cells have been identified by their production of IL-4, IL-5, and IL-13. However, analyses of peripheral tissue microenvironments coupled with the advent of single-cell sequencing technologies have also radically shaped our appreciation for the heterogeneity and plasticity of mounted type 2 responses and how these can differ between homeostasis and pathology.

Single-cell transcriptomics has recently revealed a high degree of quantitative and qualitative heterogeneity within pulmonary $CD4^+$ T cell populations in lungs of humans and mice with allergic asthma (10, 11). Lungs of asthmatic patients were enriched in Th2 cells comprising two populations of tissue-resident T cells (classical tissue-resident T cells and a novel, recirculating, tissue-migratory subset) and a population of pathogenic effector Th2 cells classified by high expression of *IL5*, *IL13*, *PPARG*, and *IL17RB* (12) (**Figure 1**). Interestingly, a subsequent study found that asthmatic individuals allergic to HDM also had greater numbers of IL-9-expressing Th2 cells that expressed *IL5*, *ZEB2*, *GZMB*, *CD109*, and *IL1RL1*, all collectively linked to increased pathogenicity and survival (10). IL-9 is a pleiotropic cytokine implicated in allergy, nematode infection, and cancer (13). Given the transient and heterogeneous way in which $CD4^+$ T cells are reported to produce IL-9, the existence of a bona fide Th9 subset in vivo is still under debate (13). A recent report claims that IL-9-producing $CD4^+$ T cells are a subpopulation of $PPAR\gamma^+$, IL-5- and IL-13-producing Th2 cells that, upon certain inflammatory conditions, adopt an IL-9-secreting phenotype (14) (**Figure 1**). This concept, however, becomes less clear when the dual Th2/Th17 nature of T cell responses is considered (15), or with the observation that other non-Th2 T cell subsets also secrete IL-9 in various inflammatory or homeostatic conditions (13).

Beyond Classical Th2 Cells

IL-4 is not only a hallmark of Th2 effector or memory Th2 cells. IL-4-secreting follicular helper T (Tfh) cells are thought of as central mediators of IgE isotype switching by B cells (16). Gowthaman et al. (6) recently expanded on this, demonstrating a dichotomy between IL-4- and IL-21-producing, BATF-driven Tfh2 cells and IL-4-, IL-5-, and IL-13-producing, GATA3-driven Tfh13 cells directing switching to antihelminth IgE and high-affinity, pro-anaphylactic IgE, respectively (**Figure 1**). Furthermore, follicular regulatory T (Tfr) cells were shown to regulate IgE class switching in B cells (17) and early germinal center responses involving Tfh13 cells with HDM (17). These functions were attributed to a high level of secretion of neuritin, in addition to IL-10, by Tfr cells that acted specifically on B cells to repress plasma cell formation and immunoglobulin class switching to Th2-associated IgG1 and IgE (18).

Also, Tregs can share features with conventional Th2 cells, such as responsiveness to IL-33 and production of IL-10. First described in the gut, IL-33-responsive, $ST2^+Foxp3^+$ Tregs express GATA-3 and the lipid transcription factor $PPAR\gamma$ (19). This subset is particularly enriched in healthy adipose tissues (20). In the lung, $ST2^+$ Tregs suppress the activation of innate γδ T cells, which are required for production of eosinophil-selective chemokines (21). $ST2^+$ Tregs seem to respond to IL-33 directly produced by DCs, whereas other $ST2^+$ effector cells, including effector Th2 cells and ILC2s, respond to epithelial IL-33 (22). The development of $ST2^+$ Tregs seems to

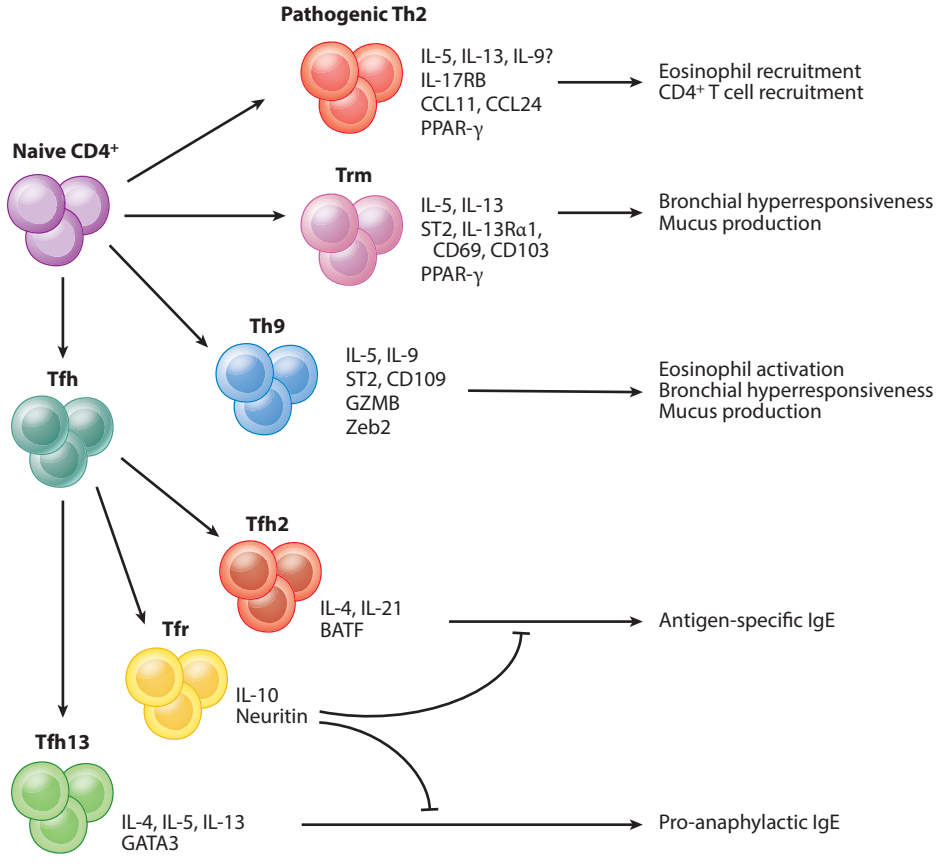

Figure 1

T cell heterogeneity in type 2 immunity. Over the last years, several populations of CD4+ T cells with different characteristics have been identified. Depending on their expression of cytokines, transcription factors, or surface markers, these T cells exert different functions ranging from eosinophil recruitment to bronchial hyperresponsiveness to mucus production to help in the production of different types of IgE. Abbreviations: Tfh, T follicular helper; Tfr, follicular regulatory T; Th2, type 2 T helper; Trm, tissue-resident memory T.

be under direct reciprocal control of Bcl6 and Blimp1, very similar to their role in development of Tfr cells (23).

ILC2s

Functionally, there is considerable overlap of Th2 cells with ILC2s enriched in barrier sites including the skin, lung, and gut. Certainly, given their dependence on tissue-derived cytokines, these cells seem to occupy very similar niches, e.g., in close contact with IL-33-producing stromal cells around the blood vessels and bronchi in airways (24). Unlike their adaptive counterparts, ILC2s do not express antigen-specific receptors and do not require prior activation by antigen-presenting DCs but are directly triggered via epithelial or stromal cytokines or ligation of stimulatory receptors. In mice, ILC2s were shown to expand during the perinatal window, when they establish a cytokine- and tissue-specific transcription signature, translating to functional differences

between different organs of residence (25, 26). Recently, ILC2s have been divided into a steady-state, natural ILC2 (nILC2) population and an inflammatory ILC2 (iILC2) population that arises under type 2 inflammatory conditions (27, 28). nILC2s are tissue resident, slowly turn over, and do not reenter the circulation (29). nILC2s transition to iILC2s in a process that depends on tissue-specific alarmins. The transcription factor BATF (28) or the cytokine IL-33 (27) has been implicated in the downstream function of iILC2s, their entry into the circulation, and their migration to lymph nodes. Furthermore, iILC2s entered the circulation once the niche size limit in peripheral tissues had been reached, and this was associated with dissemination of a type 2 response systemically (29). Inflammatory ILC2s were also recently identified in humans. $CD45RO^+$ ILC2s are transcriptionally and functionally homologous to murine iILC2s and differentiate from tissue-resident $CD45RA^+$ ILC2s in a process also dependent on BATF and IRF4 (30). $CD45RO^+$ ILC2s were enriched in peripheral blood and tissue samples of asthmatic patients and patients with chronic rhinosinusitis, and this correlated with disease severity as well as resistance to corticosteroids (30). In humans, ILC2s can also exhibit considerable plasticity. IL-10-producing $KLRG1^+$ ILC2s demonstrate a capacity to suppress type 2 immunity and are defective in patients with grass pollen allergy. However, seasonal allergen immunotherapy with grass pollen extract was able to restore IL-10 production in ILC2s of these patients (31).

The transcription factor RORα has been deemed a unique discriminating factor between ILC2s and Th2 cells, and RORα-deficient mice have been used as a model to probe ILC2 function in vivo since they lack ILC2s (5). However, recent data suggest that RORα is also active in classical Th2 cells, suppressing production of cytokines, including IL-10, and also in Tregs (32). Deletion of RORα in these adaptive cells boosts cytokine secretion and promotes allergic disease (33).

Overall, the tissue environment, coupled with inflammatory signals released upon tissue perturbation, imparts considerable heterogeneity among tissue-resident and inflammatory immune cell populations. It is important we understand how these processes are propagated and regulated differently between tissues as well as between patients with differing genetic backgrounds, especially for the development of individual targeted therapies for type 2 diseases (34).

Eosinophils

The eosinophil is a key effector cell of type 2 immune responses that can kill large extracellular parasites via release of toxic basic proteins like eosinophil cationic protein and major basic protein (35). Eosinophils also alter the quality of mucus by oxidative cross-linking of airway and gut mucins (36) and release of Charcot-Leyden crystals made up of galectin-10 (37). Recent technological advances in multiparameter flow cytometry have demonstrated that eosinophils are a heterogeneous population of effector and precursor cells, with a diverse range of tissue-specific phenotypes and functions, especially in type 2 diseases such as asthma. Eosinophils are a small fraction of immune cells in the lung and circulation at steady state. However, type 2 inflammation readily recruits new eosinophil populations. In the 1980s, a hypodense population of eosinophils was identified in the blood and bronchoalveolar lavage fluids of asthmatic patients and was associated with disease severity (38). These eosinophil populations recruited during allergic inflammation can be separated using flow cytometric markers in the lungs of mice ($CD101^{hi}CD62L^{lo}$) and humans ($IL\text{-}3R^{hi}CD62L^{lo}$). They have been termed inflammatory because they are present during disease, but functional studies describing the roles of these cells in inflammation are still lacking (39, 40).

Many recent studies have described the expression of Ly6G/Gr1, a marker conventionally used to characterize neutrophils, on murine eosinophils during allergic inflammation (41, 42). This

eosinophil population is also present in murine bone marrow. In vitro studies have shown that the type 2 cytokine IL-5 can drive the differentiation of $Ly6G^{+}SiglecF^{+}$ eosinophils from both a bone marrow–derived eosinophil population (43) and a neutrophil population (44). This has led to the idea that these cells may indeed be precursor cells, described as EoPre (45). The effect of tissue- and disease-specific cytokines in determining the phenotype of eosinophils is yet to be fully explored, but interestingly, following treatment with IL-5 and GM-CSF (granulocyte-macrophage colony-stimulating factor), eosinophils isolated from the peripheral blood of humans upregulate CD69 and dysregulate fatty acid metabolism, resembling an eosinophil counterpart found in nasal polyps (46). The individual or synergistic exposure to type 2 cytokines in disease tissue is likely to play a significant role in eosinophil phenotype, including function and longevity (47, 48).

