

Type 2 cytokines: mechanisms and therapeutic strategies

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Abstract | Type 2 immune responses are defined by the cytokines interleukin-4 (IL-4), IL-5, IL-9 and IL-13, which can either be host protective or have pathogenic activity. Type 2 immunity promotes antihelminth immunity, suppresses type 1-driven autoimmune disease, neutralizes toxins, maintains metabolic homeostasis, and regulates wound repair and tissue regeneration pathways following infection or injury. Nevertheless, when type 2 responses are dysregulated, they can become important drivers of disease. Type 2 immunity induces a complex inflammatory response characterized by eosinophils, mast cells, basophils, type 2 innate lymphoid cells, IL-4-and/or IL-13-conditioned macrophages and T helper 2 (T_H2) cells, which are crucial to the pathogenesis of many allergic and fibrotic disorders. As chronic type 2 immune responses promote disease, the mechanisms that regulate their maintenance are thought to function as crucial disease modifiers. This Review discusses the many endogenous negative regulatory mechanisms that antagonize type 2 immunity and highlights how therapies that target some of these pathways are being developed to treat type 2-mediated disease.

Crohn disease

A type of chronic inflammatory bowel disease that can affect any part of the gastrointestinal tract from the mouth to the anus. Crohn disease is caused by a combination of environmental, nutritional, immunological and bacterial factors in genetically susceptible individuals.

The type 2 immune response is characterized by T helper 2 (T_H2) cells, eosinophils, mast cells, basophils, group 2 innate lymphoid cells (ILC2s), interleukin-4 (IL-4) and/or IL-13-induced macrophages, IgE, and the cytokines IL-4, IL-5, IL-9 and IL-13. When the T_H1–T_H2 dichotomy was first described¹, type 2 immunity was not thought of as an important effector response but rather as a regulatory mechanism, the primary function of which was to limit the injurious consequences of type 1-mediated protective immunity². Although this original limited definition remains true, our understanding of the role of type 2 immunity has greatly expanded over the past 15 years. In addition to suppressing type 1 immunity and type 1-driven inflammation, type 2 immunity has emerged as a major effector response that has many important host-protective and pathogenic activities (BOX 1).

One of the most important protective functions of type 2 immunity is to promote resistance to large extra-cellular helminth parasites³. These parasites are not easily killed by type 1-mediated immune mechanisms and so type 2 immunity is activated to improve barrier defences⁴. Type 2 immunity increases mucus production, smooth muscle contractility, intestinal epithelial cell turnover and alternative macrophage activation, which together help to facilitate the expulsion of gastrointestinal parasites from the gut^{5–8}. Furthermore, type 2 immunity has been identified as a major protective

mechanism in several autoimmune diseases⁹, including arthritis, multiple sclerosis and Crohn disease^{10–12}, owing to its ability to suppress type 1-driven inflammation. In addition to suppressing the tissue-damaging effects of sustained type 1-associated inflammation, type 2 immunity also shows direct protective activity by promoting important tissue repair pathways^{13–15}. Finally, maintenance of crucial metabolic functions has also been linked with type 2 immunity, including glucose homeostasis, insulin sensitivity, adiposity and adaptive thermogenesis^{16–19}.

Although the type 2 cytokine response has important host-protective functions, dysregulated, chronic or hyperreactive type 2 immunity can contribute to the development of disease. Perhaps the most widely recognized diseases that are attributed to the overproduction of type 2 cytokines are allergic disorders, such as asthma, atopic dermatitis, allergic rhinitis, eosinophilic oesophagitis and anaphylaxis, as well as allergies to drugs, toxins and food²⁰. As type 1 and type 2 immune responses cross-regulate each other, type 2 cytokine responses also suppress the development of protective type 1 immunity to a wide range of viral, bacterial and protozoan pathogens, and thereby facilitate uncontrolled or persistent infection^{21–24}. Suppression of type 1 immunity and cytotoxic T cell development by type 2 immunity is also thought to promote tumorigenesis and tumour cell growth^{25–27}.