Much work remains to clearly delineate the in vivo phenotypes and functions of eosinophils during inflammation and how these are represented in humans. Eosinophils are a difficult target for transcriptional studies due to their low number at steady state and their high level of intrinsic RNases, which make them challenging for manipulation, but the interest in these cells and the capability to analyze them are increasing.

Exploring eosinophil heterogeneity is particularly relevant, given the advent of new therapeutics for type 2 diseases, many of which aim to deplete eosinophils via blockade of IL-5/IL-5R. An important consideration in the development of new therapeutics for severe asthma is the incomplete penetrance of these biologics in all facets of disease and in all patients. Understanding the heterogeneity and tissue-specific development and maturation of eosinophils may shed some light on the lack of efficacy of anti-IL-5/IL-5R treatments in some patients, as some tissue-resident populations appear to be refractory to this cytokine (39). The distinct phenotype of eosinophils in the nasal and lung tissues of patients with asthma ($IL\text{-}3R^{hi}CD69^{hi}$) and patients with chronic rhinosinusitis (40, 49) may reflect a reliance on local factors, such as components of the extracellular matrix (50), to instruct a subpopulation of eosinophils, especially given that the administration of mepolizumab (anti-IL-5, see below) does not attenuate the expression of these markers (CD69/IL-3R) on these cells (51).

NEUROIMMUNE PROCESSES DRIVING TYPE 2 IMMUNITY

It has been proposed that type 2 immune responses evolved to rapidly defend against parasites and toxins and to elicit rapid behaviors that lead to avoidance of the eliciting stimulus upon future contacts (52). This behavior requires rapid input to the nervous system, and not surprisingly, type 2 immunity has close intersections with the peripheral nervous system. Mast cells, alongside other tissue-resident phagocytes and ILCs, localize proximally to sensory nerves in the lung, gut, bladder, and skin (53, 54). Given that these sites are highly innervated, increased attention has been placed in recent years on the functional consequences of such proximity as well as the intersectional cross talk between neuropeptides, neurotransmitters, and cytokines in mediating type 2 responses and allergic disorders such as asthma, atopic dermatitis, and beigeing of white adipose tissue (53, 55).

ILC2s were shown to synthesize the neurotransmitter acetylcholine (ACh) in the gut and lung in response to helminths, aspergillus, or exogenous alarmins or cytokines (56, 57). ACh production enhanced type 2 cytokine production and aided downstream worm expulsion (56, 57). Similar induction of ILC2 responsiveness was also attributed to the neuropeptide neuromedin U (NMU) in the gut (58, 59) and lung (60); and pulmonary ILC2 function was found to be constrained by calcitonin gene–related peptide (CGRP) released during *Nippostrongylus brasiliensis* infection (61). Perner et al. (62) recently demonstrated that the cysteine protease papain directly stimulated skin sensory neurons that subsequently released substance P (SP). SP itself acted on proximal

CD301b$^+$ DCs via MrgprA1 to promote lymph node migration and subsequent Th2 responses. Furthermore, unlike NMU, neuromedin B (NMB) regulated ILC2 activity in a circuit dependent on innate cross talk with basophils after *N. brasiliensis* infection. In this study, basophils influenced the expression of the NMB receptor on ILC2s, which, in turn, dampened type 2 cytokine release and cell proliferative capacity (63).

Nerve- and airway-associated interstitial macrophages were also recently identified as a unique subpopulation of lung-associated macrophages with high immunoregulatory gene expression and were strongly involved in directing tissue homeostasis (64). Thus, although the bidirectional interaction of the nervous system and immune system has been known for decades (65), these recent works, coupled with the emerging concept of the neuroimmune cell unit (66), signify the importance of neuronal-immune communication for localized tissue inflammation, homeostasis, and integrity (63, 67).

RESPIRATORY VIRUSES AND TH2-MEDIATED DISEASES

In the field of type 2 immunity, it is very clear that patients with chronic airway diseases such as type 2–high asthma are at increased risk for viral infection. Asthma exacerbations are mainly caused by respiratory viruses, such as rhinoviruses and respiratory syncytial viruses (RSVs) (68). One of the possible explanations for this is that rhinoviruses and RSVs favor type 2–related immune responses, as they facilitate IL-33 and IL-25 production by airway epithelial cells, especially in allergic patients, resulting in the activation and recruitment of ILC2s, Th2 cells, and eosinophils, which participate in asthma exacerbation (69). Furthermore, in asthmatic patients, type I and type III interferon production by bronchial epithelial cells, a process required for mounting efficient antiviral responses, is impaired (70). The same holds true for plasmacytoid DCs, since IgE cross-linking—a hallmark of allergic reactions—might abrogate their maturation and IFN-α secretion and in this way dampen antiviral immune responses (71).

Type 2 Immunity in COVID-19

It is now well accepted that existing type 2 immunity can control the course of viral infections. For this reason, the recent outbreak of COVID-19, induced by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has generated questions on whether patients with Th2 responses in the lung would be at increased risk for SARS-Cov-2 infection and whether asthma would worsen in SARS-Cov-2-infected patients.

SARS-CoV-2 is a positive-sense, single-stranded RNA virus belonging to a subfamily of the *Coronaviridae* and was originally described in 2019 in Wuhan, China. SARS-CoV-2 viruses infect the upper and lower respiratory tracts and enter host cells through the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) (72). Like many other respiratory RNA viruses, including rhinoviruses and RSVs, SARS-CoV-2 viruses activate the innate immune system in the airways by binding to pattern recognition receptors and inducing expression of type I and III interferons. SARS-CoV-2 infection induces mainly a type 1 immune response, although type 2 cytokines are also elevated in COVID-19 patients, unlike in other coronavirus infections (73, 74). Increased expression of IL-33 has been observed in the bronchoalveolar lavage fluids of patients with COVID-19 (75). IL-33 can contribute to Th2 immunity but can also induce the differentiation of Tregs (19). Since patients with mild symptoms of COVID-19 have been shown to have increased numbers of Tregs (76), it is possible that in those individuals, low levels of IL-33 are able to help in the generation of TGF-β-induced Tregs and therefore contribute to the resolution of inflammation. In more symptomatic patients, higher levels of IL-33 might induce dysregulation of pulmonary responses (**Figure 2**). Indeed, IL-33 can

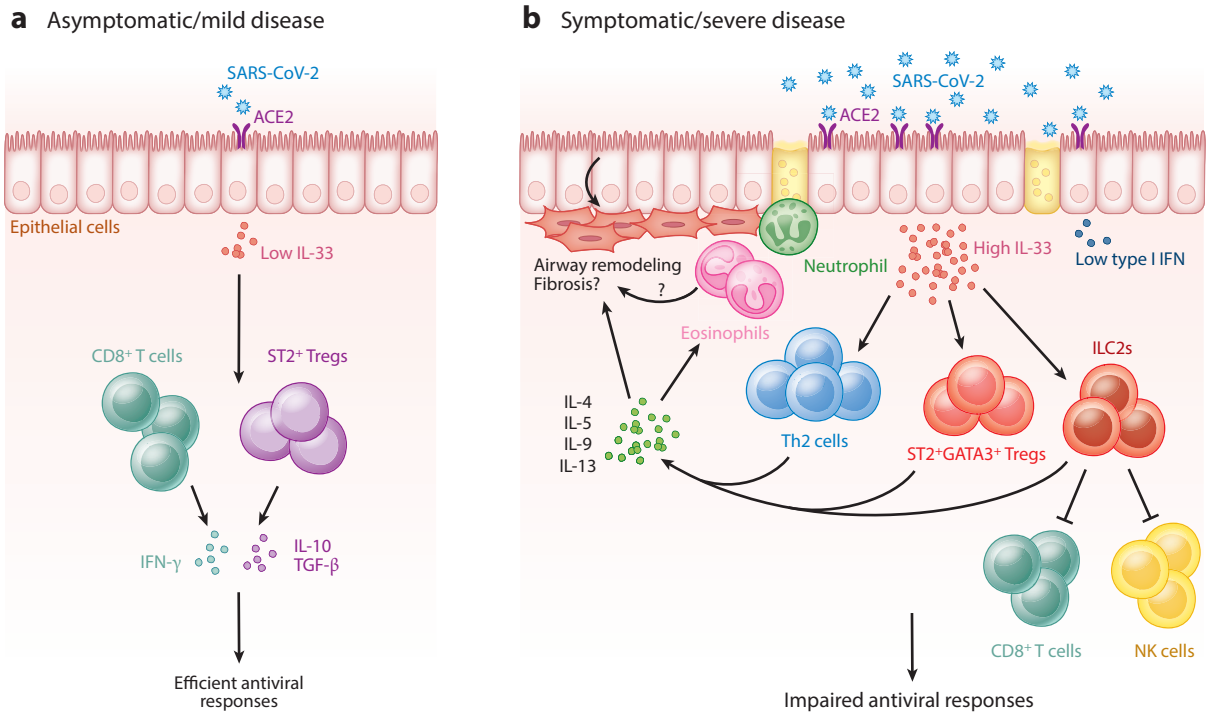

Figure 2

Type 2 immunity in patients with COVID-19. (*a*) Upon a mild infection or in asymptomatic patients, SARS-CoV-2 triggers a mild production of IL-33 by lung epithelial cells. These low levels stimulate $CD8^+$ T cells and $ST2^+$ Tregs, which produce IFN-γ and immunosuppressive cytokines like IL-10 and TGF-β, all contributing to efficient antiviral responses. (*b*) In the case of a more severe infection, SARS-CoV-2 induces copious IL-33 production by epithelial cells. IL-33 triggers Th2 cells, ILC2s and $ST2^+$ Tregs, which acquire GATA3 expression. All these cells produce type 2 cytokines (IL-4, IL-5, IL-9, and IL-13), which leads to lung eosinophilia and airway remodeling, possibly evolving into pathogenic fibrosis. In addition, activated ILC2s can inhibit $CD8^+$ T cell and NK cell responses. Altogether, the presence of type 2 cells and cytokines leads to less efficient antiviral responses. Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; ILC2, group 2 innate lymphoid cell; NK, natural killer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th2, type 2 T helper; Treg, regulatory T cell.

activate ILC2s, which can suppress NK cell cytotoxic functions and IFN-γ production (77), and this might therefore contribute to less efficient antiviral responses (78). More studies in animal models and clinical trials are needed to establish the exact contribution of IL-33 in SARS-Cov-2 infection and whether IL-33 would be a good target for treating COVID-19.

Despite data suggesting that type 2 immunity developing during SARS-Cov-2 infection might be linked to disease severity, intriguing reports point to evidence that the situation might be different when the virus infects patients with preexisting pulmonary Th2 immunity. In contrast to other respiratory viruses, human coronaviruses are not frequently observed during asthma exacerbations (68). In line with this, recent epidemiological data have demonstrated that allergic asthma and allergy are not risk factors for SARS-CoV-2 infection (79–81). In fact, it has even been suggested that allergic asthma or allergy decreases the risk of SARS-CoV-2 infection, as airway epithelial ACE2 expression tends to be lower in allergic asthma patients compared to healthy individuals (82, 83). Also, inhaled corticosteroids—which are standard care for asthma—have been associated with reduced expression of both ACE2 and TMPRSS2 (84). As these inhaled

corticosteroids also reduce levels of proinflammatory cytokines (such as GM-CSF and TNF-α), it is tempting to speculate that they exert protective effects during the inflammatory stage of COVID-19, akin to the beneficial effect of systemic steroids (85). In this regard, a recent report pointed out that the inhaled corticosteroid budesonide can be used to prevent hospitalization in nonasthmatic subjects with mild recent-onset COVID-19 (86). On the other hand, patients with nonallergic asthma did have an increased risk of SARS-CoV-2 infection, but this might be explained by the fact that these patients often have comorbidities such as obesity, diabetes, and hypertension, which are all risk factors for COVID-19 (87).