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Box 1 | Definition of type 2 immunity

In this Review, type 1 and type 2 immunity refer to both the innate and the adaptive arms of the immune response. I have intentionally limited the use of the terms T helper 1 (T_H1) cells and T_H2 cells, as this only refers to CD4⁺ T_H cell subsets. Type 1 effector responses are defined by T_H1 cells and T_H17 cells, cytotoxic T cells, group 1 and group 3 innate lymphoid cells (ILCs), and immunoglobulin M (IgM), IgA and specific IgG antibody classes. This effector response mediates immunity to many microorganisms including bacteria, viruses, fungi and protozoa. Elements of type 1 immunity also help to maintain tumour immune surveillance. By contrast, type 2 immunity provides protection against large extracellular parasites by boosting barrier defences. Elements of the type 2 immune response also help to maintain metabolic homeostasis and to promote tissue remodelling following injury. Type 2 immune responses are characterized by CD4⁺ T_H2 cells, group 2 ILCs, eosinophils, basophils, mast cells, interleukin-4 (IL-4)- and/or IL-13-activated macrophages, the IgE antibody subclass and the cytokines IL-4, IL-5, IL-9, IL-13, thymic stromal lymphopoietin (TSLP), IL-25 and IL-33.

Adaptive thermogenesis

The thermic effect of factors such as cold, fear, stress and several drugs that can increase the rate of energy expenditure above normal levels. In individuals with obesity, adaptive thermogenesis impedes weight loss, compromises the maintenance of weight loss and creates the ideal metabolic response to support rapid weight regain.

Eosinophilic oesophagitis

An allergic inflammatory condition of the oesophagus that involves eosinophils and that can lead to oesophageal narrowing, impaired swallowing, food impaction, dysphagia, vomiting and weight loss.

Chronic schistosomiasis

A chronic disease caused by parasitic worms of the genus *Schistosoma* that in some infected individuals leads to the development of severe interleukin-13-driven eosinophilic inflammation and hepatic fibrosis.

Immunostimulatory CpG sequences

Short single-stranded synthetic DNA molecules that contain a cytosine triphosphate deoxynucleotide (C) followed by a guanine triphosphate deoxynucleotide (G); they have potent immunostimulatory activity when recognized by the pattern recognition receptor Toll-like receptor 9.

In addition, the IL-4- and/or the IL-13-primed subset of monocytes or macrophages is often expanded within the tumour stroma and antagonizes the tumour-suppressing activity of type 1-activated macrophages²⁸. Finally, although the type 2 immune response facilitates tissue repair²⁹, chronic activation of wound-healing pathways may also contribute to the development of pathological fibrosis or organ scarring, as is observed in some helminth infections, in severe asthma and in many chronic fibroproliferative diseases³⁰ (FIG. 1).

As persistent or dysregulated type 2 immune responses are major drivers of disease, the mechanisms that control the intensity, maintenance and resolution of type 2 immunity are probably important regulators of disease progression. Therefore, rather than focusing on the mechanisms that initiate or that amplify type 2 immunity — a topic that has been extensively reviewed by others^{20,31–35} — this Review highlights the many endogenous regulatory mechanisms induced during an immune response that primarily function to prevent or limit the pathological consequences of sustained type 2 immunity. I also describe how many of these negative regulatory or disease-tolerance mechanisms work collaboratively or synergistically to suppress type 2-driven inflammatory responses and I briefly discuss how some of these pathways and mediators, mostly discerned from studies in mice, are being evaluated in the clinic as potential therapies for type 2-driven disease.

Endogenous type 2 inhibitory mechanisms

Type 1-associated cytokines inhibit type 2 immunity. The type 1 cytokines interferon- γ (IFN γ), IL-12 and IL-18, which initiate and maintain type 1 immune responses^{36–38}, are some of the most important mediators that suppress type 2 immunity^{39,40}. For example, immunity to leishmaniasis is mediated by antigen-specific IFN γ -producing CD4⁺ T_H1 cells, which activate important antiparasite effector responses at the same time as dampening disease-promoting type 2 immunity⁴¹. Similar cross-regulation of type 2 responses by IFN γ and IL-12 has also been reported in many helminth infections^{3,42,43}; however, rather than increasing resistance, the reduction in type 2 immunity mediated by IFN γ and IL-12 facilitates chronic infection

by reducing barrier defences and, in some cases, this can lead to the development of severe type 1-driven inflammation in the gut⁴⁴. T_H17 cell responses can also suppress type 2 effector function by upregulating the IL-13 decoy receptor IL-13Ra2 (REF. 45). Although there are many additional examples in which cross-regulation between type 1 and type 2 immunity has a major effect on susceptibility to infection or inflammation, the suppression of type 2 immunity by IFN γ and IL-12 clearly has a beneficial role in some cases. Novel strategies based on type 1-mediated immune deviation have been proposed to ameliorate type 2-driven disease. For example, the development of liver fibrosis in chronic schistosomiasis is driven by an IL-13-dependent but transforming growth factor- β 1 (TGF β 1)-independent mechanism^{4,46}, with IL-12 and IFN γ having suppressive roles in reducing the frequency of profibrotic IL-13-producing CD4⁺ T cells and eosinophils⁴⁷. IL-12 and CpG oligonucleotides, which promote IFN γ production by T cells and natural killer (NK) cells⁴⁸, have also been used as vaccine adjuvants to drive protective type 1 responses that reduce type 2-associated inflammation and fibrosis during subsequent exposures^{49,50}. Type 2 allergic asthma — which is characterized by airway hyperresponsiveness, pulmonary eosinophilia, excessive mucus production and type 2 cytokine expression — is also antagonized by IL-12 and IFN γ ⁵¹. Preclinical studies using immunostimulatory CpG sequences to ‘desensitize’ or to ‘immune deviate’ individuals with established type 2-driven allergic disorders have also been carried out, although they have only had modest effects^{52,53}. Finally, tumour-associated macrophages, which are a major component of the cancer microenvironment, are under intense investigation because they have an immunosuppressive IL-4- and/or IL-13-activated phenotype that supports metastasis and that suppresses antitumour immunity⁵⁴. By contrast, T_H1 cells, IFN γ and IFN γ -stimulated macrophages often collaborate to reduce tumour growth²⁸. Therefore, therapeutic approaches that promote IFN γ production or that switch pro-tumoural type 2-associated macrophages to a tumour-suppressive classically activated phenotype might offer a rational approach to augment cell-mediated immunity to a range of cancers^{55–57}.

Macrophages in the maintenance of type 2-driven disease. Conventional dendritic cells (DCs) and basophils are crucial to the initiation of type 2 immunity^{58–64}, and inflammatory monocytes and tissue macrophages have emerged as important regulators of established type 2 immune responses⁶⁵. Studies using mice lacking FMS-like tyrosine kinase 3 (*Flt3*^{−/−}), which lack conventional DCs, showed that monocyte-derived DCs are sufficient to induce T_H2 cell immunity following high-dose allergen challenge⁶⁶. These inflammatory DCs produce pro-inflammatory chemokines and control type 2 immunity by functioning as antigen-presenting cells in diseased tissues. Whereas studies with clodronate liposomes suggested that CD11b⁺F4/80⁺ macrophages are not required for the initiation of type 2 immune responses⁶⁴, studies