Anti–type 2 biologics during the COVID-19 pandemic. Because of evidence that allergic asthma can reduce susceptibility to SARS-CoV-2 infection and mitigate the course of COVID-19, there were some concerns about the safety of anti–type 2 cytokine biologics during the COVID-19 pandemic.

IL-4 and IL-13 blockade. Dupilumab is a human monoclonal antibody that inhibits the function of IL-4 and IL-13 by blocking their shared IL-4Rα receptor component. During COVID-19 cytokine storm, many proinflammatory Th1 cytokines are released (such as IL-2, IFN-γ, and TNF-α/β), but Th2 cytokines (such as IL-5, IL-10, and IL-13) are also elevated (73, 74). Remarkably, Donlan et al. (88) recently described IL-13 as one of the drivers of COVID-19, as anti-IL-13 was protective against severe COVID-19 in both humans and mouse models. Interestingly, these authors found that anti-IL-13 led to reduced expression of the gene coding for hyaluronan synthase 1 (*Has1*) and the hyaluronan receptor, CD44, and suggested that blocking the hyaluronan pathway might be a new target for COVID-19 treatment. In line with this, several reports have indicated that dupilumab should be continued during the pandemic, as dupilumab-treated patients did not develop stronger or prolonged COVID-19 (89, 90). However, this is still not completely clear, since others have also reported cases with a diminished antibody response against SARS-CoV-2 and prolonged viral load upon treatment with dupilumab (91).

IL-5 pathway blockade. Mepolizumab, reslizumab, and benralizumab are biologics used for eosinophil-associated diseases. Mepolizumab and reslizumab neutralize the eosinophil growth and activating factor IL-5, while benralizumab targets IL-5R and directly induces eosinophil depletion by antibody-dependent cellular cytotoxicity. In patients with type 2–high asthma, biologics that decrease pulmonary eosinophil numbers reduce virus-induced asthma exacerbations (92, 93). In view of these results, and because eosinophils were shown to have antiviral functions (94), the contribution of the IL-5 pathway and of eosinophils in SARS-Cov-2 infections was also addressed. When investigators looked at the number of circulating eosinophils in patients with COVID-19, the data were very controversial. Some found higher numbers of eosinophils in patients with severe COVID-19 (95), and others reported blood eosinopenia in such patients (96–98). However, increased expression of eosinophil-specific genes such as Galectin-10 and EDN was present in the postmortem lung tissue of COVID-19 patients (99), suggesting that eosinophils might contribute to COVID-19 inflammation. Given that during the pandemic asthma patients being treated with anti-IL-5 and anti-IL-5R biologics did not get more severe COVID-19 (100), it would be interesting to test whether such biologics represent an effective therapeutic strategy for patients with elevated eosinophil markers in their lungs.

Thus, based on the current literature, biologics blocking type 2 cytokines appear to be safe during the COVID-19 pandemic. However, these biologics are currently used in patients with asthma. Their value in patients who develop a type 2 signature in response to SARS-CoV-2 remains to be fully addressed.

Type 2 immunity during post-COVID-19 pulmonary fibrosis. Some patients who have overcome COVID-19 develop long-term sequelae (101). One of the most devastating post-COVID-19 symptoms is pulmonary fibrosis, which is characterized by excessive collagen and extracellular matrix deposition within the lung interstitium. This fibrotic tissue leads to destruction of the normal lung parenchymal structure and to progressive loss of pulmonary function (102). A systematic review reported that about 30% of COVID-19 patients had evidence of fibrotic sequelae that persisted at least for six months after infection, although more studies are clearly needed and the real incidence of fibrosis after COVID-19 may be well below 5%. It is also still too early to determine whether these fibrotic changes in the lung are irreversible. Previous follow-up studies with SARS-CoV and Middle East respiratory syndrome (MERS) patients have indicated that these fibrotic insults might persist for more than a year (103).

The pathogenesis of (idiopathic) pulmonary fibrosis involves repeated microinjury to the alveolar epithelium that leads to an aberrant and ineffective repair response and epithelial dysfunction. Upon activation and secretion of TGF-β by airway epithelial cells, TGF-β will stimulate the transdifferentiation of fibroblasts into myofibroblasts. TGF-β will also activate these myofibroblasts, resulting in the deposition of more extracellular matrix material in the interstitial lung tissue and thus fibrosis (102). Besides TGF-β, type 2 cytokines and especially IL-13 have been identified as cytokines driving fibrogenesis. Indeed, increased expression of both IL-13 and its receptors IL-13Rα1 and IL-13Rα2 has been observed in patients with pulmonary fibrosis (104). Furthermore, Murray et al. reported that blockade of IL-13 significantly reduced pulmonary fibrosis and stimulated epithelial repair in a humanized severe combined immunodeficiency (SCID) mouse model of idiopathic pulmonary fibrosis (IPF), in which mice are infused with fibroblasts from patients with IPF (105). Interestingly, a compensatory increase in IFN-γ has been observed during IL-13 blockade and resulted in elevated type 1 cytotoxicity and necrosis. Therefore, dual blockade of IL-13 and IFN-γ has been proposed to be a better treatment option for pulmonary fibrosis than anti-IL-13 alone (106).

Although there is ample evidence that type 2 immunity is involved in the pathogenesis of (idiopathic) pulmonary fibrosis, whether the same mechanisms also drive post-COVID-19 fibrosis is not clear yet. Therefore, in future studies, it will be important to thoroughly monitor the long-term consequences of COVID-19, in terms of both epidemiology and pathogenesis. Current and future anti-type-2 biologics and antifibrotic agents might have beneficial effects, but multiblockade strategies might be more promising to combat rebound cytotoxic type 1 responses. Given the tremendous impact of the COVID-19 pandemic, even if only a small fraction of SARS-CoV-2-infected individuals develop post-COVID-19 sequelae, it will still be an enormous challenge for the health care system to support all these patients with suitable treatments.

TYPE 2 IMMUNITY IN CANCER

Antitumor immunity and tumor cell killing are usually associated with type 1 immune responses. Antitumoral functions are mainly executed by NK cells and by $CD8^+$ cytotoxic T cells, which are activated by tumor-loaded type 1 conventional DCs (cDC1s). Macrophages also have an important role in controlling anticancer immunity. It is generally believed that M1-like macrophages can directly mediate cytotoxicity and kill tumor cells or that they can do so using antibody-dependent cell-mediated cytotoxicity (ADCC). The discovery of tumor-associated macrophages (TAMs) as being more "alternatively activated"–like cells that promote tumor growth and support the survival of Tregs has challenged the concept that the tumor microenvironment is dictated solely by a type 1 immune response (107). The alternatively activated phenotype and immunosuppressive role of TAMs are regulated by several factors, including tumor cell–derived molecules such as sonic hedgehog or CSF-1, and the hypoxic condition of the tumor microenvironment (107–109).

The transcription factor FoxO1, involved in macrophage polarization, gets downregulated and promotes an alternatively activated differentiation program along with a reduction in MHC-II expression (110). The alternatively activated program of TAMs is also controlled by Th2 cytokines like IL-4 and IL-13 that are produced by Th2 cells and ILC2s and influence not only macrophages but also cDCs to adopt a Th2-inducing mode. The repeated observations that Th2-associated cytokines and cell populations are present in some types of cancers have encouraged research groups to better define the role of type 2 immunity in cancer development.

Evidence for a Role of Th2 Cytokines in Cancer

Type 2 immunity includes cells and molecules normally involved in responses to helminths and allergens but also those involved in wound healing processes and that often rely on proliferation and differentiation of stem cells. In the gut for instance, IL-13 production by ILC2s can contribute to homeostasis by promoting the self-renewal of IL-4Rα$^+$ intestinal stem cells (111). Interestingly, polymorphisms in IL-4, IL-13, and IL-4Rα genes are associated with the development of some cancers such as colorectal cancer. In line with this, several studies support a protumorigenic effect of Th2 cytokines. In obese mice, which have higher levels of IL-13 in the serum and higher expression of IL-13Rα2 in colon tissue, the number of tumors was higher than in wild-type littermates (112). In colorectal cancer, IL-4 and IL-13 can induce an increase in the concentrations of reactive oxygen species (ROS), therefore contributing to the establishment of an oxidant milieu, a driver of inflammation-dependent cell proliferation and tumor progression (113). In addition, in a model of non–small cell lung cancer, a recent study identified mature cDCs enriched in immunoregulatory molecules (mregDCs) characterized by the expression of Th2-associated genes, including that encoding IL-4Rα. In this model, the presence of IL-4 inhibited IL-4Rα$^+$ mregDC functions by reducing IL-12 production and by limiting their capacity to activate efficient CD8$^+$ T cell responses. The blockade of IL-4 signaling restored mregDC functions and reduced tumor burden (114) (**Figure 3**). These data nicely show that both IL-4 and IL-13 can promote tumor growth and be a therapeutic target in cancers where their presence is proven.

Despite evidence showing the deleterious effect of Th2 cytokines in cancer, there are also data proposing a role for Th2 cytokines in restraining tumor progression. Recently, in a murine model of breast cancer, in the absence of the suppressive cytokine TGF-β in the tumor microenvironment, CD4$^+$ T cell–derived IL-4 reduced tumor development. This IL-4-mediated halt in cancer progression was the result of blood vessel remodeling that caused hypoxia and cell death in avascularized regions (115). Interestingly, when studying patients with different types of cancer, the authors of this report found a strong type 2 signature in less aggressive types of cancer (115). Type 2 immunity is traditionally associated with IgE responses. Engineered IgE directed against cancer epitopes can potentially be used to elicit stronger antitumoral immunity, a field or research now called AllergoOncology (116). Cross-linking of IgE on a trimeric IgE receptor of human monocytes indeed elicits strong ADCC and monocyte activation, and better control of tumor growth (116).

Collectively, these data show that the role for type 2 cytokines in cancer is still controversial and depends on the type of tumors studied. Because Th2 cytokines can contribute to tumor growth in some types of cancer, it would be interesting to see whether some of the recently developed anti–type 2 cytokine therapies such as dupilumab (which targets IL-4Rα) that are used to treat Th2-associated diseases would also be beneficial in some cancer patients.

A Role for Epithelium-Derived Cytokines in Cancer Development?