with *Cd11b*-DTR mice — which, following exposure to diphtheria toxin, lack CD11b^{hi}F4/80⁺ macrophages but have conventional DCs — suggested that macrophages are crucial for the maintenance of type 2 immunity within affected tissues but not within secondary lymphoid organs⁶⁷. Direct depletion of CD11b⁺ monocytes and macrophages with diphtheria toxin during the maintenance or resolution phases of secondary *Schistosoma mansoni* egg-induced granuloma formation resulted in a marked decrease in inflammation, fibrosis and type 2 cytokine expression in the lungs (FIG. 2). Depletion of CD11b⁺F4/80⁺ macrophages caused a similar reduction in chronic house dust mite-induced allergic lung inflammation and IL-13-dependent immunity to the nematode parasite *Nippostrongylus brasiliensis*. However, experiments using chimeric *Cd11c*-DTR mice and transgenic mice with both *Cd11b*-DTR and *Cd11c*-DTR suggested that CD11b⁺ monocytes and macrophages, but not CD11c⁺ DCs, are the crucial populations controlling the maintenance of secondary type 2 immunity in non-lymphoid tissues⁶⁷. Strategies that disrupt the recruitment^{68,69}, the expansion^{70,71} or the maintenance^{19,72} of crucial myeloid cell populations in diseased tissues could consequently emerge as novel therapeutic approaches for a range of type 2-driven diseases.

IFN γ -activated macrophages and nitric oxide. Although monocyte-derived macrophages are important for the maintenance of type 2 immune responses, there is evidence that once macrophages develop an activated phenotype⁵⁷, they have important regulatory and suppressive activities¹⁹. Macrophages can have a wide range of activated-macrophage phenotypes⁷³; IL-4- and/or IL-13-activated macrophages and IFN γ -activated macrophages are believed to represent phenotypes at opposite extremes⁵⁷, and these subsets show distinct gene expression profiles and functional capabilities^{19,74}. The IL-4- and/or IL-13-activated subset has important homeostatic functions and is intimately involved in the control of type 2-driven inflammation and immunity⁷⁵. Indeed, these cells produce a wide range of cytokines, growth factors and chemokines that regulate cell recruitment, vascular permeability, angiogenesis, metabolic functions, atherosclerosis, malignancy and wound repair⁷⁶. Although IFN γ and IL-4 and/or IL-13 exert antagonistic effects on macrophage activation by differentially phosphorylating signal transducer and activator of transcription 1 (STAT1) and STAT6 (REF. 77), recent studies have also identified the transcription factors IFN-regulatory factor 4 (IRF4) and IRF5 as crucial regulators of macrophage development primed by IL-4 and/or IL-13 and by IFN γ , respectively^{78,79}. Importantly, IRF5 activates IL-12p40, IL-12p35, and IL-23p19 expression and simultaneously represses IL-10 expression⁷⁸, which directly influences the development of polarized type 2 immune responses^{80,81}. Thus, activation of macrophages by IFN γ can have a direct inhibitory effect on type 2 immunity and M2 macrophage development. Moreover, as many of the downstream functions of IL-4- and/or IL-13-primed macrophages are antagonized by IFN γ -activated macrophages, a relative



Figure 1 | **The yin and yang of type 2 immunity.** The detrimental (shaded) and the beneficial (open) sides of type 2 immunity are shown.

increase in the frequency of IFN γ -primed cells can also lead to the suppression of type 2 effector function⁸². The production of high concentrations of nitric oxide by IFN γ -primed macrophages has also been shown to suppress the proliferation and development of both T_H1 cells and T_H2 cells^{83,84}. The anti-inflammatory and antifibrotic effects of IL-12 are also dependent on inducible nitric oxide synthase (NOS2)⁸⁵. Studies have suggested that NOS2-expressing IFN γ -primed macrophages suppress type 2-associated fibrosis by competing with activated myofibroblasts that require the metabolites L-arginine and L-proline for collagen synthesis⁸⁵. However, the timing and/or the dose of nitric oxide may be important, as a related study suggested that NOS2 might help to polarize T_H2 cell-driven disease by preferentially suppressing the development of T_H1 cells⁸⁶. Nevertheless, the prevailing dogma suggests that IFN γ -primed macrophages primarily antagonize type 2 immunity and type 2-driven disease.