TSLP is primarily expressed in epithelial cells at barrier sites, with the highest expression levels in skin, gut, and lung. TSLP has been involved in allergic diseases, where it helps to create a

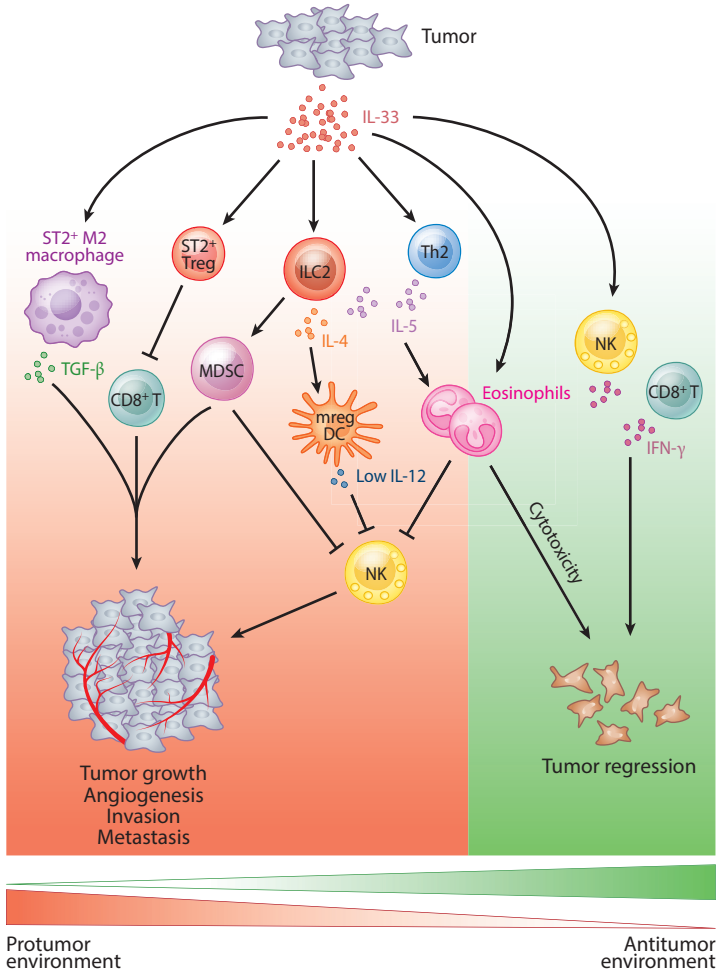

Figure 3

The two faces of IL-33 in cancer. (*Left*) IL-33 production by tumors leads to the activation of ILC2s, Th2 cells, ST2$^+$ Tregs, and M2-like macrophages. The production of IL-5 by ILC2s and Th2 cells induces the activation of eosinophils, which can inhibit NK cell functions and contribute to tumor growth. IL-4 production by ILC2s and/or Th2 cells induces low IL-12 production by mregDC functions, which can inhibit NK cell functions. In addition, ILC2s induce MDSCs that contribute to a general immunosuppressive environment and to tumor growth. (*Right*) IL-33 sometimes contributes to tumor regression. IL-33 can also directly stimulate CD8$^+$ T cells and NK cells, which produce IFN-γ, leading to tumor regression. IL-33 can also directly activate eosinophils to release their cytotoxic granules, leading to tumor destruction. Abbreviations: ILC2, group 2 innate lymphoid cell; MDSC, myeloid-derived suppressor cell; mregDC, mature conventional dendritic cell enriched in immunoregulatory molecules; NK, natural killer; Th2, type 2 T helper; Treg, regulatory T cell.

predominantly Th2 microenvironment, mostly through DC activation. Recently, a role for TSLP in cancer has been proposed (117). However, data are scarce and quite unclear because of the fact that in humans, TSLP expression has always been associated with tumor progression whereas in mice, antitumor functions have been reported (reviewed in 117). Given the strong association between cancer and TSLP in humans, this cytokine is an interesting target. In tumors where

TSLP expression is established, it will be interesting to test the effects of tezepelumab, an anti-TSLP monoclonal antibody likely soon to be approved as a biologic to treat asthma (118). It will be interesting to test the effects of tezepelumab in tumors where TSLP expression is established.

IL-33 is another Th2-associated cytokine expressed by a variety of cells including fibroblasts, endothelial cells, and epithelial cells. The presence of IL-33 has been reported in several types of tumors, but its biological function there is not fully understood. Antitumor immunity classically involves type 1 immune cells such as $CD8^+$ T cells and NK cells, both of which can express the IL-33 receptor, ST2. IL-33 reinforces the functions of $CD8^+$ T cells and of NK cells by increasing their ability to produce IFN-γ, thereby inducing an environment that would support tumor rejection and where IL-33 would therefore have antitumor activities (119, 120) (**Figure 3**). However, in other types of cancer, IL-33 is associated with the accumulation of $ST2^+$ Tregs, a specific subset previously identified in mucosae where it relies on IL-33 for its suppressive capacities, unlike classical $Foxp3^+$ Tregs (19). In tumors, the presence of IL-33 renders $ST2^+$ Tregs unable to inhibit T cell effector functions, indicating that this IL-33–$ST2^+$ Treg axis might contribute to the development of a protumorigenic environment (121, 122) (**Figure 3**). Also, in a model of squamous cell carcinoma, IL-33 production by tumor-initiating cells induced the accumulation of $ST2^+FcεRI^+MHCII^{lo}$ TAMs that produced TGF-β. This TAM-derived TGF-β stimulates the invasive properties of tumor cells and more IL-33 production by these cells (123). This signaling loop could be a critical driver of invasive cancer progression in squamous cell carcinoma. In conclusion, IL-33 seems to harbor a dual role in cancer that depends on cancer type, but it is certainly an interesting target for immunotherapy to limit tumor growth and invasiveness.

A Role for ILC2s in Cancer

Because IL-33 has been reported in several types of tumors, it is not surprising that researchers have tried to understand the role of ILC2s, the best-known target for IL-33, in cancer immunity. ILC2s produce high amounts of the type 2 cytokines IL-4, IL-5, IL-9, and IL-13, as well as amphiregulin, which is involved in tissue repair. ILC2s can be found in different types of tumors in which high levels of IL-33 are detected, and they usually promote tumor growth, angiogenesis, and metastasis (124) (**Figure 3**). These findings fit very well with the observations that high levels of IL-33 are often associated with poor prognosis (125). In breast cancer models, the use of $ST2^{-/-}$ animals strongly reduced the number of both ILC2s and myeloid-derived suppressor cells (MDSCs), suggesting that MDSCs can be recruited by ILC2s. Recently, a similar ILC2-MDSC link was shown to be present in human patients with acute promyelocytic leukemia (APL) (126). In APL, high levels of PGD2 and B7-H6 present in the tumor microenvironment were able to expand and activate ILC2s. High levels of ILC2-derived IL-13 led to a strong immunosuppressive environment permissive for tumor growth (126). Again, in this study, the evidence was circumstantial, and the exact nature of the MDSC-ILC2 cross talk still needs to be elucidated. Whether IL-13 or other ILC2-derived Th2 cytokines present in the tumor microenvironment contribute in any way to MDSC functions remains to be addressed. These data point to a role for ILC2-derived cytokines in setting up a protumorigenic environment. Interestingly, a recent report identified PPARγ expression in ILC2s as an important driver of the protumorigenic functions of these cells because they favor Th2 cytokine production (127). Since PPARγ expression is equally important to drive IL-5 and IL-13 production by Th2 cells (128), it would be interesting to determine whether $PPARγ^+$ Th2 cells can also contribute to a protumorigenic environment, or whether this is an exclusive function of ILC2s.

While Th2 cytokine production by ILC2s is able to set the stage for tumor development, some reports state that ILC2s can directly favor the differentiation of Tregs through their

expression of ICOSL (129). In turn, ILC2-induced Tregs can inhibit ILC2 proliferation and activation. Whether Tregs can turn ILC2s into some sorts of regulatory ILCs, or whether ILC2s adopt a more Treg cytokine–producing signature, as seen following allergen immunotherapy (31), is not clear, but together this would all help sustain a suppressive tumor microenvironment.

Despite the well-documented protumorigenic role of ILC2s, some reports also provide evidence of antitumor activities of ILC2s, at least in certain types of cancer. In colorectal cancer, ILC2-derived IL-13 was shown to be able to activate DCs, which became better at inducing cytotoxic $CD8^+$ T cells, therefore conferring better antitumor immunity (125). More recently, IL-9-producing ILC2s were shown to be the dominant ILC2 subset in colorectal cancer. ILC2-derived IL-9 promotes the antitumor effects of $CD8^+$ T cells, and in this way, ILC2s contribute to limiting cancer progression (130).

In sum, the role of ILC2s in cancer immunity is still controversial, and more work is needed to better understand the mechanisms behind ILC2 pro- and antitumor functions.

Eosinophils in Cancer

Despite early data showing the presence of eosinophils in the tumor microenvironment of many human tumors (131), the role of eosinophils in cancer has been largely overlooked for a long time. Recent data indicate that these cells are potent effectors and regulators within the tumor microenvironment with potential prognostic and/or predictive roles in human cancers. An antitumoral role of eosinophils has been described in colon cancer, melanoma, lung cancer, and oral squamous cell carcinoma (132). In murine models of hepatocellular carcinoma and breast cancer, the increased recruitment of eosinophils into tumors induced by dipeptidyl peptidase 4 (DPP4) inhibition led to increased antitumor immunity (133). The Munitz lab (134) elegantly demonstrated an antitumorigenic role of eosinophils during tumor development in mouse and human colorectal cancer. In this study, the authors found a negative correlation between the number of tumor eosinophils and tumor stage. Moreover, they showed that eosinophils recruited into the tumors could reject the tumors, independently of $CD8^+$ T cells (134). Eosinophils contribute to antitumor immunity by means of their cytotoxic granules that can create cell damage (**Figure 3**). In addition, the antitumor functions of eosinophils can be induced by cytokines present in the tumor microenvironment. GM-CSF was recently shown to activate IRF5 signaling in eosinophils, and this was necessary to endow eosinophils with antitumor activities. In the absence of eosinophils, colorectal cancer cells grew faster and animals had larger tumors (135). In addition, in IL-33-rich tumor environments, IL-33 was able to expand and activate eosinophils to become more cytotoxic through lytic granule convergence, a mechanism similar to the one used by NK cells (136). Although IL-33 can directly activate eosinophils, it is also likely that eosinophils get recruited to tumors by ILC2-derived IL-5 (125). Although eosinophils are often associated with antitumor immunity and although their presence in patients with cancer is often associated with a good prognosis, a recent study challenged this dogma. The Halim group reported that a preexisting Th2 environment in the lung promoted the metastatic seeding of B16 melanoma cancer cells to this organ. In this model, highly metabolically active eosinophils recruited by ILC2s could directly inhibit NK cell functions by stealing nutrients and limiting NK cell metabolic fitness (77). More work is clearly needed to clarify the exact contribution of eosinophils in cancer. Reassuring is that so far, investigators who have studied human eosinophil knock-outs—patients treated with the eosinophil-depleting drug benralizumab—have not yet reported an increased incidence of cancer after three years of treatment, although longer observation periods are still warranted (35, 137).

Mast Cells and Basophils in Cancer

It is clear that mast cells are present in tumors of different types of cancer, but what is the role of tumor-associated mast cells? Mast cells produce several mediators with proinflammatory, anti-inflammatory, and angiogenic properties and can therefore play a role in tumor immunology. The prognostic value of mast cells in human tumors has been shown in several types of cancers. In breast cancer or in non–small cell lung cancer, high mast cell infiltration was considered an indicator of good prognosis, independently of tumor stage (138, 139). However, in other types of cancer like pancreatic cancer and prostate cancer, high numbers of tumor-associated mast cells were associated with tumor progression and worse prognosis in patients (140). The potential antitumoral effects of mast cells have mainly come from early murine studies showing that mice lacking mast cells had increased tumor incidence and growth (141). Also, TLR-activated mast cells were shown to promote antitumor immunity by recruiting NK and $CD8^+$ T cells to the tumor site (142). Despite these reports on the antitumor effects of mast cells, it is becoming increasingly clear that mast cells can also exert protumoral roles. The mechanisms that potentially mediate mast cells' protumoral functions include induction of tumor cell growth; induction of an immunosuppressive tumor microenvironment; promotion of angiogenesis and lymphangiogenesis through the release of VEGF, TNF-α, FGF, TGF-β, or tryptase; and facilitation of invasion and metastasis (through tryptase, chymase, and metalloproteases) (132, 143–145). It is unclear at present what role basophils play in cancer progression. Altogether, the studies performed so far show that the roles of mast cells and basophils in cancer are controversial and depend on the type of cancer.

TYPE 2 IMMUNITY IN METABOLISM AND OBESITY

Obesity is a complex metabolic disorder caused by an interplay between genetic and environmental factors. It is characterized by an increased size of white adipose tissue (WAT) caused by the accumulation of fat in the body. The main purpose of these fat depots in WAT is to store fat for later use as a source of energy in homeostasis. However, upon exposure to sustained cold, beigeing of adipocytes is induced and helps to maintain energy expenditure. Particularly in subcutaneous WAT, the beigeing or browning of adipocytes dissipates energy through thermogenesis via uncoupling of the mitochondrial electron transport chain, and loss of this adaptation can lead to obesity (55). The repeated and prolonged accumulation of fat in WAT is associated with low-grade inflammation, which is a risk factor for cardiovascular diseases and type 2 diabetes (146).

Type 2 Immunity Contributes to the Health Status of Adipose Tissue

The cellular composition of adipose tissue in healthy, lean individuals is mostly related to type 2 immunity. Initially, $PPAR\gamma^+$ alternatively activated macrophages and eosinophils had been shown to promote tissue homeostasis by producing anti-inflammatory mediators that modulate adipocyte functions and contribute to repair. The specific deletion of PPARγ in macrophages led to their inability to polarize into alternatively activated cells and was associated with insulin resistance and weight gain (147). In adipose tissue, the alternative activation of macrophages is controlled by eosinophil-derived IL-4 production (148). As an important source of type 2 cytokines, ILC2s have also been added to the list of players controlling the healthy status of WAT (**Figure 4**). Through their production of IL-5 and IL-13, ILC2s contribute to eosinophilia and alternative activation in this tissue. In addition, Molofsky and colleagues (149) demonstrated that IL-33 is necessary for the activation of ILC2s and the accumulation of eosinophils in WAT.

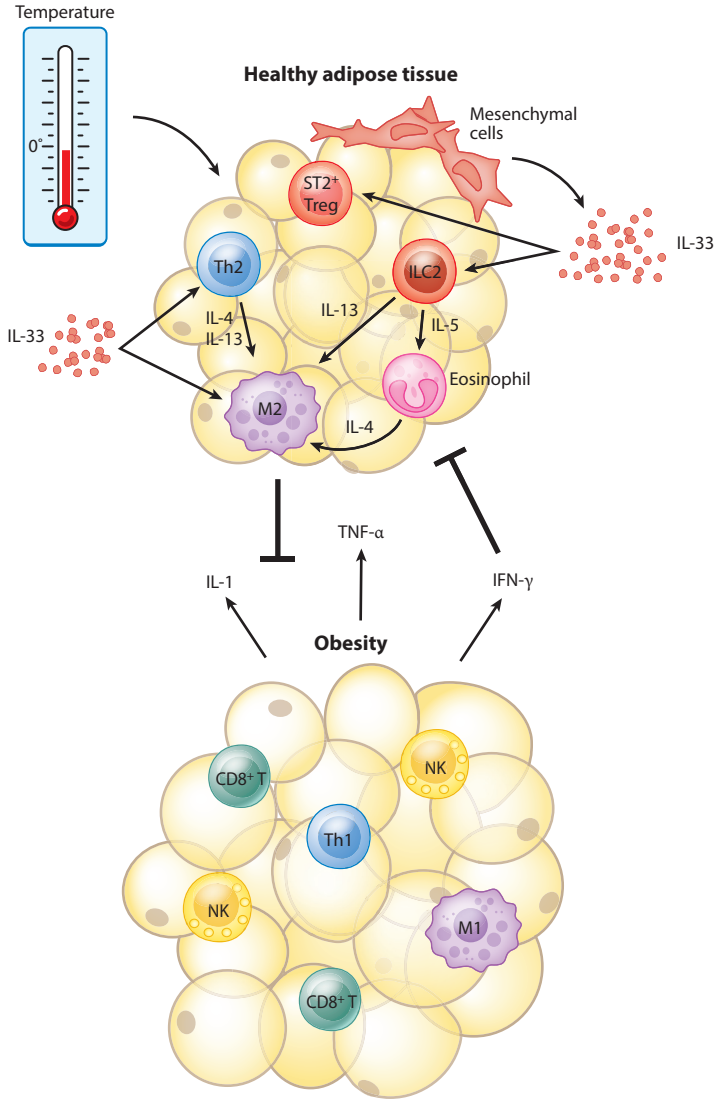

Figure 4

Type 2 immunity in adipose tissue homeostasis. In healthy, lean adipose tissue, IL-33 production by mesenchymal cells induces the activation of ILC2s, Th2 cells, ST2$^+$ Tregs, and M2-like macrophages. IL-5 production by ILC2s induces tissue eosinophilia whereas IL-13 release by Th2 cells contributes to M2-like polarization of macrophages. In obesity, the adipose tissue is more characterized by the presence of Th1 cells, CD8$^+$ T cells, NK cells, and M1-like macrophages, which produce IFN-γ, IL-1, and TNF-α. Abbreviations: ILC2, group 2 innate lymphoid cell; NK, natural killer; Th2, type 2 T helper; Treg, regulatory T cell.

Determination of the contribution of IL-33 in adipose tissue led to the identification of a unique subset of ST2$^+$GATA-3$^+$PPARγ$^+$ regulatory T cells in adipose tissue (20, 150). More recently, a new population of Trem2$^+$ lipid-associated macrophages has been identified. Although the origin of these macrophages is still unknown, they share some of the genes from alternatively activated cells, and have the potential to prevent the development of metabolic diseases (151).

Because IL-33 seems to be central in the control of adipose tissue homeostasis, several groups have tried to identify its cellular source. Although this needs further work, several initial studies point to production being restricted to the stromal compartment. Spallanzani et al. (152) found IL-33 to be expressed by PDGFRα$^+$Sca-1$^+$ mesenchymal stem cells, whereas others located IL-33 production in adipose stem and progenitor cells spread throughout adipose tissue (153). Finally, McKenzie's group (154) discovered that WAT-resident multipotent stromal cells act as a reservoir for IL-33 and support ILC2 proliferation and activation. In turn, IL-4 and IL-13 production by ILC2s induces eotaxin release by WAT multipotent stromal cells, contributing to eosinophil recruitment.

There is now compelling evidence that type 2 immunity contributes to the homeostasis of adipose tissue. In obesity, low-grade inflammation changes into a milieu where Th1 cytokines are predominant. Hypertrophic adipocytes secrete proinflammatory mediators that include TNF-α, IL-1, IL-6, IL-8, and leptin and attract immune cells such as macrophages, neutrophils, and cytotoxic CD8$^+$ T cells. The accumulation of M1-like macrophages is also tightly linked to the development of insulin resistance (155) (**Figure 4**).

Is Long-Lasting Adipose Tissue Inflammation Reversible?

Long-lasting inflammation in obese people may have long-term consequences due to trained immunity (156). This idea was recently evidenced by studies showing that myeloid cells of mice that were first fed a Western, high-fat diet and then switched to chow still exhibited Western diet-induced epigenetic and transcriptional reprogramming long after they were switched to chow (157). Even if the body mass and glucose intolerance reverted after the switch from a high-calorie to a low-calorie diet, the adipose tissue still showed signs of inflammation for a long period of time, although whether type 2–associated cell numbers were affected or not has not been addressed (158). This trained immunity in obese individuals may have important clinical implications. The exaggerated proinflammatory milieu provided by adipocytes and immune cells could potentially put people at higher risk for severe forms of diseases. As an example, during the recent COVID-19 pandemic, obesity has been clearly correlated with an increased risk of severe forms of the disease leading to intensive care unit admission and even death (159, 160). Another better-studied example is the link between obesity and asthma. Indeed, several studies have found that obese patients often present with more severe asthma (161). The reasons obesity impacts lung diseases so much is unclear, and whether or not the altered type 2 immune responses in obese patients are involved in this phenomenon is unknown. Recently, an intriguing concept has been put forward to explain why obese people are more at risk for pulmonary diseases. Postmortem analysis of fatal asthma cases found adipose tissue in the outer wall of large airways, which were therefore named fatty airways, and a greater quantity of this tissue was associated with higher body mass index, greater wall thickness, and a larger number of inflammatory cells (162). Interestingly, the lung inflammation included the presence of both neutrophils and eosinophils and correlated with the amount of adipose tissue in the airway (163). It is possible that these fat depots in the lung are an epiphenomenon, but they may also be a source of cytokines and leptin that could fuel inflammation in the airways. Whether such depots also exist in obese patients with severe COVID-19 or in those with increased eosinophil numbers in their lungs remains to be seen. Further studies are definitely warranted to fully understand the contribution of these fatty airways to severe asthma and respiratory viral infections.

CONCLUSION

It is now clear that type 2 immunity has broader roles than just defense against parasites or causing allergic inflammation. The recent findings highlighting the involvement of Th2 immunity in

repair processes, cancer, viral infections, and obesity mainly in murine models have taught us that type 2 immunity has two faces: a good one and a bad one. While type 2 immunity can be beneficial in some cases like parasitic infection; some cancers; or healthy, lean adipose tissue, it can become pathogenic in other circumstances like other types of cancer, some respiratory viral infections, and asthma. Several biologics targeting eosinophils, IL-5, or both IL-4 and IL-13 have been developed for patients with a type 2 signature who do not respond well to standard treatments. Such biologics have changed the lives of patients affected by eosinophil-associated diseases, and it would be interesting to investigate whether they could also be used in other types of disorders where eosinophils, Th2 cells, or ILC2s are pathogenic. Given that eosinophils and type 2 immune cells contribute to tumor rejection and organismal metabolic homeostasis in murine models, the effects of such treatments in humans on cancer risk and their metabolic side effects will need to be monitored closely over a long period of time before we determine the long-term safety of interfering with type 2 immunity in humans.

DISCLOSURE STATEMENT

B.N.L. has received consultancy fees from GSK, AstraZeneca, Sanofi, and Argenx.