Inhibition by IL-4-primed macrophages and arginase 1. Perhaps not surprisingly, IL-4- and/or IL-13-primed macrophages also cross-regulate type 1 immunity and suppress the activity of IFN γ -stimulated macrophages^{82,87}. In support of this conclusion, mice expressing Cre recombinase in the regulatory region of the lysozyme M gene (*LysM*; also known as *Lyz2*) were crossed to IL-4R α ^{lox/delta} mice to generate mice with a conditional deletion of the IL-4 receptor α -chain (IL-4R α) in macrophages and neutrophils (*Il4ra*^{lox/delta}*LysM*-Cre mice)⁸⁸. These mice developed normal type 2 immunity in response to the nematode parasite *N. brasiliensis* but when infected with a high dose of *S. mansoni* cercariae larvae — a parasite that establishes chronic infections — the mice quickly succumbed to an overwhelming type 1-driven inflammatory response⁸⁸. This confirms that IL-4- and/or IL-13-primed macrophages

Clodronate liposomes
Liposome-encapsulated clodronate is a commonly used tool that is used to deplete phagocytic cells such as macrophages *in vivo*. At a certain intracellular concentration, clodronate induces macrophage apoptosis.

***Cd11b*-DTR mice**
Cd11b-transgenic mice that have a diphtheria toxin-inducible system that transiently depletes macrophages in various tissues. Intraperitoneal injection of diphtheria toxin ablates CD11b⁺ monocytes and/or macrophages.

Polarized type 2 immune responses
Immune responses that are dominated by the production of interleukin-4 (IL-4), IL-5, IL-9 and/or IL-13.

Cre recombinase
An enzyme that facilitates site-specific recombination events and is commonly used in genome modification strategies.

synthesis by neighbouring activated myofibroblasts. L-proline is required for extracellular matrix (ECM) production by myofibroblasts. Local amino acid competition between activated macrophages and T_H2 cells can also ameliorate type 2 immunity in the local microenvironment by reducing T_H2 cell proliferation. Similarly to IL-4- and/or IL-13-activated macrophages, inducible nitric oxide synthase (NOS2)-expressing M1-like macrophages may also suppress tissue repair and fibrosis by depleting local stores of L-arginine (via solute carrier family 7 member 2 (SLC7A2)-mediated uptake) and by suppressing expansion of the T_H2 cell population. However, during a type 2-skewed immune response, transforming growth factor- β 1 (TGF β 1) production by macrophages suppresses type 1 immunity and the development of interferon- γ (IFN γ)-primed macrophages. Therefore, monocytes and macrophages that have an IL-4- and/or IL-13-activated phenotype are the dominant suppressive myeloid cell populations during a polarized or chronic type 2 immune response. FGF, fibroblast growth factor; IGF1, insulin-like growth factor 1; IRF, IFN-regulatory factor; OX40L, OX40 ligand (also known as TNFSF4); PDGF, platelet-derived growth factor; STAT, signal transducer and activator of transcription; TCR, T cell receptor.

enzymatic activity^{91–93}. The findings in the schistosomiasis model clearly show that arginase 1-expressing macrophages are not required for the development of fibrosis or wound repair, but rather that they have an important inhibitory role⁹⁰. Studies with *Arg1^{lox/delta}LysM–Cre* mice and *Arg1^{lox/delta}Tie2–Cre* mice identified inflammatory monocytes as the key IL-4- and/or IL-13-activated subset that mediates the suppression of IL-13-driven fibrosis⁹⁰. By contrast, studies with *Il4ra^{lox/delta}LysM–Cre* mice identified mature *LysM*-expressing tissue macrophages as the dominant IL-4- and/or IL-13-primed population that mediates the inhibition of type 2 inflammation⁸⁹.