LITERATURE CITED

1. El-Naccache DW, Hasko G, Gause WC. 2021. Early events triggering the initiation of a type 2 immune response. *Trends Immunol.* 42:151–64
2. Starkl P, Gaudenzio N, Marichal T, Reber LL, Sibilano R, et al. 2021. IgE antibodies increase honeybee venom responsiveness and detoxification efficiency of mast cells. *Allergy* 77:499–512
3. Marichal T, Starkl P, Reber LL, Kalesnikoff J, Oettgen HC, et al. 2013. A beneficial role for immunoglobulin E in host defense against honeybee venom. *Immunity* 39:963–75
4. Bosteels C, Neyt K, Vanheerswynghels M, van Helden MJ, Sichien D, et al. 2020. Inflammatory type 2 cDCs acquire features of cDC1s and macrophages to orchestrate immunity to respiratory virus infection. *Immunity* 52:1039–56.e9
5. Halim TY, Steer CA, Matha L, Gold MJ, Martinez-Gonzalez I, et al. 2014. Group 2 innate lymphoid cells are critical for the initiation of adaptive T helper 2 cell-mediated allergic lung inflammation. *Immunity* 40:425–35
6. Gowthaman U, Chen JS, Zhang B, Flynn WF, Lu Y, et al. 2019. Identification of a T follicular helper cell subset that drives anaphylactic IgE. *Science* 365:eaaw6433
7. Henderson NC, Rieder F, Wynn TA. 2020. Fibrosis: from mechanisms to medicines. *Nature* 587:555–66
8. Morimoto Y, Hirahara K, Kiuchi M, Wada T, Ichikawa T, et al. 2018. Amphiregulin-producing pathogenic memory T helper 2 cells instruct eosinophils to secrete osteopontin and facilitate airway fibrosis. *Immunity* 49:134–50.e6
9. Sicklinger F, Meyer IS, Li X, Radtke D, Dicks S, et al. 2021. Basophils balance healing after myocardial infarction via IL-4/IL-13. *J. Clin. Investig.* 131:e136778
10. Seumois G, Ramirez-Suastegui C, Schmiedel BJ, Liang S, Peters B, et al. 2020. Single-cell transcriptomic analysis of allergen-specific T cells in allergy and asthma. *Sci. Immunol.* 5:eaba6087
11. Tibbitt CA, Stark JM, Martens L, Ma J, Mold JE, et al. 2019. Single-cell RNA sequencing of the T helper cell response to house dust mites defines a distinct gene expression signature in airway Th2 cells. *Immunity* 51:169–84.e5
12. Vieira Braga FA, Kar G, Berg M, Carpaij OA, Polanski K, et al. 2019. A cellular census of human lungs identifies novel cell states in health and in asthma. *Nat. Med.* 25:1153–63
13. Angkasekwinai P, Dong C. 2021. IL-9-producing T cells: potential players in allergy and cancer. *Nat. Rev. Immunol.* 21:37–48
14. Micosse C, von Meyenn L, Steck O, Kipfer E, Adam C, et al. 2019. Human "T_H9" cells are a subpopulation of PPAR-γ^+ T_H2 cells. *Sci. Immunol.* 4:eaat5943

15. Irvin C, Zafar I, Good J, Rollins D, Christianson C, et al. 2014. Increased frequency of dual-positive T_H2/T_H17 cells in bronchoalveolar lavage fluid characterizes a population of patients with severe asthma. *J. Allergy Clin. Immunol.* 134:1175–86.e7
16. Hammad H, Lambrecht BN. 2021. The basic immunology of asthma. *Cell* 184:1469–85
17. Clement RL, Daccache J, Mohammed MT, Diallo A, Blazar BR, et al. 2019. Follicular regulatory T cells control humoral and allergic immunity by restraining early B cell responses. *Nat. Immunol.* 20:1360–71
18. Canete PF, Sweet RA, Gonzalez-Figueroa P, Papa I, Ohkura N, et al. 2019. Regulatory roles of IL-10-producing human follicular T cells. *J. Exp. Med.* 216:1843–56
19. Schiering C, Krausgruber T, Chomka A, Frohlich A, Adelmann K, et al. 2014. The alarmin IL-33 promotes regulatory T-cell function in the intestine. *Nature* 513:564–68
20. Kolodin D, van Panhuys N, Li C, Magnuson AM, Cipolletta D, et al. 2015. Antigen- and cytokine-driven accumulation of regulatory T cells in visceral adipose tissue of lean mice. *Cell Metab.* 21:543–57
21. Faustino LD, Griffith JW, Rahimi RA, Nepal K, Hamilos DL, et al. 2020. Interleukin-33 activates regulatory T cells to suppress innate γδ T cell responses in the lung. *Nat. Immunol.* 21:1371–83
22. Hung L-Y, Tanaka Y, Herbine K, Pastore C, Singh B, et al. 2020. Cellular context of IL-33 expression dictates impact on anti-helminth immunity. *Sci. Immunol.* 5:eabc6259
23. Koh B, Ulrich BJ, Nelson AS, Panangipalli G, Kharwadkar R, et al. 2020. Bcl6 and Blimp1 reciprocally regulate $ST2^+$ Treg-cell development in the context of allergic airway inflammation. *J. Allergy Clin. Immunol.* 146:1121–36.e9
24. Dahlgren MW, Jones SW, Cautivo KM, Dubinin A, Ortiz-Carpena JF, et al. 2019. Adventitial stromal cells define group 2 innate lymphoid cell tissue niches. *Immunity* 50:707–22.e6
25. Ricardo-Gonzalez RR, Van Dyken SJ, Schneider C, Lee J, Nussbaum JC, et al. 2018. Tissue signals imprint ILC2 identity with anticipatory function. *Nat. Immunol* 19:1093–99
26. Schneider C, Lee J, Koga S, Ricardo-Gonzalez RR, Nussbaum JC, et al. 2019. Tissue-resident group 2 innate lymphoid cells differentiate by layered ontogeny and in situ perinatal priming. *Immunity* 50:1425–38.e5
27. Flamar AL, Klose CSN, Moeller JB, Mahlakoiv T, Bessman NJ, et al. 2020. Interleukin-33 induces the enzyme tryptophan hydroxylase 1 to promote inflammatory group 2 innate lymphoid cell-mediated immunity. *Immunity* 52:606–19.e6
28. Miller MM, Patel PS, Bao K, Danhorn T, O'Connor BP, Reinhardt RL. 2020. BATF acts as an essential regulator of IL-25-responsive migratory ILC2 cell fate and function. *Sci. Immunol.* 5:eaay3994
29. Ricardo-Gonzalez RR, Schneider C, Liao C, Lee J, Liang HE, Locksley RM. 2020. Tissue-specific pathways extrude activated ILC2s to disseminate type 2 immunity. *J. Exp. Med.* 217:e20191172
30. van der Ploeg EK, Golebski K, van Nimwegen M, Fergusson JR, Heesters BA, et al. 2021. Steroid-resistant human inflammatory ILC2s are marked by CD45RO and elevated in type 2 respiratory diseases. *Sci. Immunol.* 6:eabd3489
31. Golebski K, Layhadi JA, Sahiner U, Steveling-Klein EH, Lenormand MM, et al. 2021. Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response. *Immunity* 54:291–307.e7
32. Haim-Vilmovsky L, Henriksson J, Walker JA, Miao Z, Natan E, et al. 2021. Mapping Rora expression in resting and activated $CD4^+$ T cells. *PLOS ONE* 16:e0251233
33. Malhotra N, Leyva-Castillo JM, Jadhav U, Barreiro O, Kam C, et al. 2018. RORα-expressing T regulatory cells restrain allergic skin inflammation. *Sci. Immunol.* 3:eaao6923
34. Gause WC, Rothlin C, Loke P. 2020. Heterogeneity in the initiation, development and function of type 2 immunity. *Nat. Rev. Immunol.* 20:603–14
35. Jacobsen EA, Jackson DJ, Heffler E, Mathur SK, Bredenoord AJ, et al. 2021. Eosinophil knockout humans: uncovering the role of eosinophils through eosinophil-directed biological therapies. *Annu. Rev. Immunol.* 39:719–57
36. Yuan S, Hollinger M, Lachowicz-Scroggins ME, Kerr SC, Dunican EM, et al. 2015. Oxidation increases mucin polymer cross-links to stiffen airway mucus gels. *Sci. Transl. Med.* 7:276ra27
37. Persson EK, Verstraete K, Heyndrickx I, Gevaert E, Aegerter H, et al. 2019. Protein crystallization promotes type 2 immunity and is reversible by antibody treatment. *Science* 364:eaaw4295

38. Kuo HP, Yu TR, Yu CT. 1994. Hypodense eosinophil number relates to clinical severity, airway hyperresponsiveness and response to inhaled corticosteroids in asthmatic subjects. *Eur. Respir. J.* 7:1452–59
39. Mesnil C, Raulier S, Paulissen G, Xiao X, Birrell MA, et al. 2016. Lung-resident eosinophils represent a distinct regulatory eosinophil subset. *J. Clin. Investig.* 126:3279–95
40. Stewart E, Wang X, Chupp GL, Montgomery RR. 2020. Profiling cellular heterogeneity in asthma with single cell multiparameter CyTOF. *J. Leukoc. Biol.* 108:1555–64
41. Lacy P. 2020. Gr1 makes an unexpected cameo appearance in eosinophils. *J. Leukoc. Biol.* 107:363–65
42. Percopo CM, Brenner TA, Ma M, Kraemer LS, Hakeem RM, et al. 2017. SiglecF^{+}Gr1^{hi} eosinophils are a distinct subpopulation within the lungs of allergen-challenged mice. *J. Leukoc. Biol.* 101:321–28
43. Limkar AR, Mai E, Sek AC, Percopo CM, Rosenberg HF. 2020. Frontline Science: Cytokine-mediated developmental phenotype of mouse eosinophils; IL-5-associated expression of the Ly6G/Gr1 surface Ag. *J. Leukoc. Biol.* 107:367–77
44. Jeong BM, Walker MT, Rodriguez R, Coden ME, Nagasaka R, et al. 2021. More than neutrophils: Lin^{+}Ly6G^{+}IL-5Rα^{+} multipotent myeloid cells (MMCs) are dominant in normal murine bone marrow and retain capacity to differentiate into eosinophils and monocytes. *J. Leukoc. Biol.* 111:113–22
45. Berdnikovs S. 2021. The twilight zone: plasticity and mixed ontogeny of neutrophil and eosinophil granulocyte subsets. *Semin. Immunopathol.* 43(3):337–46
46. Miyata J, Fukunaga K, Kawashima Y, Watanabe T, Saitoh A, et al. 2019. Dysregulated fatty acid metabolism in nasal polyp-derived eosinophils from patients with chronic rhinosinusitis. *Allergy* 74:1113–24
47. Beckert H, Meyer-Martin H, Buhl R, Taube C, Reuter S. 2020. Single and synergistic effects of type 2 cytokines on eosinophils and asthma hallmarks. *J. Immunol.* 204:550–58
48. Marichal T, Mesnil C, Bureau F. 2017. Homeostatic eosinophils: characteristics and functions. *Front. Med.* 4:101
49. Yun Y, Kanda A, Kobayashi Y, Van Bui D, Suzuki K, et al. 2020. Increased CD69 expression on activated eosinophils in eosinophilic chronic rhinosinusitis correlates with clinical findings. *Allergol. Int.* 69:232–38
50. Doan TC, Jeong BM, Coden ME, Loffredo LF, Bhattacharyya S, et al. 2018. Matrix protein tenascin-C expands and reversibly blocks maturation of murine eosinophil progenitors. *J. Allergy Clin. Immunol.* 142:695–98.e4
51. Kelly EA, Esnault S, Liu LY, Evans MD, Johansson MW, et al. 2017. Mepolizumab attenuates airway eosinophil numbers, but not their functional phenotype, in asthma. *Am. J. Respir. Crit. Care Med.* 196:1385–95
52. Medzhitov R, Schneider DS, Soares MP. 2012. Disease tolerance as a defense strategy. *Science* 335:936–41
53. Kabata H, Artis D. 2019. Neuro-immune crosstalk and allergic inflammation. *J. Clin. Investig.* 129:1475–82
54. Chesne J, Cardoso V, Veiga-Fernandes H. 2019. Neuro-immune regulation of mucosal physiology. *Mucosal Immunol.* 12:10–20
55. Wang W, Seale P. 2016. Control of brown and beige fat development. *Nat. Rev. Mol. Cell Biol.* 17:691–702
56. Roberts LB, Schnoeller C, Berkachy R, Darby M, Pillaye J, et al. 2021. Acetylcholine production by group 2 innate lymphoid cells promotes mucosal immunity to helminths. *Sci. Immunol.* 6:eabd0359
57. Chu C, Parkhurst CN, Zhang W, Zhou L, Yano H, et al. 2021. The ChAT-acetylcholine pathway promotes group 2 innate lymphoid cell responses and anti-helminth immunity. *Sci. Immunol.* 6:eabe3218
58. Klose CSN, Mahlakoiv T, Moeller JB, Rankin LC, Flamar AL, et al. 2017. The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature* 549:282–86
59. Cardoso V, Chesne J, Ribeiro H, Garcia-Cassani B, Carvalho T, et al. 2017. Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. *Nature* 549:277–81
60. Wallrapp A, Riesenfeld SJ, Burkett PR, Abdulnour RE, Nyman J, et al. 2017. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature* 549:351–56. Erratum. 2017. *Nature* 551:658
61. Nagashima H, Mahlakoiv T, Shih HY, Davis FP, Meylan F, et al. 2019. Neuropeptide CGRP limits group 2 innate lymphoid cell responses and constrains type 2 inflammation. *Immunity* 51:682–95.e6

62. Perner C, Flayer CH, Zhu X, Aderhold PA, Dewan ZNA, et al. 2020. Substance P release by sensory neurons triggers dendritic cell migration and initiates the type-2 immune response to allergens. *Immunity* 53:1063–77.e7
63. Inclan-Rico JM, Ponessa JJ, Valero-Pacheco N, Hernandez CM, Sy CB, et al. 2020. Basophils prime group 2 innate lymphoid cells for neuropeptide-mediated inhibition. *Nat. Immunol.* 21:1181–93
64. Ural BB, Yeung ST, Damani-Yokota P, Devlin JC, de Vries M, et al. 2020. Identification of a nerve-associated, lung-resident interstitial macrophage subset with distinct localization and immunoregulatory properties. *Sci. Immunol.* 5:eaax8756
65. Lambrecht BN. 2001. Immunologists getting nervous: neuropeptides, dendritic cells and T cell activation. *Respir. Res.* 2:133–38
66. Veiga-Fernandes H, Pachnis V. 2017. Neuroimmune regulation during intestinal development and homeostasis. *Nat. Immunol.* 18:116–22
67. Veiga-Fernandes H, Artis D. 2018. Neuronal-immune system cross-talk in homeostasis. *Science* 359:1465–66
68. Feddema JJ, Claassen E. 2020. Prevalence of viral respiratory infections amongst asthmatics: results of a meta-regression analysis. *Respir. Med.* 173:106020
69. Hansel TT, Tunstall T, Trujillo-Torralbo MB, Shamji B, Del-Rosario A, et al. 2017. A comprehensive evaluation of nasal and bronchial cytokines and chemokines following experimental rhinovirus infection in allergic asthma: increased interferons (IFN-γ and IFN-λ) and type 2 inflammation (IL-5 and IL-13). *EBioMedicine* 19:128–38
70. Zhu J, Message SD, Mallia P, Kebadze T, Contoli M, et al. 2019. Bronchial mucosal IFN-α/β and pattern recognition receptor expression in patients with experimental rhinovirus-induced asthma exacerbations. *J. Allergy Clin. Immunol.* 143:114–25.e4
71. Gill MA, Bajwa G, George TA, Dong CC, Dougherty II, et al. 2010. Counterregulation between the FcεRI pathway and antiviral responses in human plasmacytoid dendritic cells. *J. Immunol.* 184:5999–6006
72. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, et al. 2020. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—an update on the status. *Mil. Med. Res.* 7:11
73. Kalfaoglu B, Almeida-Santos J, Tye CA, Satou Y, Ono M. 2020. T-cell hyperactivation and paralysis in severe COVID-19 infection revealed by single-cell analysis. *Front. Immunol.* 11:589380
74. Weiskopf D, Schmitz KS, Raadsen MP, Grifoni A, Okba NMA, et al. 2020. Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome. *Sci. Immunol.* 5:eabd2071
75. Xiong Y, Liu Y, Cao L, Wang D, Guo M, et al. 2020. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerg. Microbes Infect.* 9:761–70
76. Tan M, Liu Y, Zhou R, Deng X, Li F, et al. 2020. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. *Immunology* 160:261–68
77. Schuijs MJ, Png S, Richard AC, Tsyben A, Hamm G, et al. 2020. ILC2-driven innate immune checkpoint mechanism antagonizes NK cell antimetastatic function in the lung. *Nat. Immunol.* 21:998–1009
78. Lynch JP, Werder RB, Simpson J, Loh Z, Zhang V, et al. 2016. Aeroallergen-induced IL-33 predisposes to respiratory virus-induced asthma by dampening antiviral immunity. *J Allergy Clin. Immunol.* 138:1326–37
79. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, et al. 2020. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 323:1574–81
80. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, et al. 2020. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur. Respir. J.* 55:2000547
81. Hanon S, Brusselle G, Deschampheleire M, Louis R, Michils A, et al. 2020. COVID-19 and biologics in severe asthma: data from the Belgian Severe Asthma Registry. *Eur. Respir. J.* 56(6):2002857
82. Kimura H, Francisco D, Conway M, Martinez FD, Vercelli D, et al. 2020. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. *J. Allergy Clin. Immunol.* 146:80–88.e8

83. Sajuthi SP, DeFord P, Li Y, Jackson ND, Montgomery MT, et al. 2020. Type 2 and interferon inflammation regulate SARS-CoV-2 entry factor expression in the airway epithelium. *Nat. Commun.* 11:5139
84. Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, et al. 2020. COVID-19-related genes in sputum cells in asthma: relationship to demographic features and corticosteroids. *Am. J. Respir. Crit. Care Med.* 202:83–90
85. WHO Rapid Evid. Apprais. COVID-19 Ther. (REACT) Work. Group. 2020. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 324:1330–41
86. Ramakrishnan S, Russell R. 2020. In the race at last: post-hoc analysis of GALATHEA and TERRANOVA. *Lancet Respir. Med.* 8:127–29
87. Yang J, Zheng Y, Gou X, Pu K, Chen Z, et al. 2020. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int. J. Infect. Dis.* 94:91–95
88. Donlan AN, Sutherland TE, Marie C, Preissner S, Bradley BT, et al. 2021. IL-13 is a driver of COVID-19 severity. *JCI Insight* 6(15):e150107
89. Napolitano M, Patruno C, Ruggiero A, Nocerino M, Fabbrocini G. 2020. Safety of dupilumab in atopic patients during COVID-19 outbreak. *J. Dermatolog. Treat.* 33:600–1
90. Patruno C, Stingeni L, Fabbrocini G, Hansel K, Napolitano M. 2020. Dupilumab and COVID-19: What should we expect? *Dermatolog. Ther.* 33:e13502
91. Bhalla A, Mukherjee M, Radford K, Nazy I, Kjarsgaard M, et al. 2021. Dupilumab, severe asthma airway responses, and SARS-CoV-2 serology. *Allergy* 76:957–58
92. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, et al. 2019. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir. Med.* 7:46–59
93. Jackson DJ, Busse WW, Bacharier LB, Kattan M, O'Connor GT, et al. 2020. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. *J. Allergy Clin. Immunol.* 146:203–6.e3
94. Samarasinghe AE, Melo RC, Duan S, LeMessurier KS, Liedmann S, et al. 2017. Eosinophils promote antiviral immunity in mice infected with influenza A virus. *J. Immunol.* 198:3214–26
95. Lucas C, Wong P, Klein J, Castro TBR, Silva J, et al. 2020. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 584:463–69
96. Liao D, Zhou F, Luo L, Xu M, Wang H, et al. 2020. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. *Lancet Haematol.* 7:e671–78
97. Qin C, Zhou L, Hu Z, Zhang S, Yang S, et al. 2020. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin. Infect. Dis.* 71:762–68
98. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, et al. 2020. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 75:1730–41
99. Gebremeskel S, Schanin J, Coyle KM, Butuci M, Luu T, et al. 2021. Mast cell and eosinophil activation are associated with COVID-19 and TLR-mediated viral inflammation: implications for an anti-Siglec-8 antibody. *Front. Immunol.* 12:650331
100. Aksu K, Yesilkaya S, Topel M, Turkyilmaz S, Ercelebi DC, et al. 2021. COVID-19 in a patient with severe asthma using mepolizumab. *Allergy Asthma Proc.* 42:e55–57
101. Chun HJ, Coutavas E, Pine A, Lee AI, Yu V, et al. 2021. Immuno-fibrotic drivers of impaired lung function in post-COVID-19 syndrome. medRxiv 2021.01.31.21250870. **https://doi.org/10.1101/2021.01.31.21250870**
102. Sgalla G, Iovene B, Calvello M, Ori M, Varone F, Richeldi L. 2018. Idiopathic pulmonary fibrosis: pathogenesis and management. *Respir. Res.* 19:32
103. Fabbri L, Jones S. 2021. Changing priorities for pulmonary fibrosis: The patient will see you now! *Thorax* 76:534–35
104. Murray LA, Argentieri RL, Farrell FX, Bracht M, Sheng H, et al. 2008. Hyper-responsiveness of IPF/UIP fibroblasts: interplay between TGFβ1, IL-13 and CCL2. *Int. J. Biochem. Cell Biol.* 40:2174–82

105. Murray LA, Zhang H, Oak SR, Coelho AL, Herath A, et al. 2014. Targeting interleukin-13 with tralokinumab attenuates lung fibrosis and epithelial damage in a humanized SCID idiopathic pulmonary fibrosis model. *Am. J. Respir. Cell Mol. Biol.* 50:985–94
106. Ramalingam TR, Gieseck RL, Acciani TH, Hart KM, Cheever AW, et al. 2016. Enhanced protection from fibrosis and inflammation in the combined absence of IL-13 and IFN-γ. *J. Pathol.* 239:344–54
107. Casanova-Acebes M, Dalla E, Leader AM, LeBerichel J, Nikolic J, et al. 2021. Tissue-resident macrophages provide a pro-tumorigenic niche to early NSCLC cells. *Nature* 595(7868):578–84
108. Petty AJ, Li A, Wang X, Dai R, Heyman B, et al. 2019. Hedgehog signaling promotes tumor-associated macrophage polarization to suppress intratumoral $CD8^+$ T cell recruitment. *J. Clin. Investig.* 129:5151–62
109. Tan IL, Arifa RDN, Rallapalli H, Kana V, Lao Z, et al. 2021. CSF1R inhibition depletes tumor-associated macrophages and attenuates tumor progression in a mouse sonic hedgehog-medulloblastoma model. *Oncogene* 40:396–407
110. Yang JB, Zhao ZB, Liu QZ, Hu TD, Long J, et al. 2018. FoxO1 is a regulator of MHC-II expression and anti-tumor effect of tumor-associated macrophages. *Oncogene* 37:1192–204
111. Zhu P, Zhu X, Wu J, He L, Lu T, et al. 2019. IL-13 secreted by ILC2s promotes the self-renewal of intestinal stem cells through circular RNA circPan3. *Nat. Immunol.* 20:183–94
112. Matsui S, Okabayashi K, Tsuruta M, Shigeta K, Seishima R, et al. 2019. Interleukin-13 and its signaling pathway is associated with obesity-related colorectal tumorigenesis. *Cancer Sci.* 110:2156–65
113. Wu Y, Konate MM, Lu J, Makhlouf H, Chuaqui R, et al. 2019. IL-4 and IL-17A cooperatively promote hydrogen peroxide production, oxidative DNA damage, and upregulation of dual oxidase 2 in human colon and pancreatic cancer cells. *J. Immunol.* 203:2532–44
114. Maier B, Leader AM, Chen ST, Tung N, Chang C, et al. 2020. A conserved dendritic-cell regulatory program limits antitumour immunity. *Nature* 580:257–62
115. Liu M, Kuo F, Capistrano KJ, Kang D, Nixon BG, et al. 2020. TGF-β suppresses type 2 immunity to cancer. *Nature* 587:115–20
116. Nakamura M, Souri EA, Osborn G, Laddach R, Chauhan J, et al. 2020. IgE activates monocytes from cancer patients to acquire a pro-inflammatory phenotype. *Cancers* 12:3376
117. Protti MP, De Monte L. 2020. Thymic stromal lymphopoietin and cancer: Th2-dependent and -independent mechanisms. *Front. Immunol.* 11:2088
118. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, et al. 2021. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N. Engl. J. Med.* 384:1800–9
119. Lucarini V, Zicchedda G, Macchia I, La Sorsa V, Peschiaroli F, et al. 2017. IL-33 restricts tumor growth and inhibits pulmonary metastasis in melanoma-bearing mice through eosinophils. *OncoImmunology* 6:e1317420
120. Gao X, Wang X, Yang Q, Zhao X, Wen W, et al. 2015. Tumoral expression of IL-33 inhibits tumor growth and modifies the tumor microenvironment through $CD8^+$ T and NK cells. *J. Immunol.* 194:438–45
121. Hatzioannou A, Banos A, Sakelaropoulos T, Fedonidis C, Vidali MS, et al. 2020. An intrinsic role of IL-33 in Treg cell-mediated tumor immunoevasion. *Nat. Immunol.* 21:75–85
122. Ameri AH, Moradi Tuchayi S, Zaalberg A, Park JH, Ngo KH, et al. 2019. IL-33/regulatory T cell axis triggers the development of a tumor-promoting immune environment in chronic inflammation. *PNAS* 116:2646–51
123. Taniguchi S, Elhance A, Van Duzer A, Kumar S, Leitenberger JJ, Oshimori N. 2020. Tumor-initiating cells establish an IL-33–TGF-β niche signaling loop to promote cancer progression. *Science* 369:eaay1813
124. Salimi M, Wang R, Yao X, Li X, Wang X, et al. 2018. Activated innate lymphoid cell populations accumulate in human tumour tissues. *BMC Cancer* 18:341
125. Loyon R, Jary M, Salome B, Gomez-Cadena A, Galaine J, et al. 2019. Peripheral innate lymphoid cells are increased in first line metastatic colorectal carcinoma patients: a negative correlation with Th1 immune responses. *Front. Immunol.* 10:2121

126. Trabanelli S, Chevalier MF, Martinez-Usatorre A, Gomez-Cadena A, Salome B, et al. 2017. Tumour-derived PGD2 and NKp30-B7H6 engagement drives an immunosuppressive ILC2-MDSC axis. *Nat. Commun.* 8:593
127. Ercolano G, Gomez-Cadena A, Dumauthioz N, Vanoni G, Kreutzfeldt M, et al. 2021. PPAR drives IL-33-dependent ILC2 pro-tumoral functions. *Nat. Commun.* 12:2538
128. Chen T, Tibbitt CA, Feng X, Stark JM, Rohrbeck L, et al. 2017. PPAR-gamma promotes type 2 immune responses in allergy and nematode infection. *Sci. Immunol.* 2:eaal5196
129. Rigas D, Lewis G, Aron JL, Wang B, Banie H, et al. 2017. Type 2 innate lymphoid cell suppression by regulatory T cells attenuates airway hyperreactivity and requires inducible T-cell costimulator-inducible T-cell costimulator ligand interaction. *J. Allergy Clin. Immunol.* 139:1468–77.e2
130. Wan J, Wu Y, Huang L, Tian Y, Ji X, et al. 2021. ILC2-derived IL-9 inhibits colorectal cancer progression by activating $CD8^+$ T cells. *Cancer Lett.* 502:34–43
131. Lotfi R, Lee JJ, Lotze MT. 2007. Eosinophilic granulocytes and damage-associated molecular pattern molecules (DAMPs): role in the inflammatory response within tumors. *J. Immunother.* 30:16–28
132. Varricchi G, Loffredo S, Galdiero MR, Marone G, Cristinziano L, et al. 2018. Innate effector cells in angiogenesis and lymphangiogenesis. *Curr. Opin. Immunol.* 53:152–60
133. Hollande C, Boussier J, Ziai J, Nozawa T, Bondet V, et al. 2019. Inhibition of the dipeptidyl peptidase DPP4 (CD26) reveals IL-33-dependent eosinophil-mediated control of tumor growth. *Nat. Immunol.* 20:257–64
134. Reichman H, Itan M, Rozenberg P, Yarmolovski T, Brazowski E, et al. 2019. Activated eosinophils exert antitumorigenic activities in colorectal cancer. *Cancer Immunol. Res.* 7:388–400
135. Arnold IC, Artola-Boran M, Gurtner A, Bertram K, Bauer M, et al. 2020. The GM-CSF-IRF5 signaling axis in eosinophils promotes antitumor immunity through activation of type 1 T cell responses. *J. Exp. Med.* 217:e20190706
136. Andreone S, Spadaro F, Buccione C, Mancini J, Tinari A, et al. 2019. IL-33 promotes CD11b/CD18-mediated adhesion of eosinophils to cancer cells and synapse-polarized degranulation leading to tumor cell killing. *Cancers* 11:1664
137. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, et al. 2021. Benralizumab for adolescent patients with severe, eosinophilic asthma: safety and efficacy after 3 years of treatment. *J. Allergy Clin. Immunol.* 148:266–71.e2
138. Shikotra A, Ohri CM, Green RH, Waller DA, Bradding P. 2016. Mast cell phenotype, TNF expression and degranulation status in non-small cell lung cancer. *Sci. Rep.* 6:38352
139. Glajcar A, Szpor J, Pacek A, Tyrak KE, Chan F, et al. 2017. The relationship between breast cancer molecular subtypes and mast cell populations in tumor microenvironment. *Virchows Arch.* 470:505–15
140. Porcelli L, Iacobazzi RM, Di Fonte R, Serrati S, Intini A, et al. 2019. CAFs and TGF-β signaling activation by mast cells contribute to resistance to gemcitabine/nabpaclitaxel in pancreatic cancer. *Cancers* 11:330
141. Siebenhaar F, Metz M, Maurer M. 2014. Mast cells protect from skin tumor development and limit tumor growth during cutaneous de novo carcinogenesis in a Kit-dependent mouse model. *Exp. Dermatolog.* 23:159–64
142. Oldford SA, Haidl ID, Howatt MA, Leiva CA, Johnston B, Marshall JS. 2010. A critical role for mast cells and mast cell-derived IL-6 in TLR2-mediated inhibition of tumor growth. *J. Immunol.* 185:7067–76
143. Lv Y, Zhao Y, Wang X, Chen N, Mao F, et al. 2019. Increased intratumoral mast cells foster immune suppression and gastric cancer progression through TNF-alpha-PD-L1 pathway. *J. Immunother. Cancer* 7:54
144. Keser SH, Kandemir NO, Ece D, Gecmen GG, Gul AE, et al. 2017. Relationship of mast cell density with lymphangiogenesis and prognostic parameters in breast carcinoma. *Kaohsiung J. Med. Sci.* 33:171–80
145. Kabiraj A, Jaiswal R, Singh A, Gupta J, Singh A, Samadi FM. 2018. Immunohistochemical evaluation of tumor angiogenesis and the role of mast cells in oral squamous cell carcinoma. *J. Cancer Res. Ther.* 14:495–502
146. Gonzalez-Muniesa P, Martinez-Gonzalez MA, Hu FB, Despres JP, Matsuzawa Y, et al. 2017. Obesity. *Nat. Rev. Dis. Primers* 3:17034

147. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, Morel CR, Subramanian V, et al. 2007. Macrophage-specific PPARγ controls alternative activation and improves insulin resistance. *Nature* 447:1116–20
148. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, et al. 2011. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science* 332:243–47
149. Molofsky AB, Nussbaum JC, Liang HE, Van Dyken SJ, Cheng LE, et al. 2013. Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *J. Exp. Med.* 210:535–49
150. Vasanthakumar A, Moro K, Xin A, Liao Y, Gloury R, et al. 2015. The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue-resident regulatory T cells. *Nat. Immunol.* 16:276–85
151. Jaitin DA, Adlung L, Thaiss CA, Weiner A, Li B, et al. 2019. Lipid-associated macrophages control metabolic homeostasis in a Trem2-dependent manner. *Cell* 178:686–98.e14
152. Spallanzani RG, Zemmour D, Xiao T, Jayewickreme T, Li C, et al. 2019. Distinct immunocyte-promoting and adipocyte-generating stromal components coordinate adipose tissue immune and metabolic tenors. *Sci. Immunol.* 4:eaaw3658
153. Mahlakoiv T, Flamar AL, Johnston LK, Moriyama S, Putzel GG, et al. 2019. Stromal cells maintain immune cell homeostasis in adipose tissue via production of interleukin-33. *Sci. Immunol.* 4:eaax0416
154. Rana BMJ, Jou E, Barlow JL, Rodriguez-Rodriguez N, Walker JA, et al. 2019. A stromal cell niche sustains ILC2-mediated type-2 conditioning in adipose tissue. *J. Exp. Med.* 216:1999–2009
155. McLaughlin T, Ackerman SE, Shen L, Engleman E. 2017. Role of innate and adaptive immunity in obesity-associated metabolic disease. *J. Clin. Investig.* 127:5–13
156. Penkov S, Mitroulis I, Hajishengallis G, Chavakis T. 2019. Immunometabolic crosstalk: an ancestral principle of trained immunity? *Trends Immunol.* 40:1–11
157. Christ A, Gunther P, Lauterbach MAR, Duewell P, Biswas D, et al. 2018. Western diet triggers NLRP3-dependent innate immune reprogramming. *Cell* 172:162–75.e14
158. Fischer IP, Irmler M, Meyer CW, Sachs SJ, Neff F, et al. 2018. A history of obesity leaves an inflammatory fingerprint in liver and adipose tissue. *Int. J. Obes.* 42:507–17
159. Chiappetta S, Sharma AM, Bottino V, Stier C. 2020. COVID-19 and the role of chronic inflammation in patients with obesity. *Int. J. Obes.* 44:1790–92
160. Huang Y, Lu Y, Huang YM, Wang M, Ling W, et al. 2020. Obesity in patients with COVID-19: a systematic review and meta-analysis. *Metabolism* 113:154378
161. Rogliani P, Sforza M, Calzetta L. 2020. The impact of comorbidities on severe asthma. *Curr. Opin. Pulm. Med.* 26:47–55
162. Brightling CE, Tobin AB, Milligan G. 2019. Fatty airways: a source of good and bad fats? *Eur. Respir. J.* 54:1902060
163. Elliot JG, Donovan GM, Wang KCW, Green FHY, James AL, Noble PB. 2019. Fatty airways: implications for obstructive disease. *Eur. Respir. J.* 54:1900857