IL-4- and/or IL-13-primed macrophages expressing arginase 1 inhibit IL-13-driven fibrosis, at least partly, by suppressing the expansion of the CD4⁺ T_H2 cell population^{84,90}. It is also possible that IL-4- and/or IL-13-activated macrophages, similarly to IFN γ -stimulated macrophages, directly suppress the collagen-synthesizing activity of neighbouring myofibroblasts by competing for the L-arginine that is available in the local milieu⁹⁴. This may be an explanation for why IL-4- and/or IL-13-primed and arginase 1-expressing macrophages show little or no regulatory activity in models of allergic lung inflammation^{95,96} but show substantial inhibitory roles in granuloma formation and antitumour immunity, in which local substrate competition between macrophages, fibroblasts and T cells is probably more robust^{54,90,97}. Finally, related studies have shown that inflammatory monocytes recruited to allergic skin rapidly acquire a suppressive IL-4-activated phenotype⁹⁸. Disruptions in other M2-associated genes, such as *Retnla* (which encodes resistin-like molecule- α (RELM α)), have also resulted in increased type 2-driven inflammation during helminth infection^{99,100}. Therefore, IL-4- and/or IL-13-activated monocytes and macrophages probably have suppressive activity in many type 2-driven inflammatory diseases^{99,100} (FIG. 2).

Inhibitory activity by IL-10 and T_{Reg} cells. IL-10 was originally described as an immunosuppressive cytokine that inhibits cytokine production by T_H1 cells¹⁰¹. Although some studies have shown that IL-10 helps to polarize type 2 immune responses by preferentially suppressing IL-12 and IFN γ production^{59,102–104}, many additional studies have shown that IL-10 also has a major inhibitory role in type 2 immunity¹⁰⁵. For example, IL-10 was identified as an endogenous inhibitor of type 2 cytokine production and inflammation in a mouse model of allergic bronchopulmonary aspergillosis¹⁰⁶. Suppression of type 2 immunity was crucially dependent on the production of IL-10 by DCs, which preferentially stimulate the development of IL-10-producing regulatory T (T_{Reg}) cells in the lungs¹⁰⁷. Consistent with these observations, the balance between allergen-specific T_{Reg} cells and T_H2 cells is thought to have a decisive role in the development of allergic inflammation in healthy individuals versus individuals with allergies¹⁰⁸, and persistent or high-dose allergen challenge is associated with the emergence of protective IL-10-producing T_{Reg} cells that mediate tolerance to allergens in non-allergic individuals¹⁰⁹. Indeed, established airway inflammation and hyperreactivity

is attenuated in mice receiving IL-10-producing T_{Reg} cells via adoptive transfer¹¹⁰. IL-10 also suppresses type 2-associated inflammation in chronic schistosomiasis¹⁰³ and works collaboratively with IL-12 to antagonize T_H2 cell differentiation following infection with a range of helminth parasites^{81,104}. IL-27–IL-27 receptor α -chain (IL-27RA) signalling was also identified as an important inducer of IL-10 production by T cells^{111,112}, and mice that are deficient in IL-27RA develop exacerbated type 2 immune responses when challenged with allergens or following helminth infection^{113,114}. Although T_{Reg} cells are an important source of IL-10 and inhibit the development of type 2 immunity^{31,115}, additional studies have suggested that IL-10 is produced by a range of cell types, including macrophages, B cells and T_H2 cells, with each population participating in the suppression of type 2 immunity during helminth infection^{116–118}.

As IL-10 and T_{Reg} cells antagonize type 2 immunity, therapeutic strategies that preferentially expand IL-10-producing T_{Reg} cell populations could be used as therapies for type 2-driven disease. For example, *in vivo* expansion of forkhead box P3 (FOXP3)-expressing CD4⁺ T_{Reg} cells that are induced by tumour necrosis factor receptor superfamily member 25 (TNFRSF25; also known as CD40) has been shown to provide substantial protection from allergic inflammation by reducing the frequency of effector T cells compared with T_{Reg} cells in the lungs¹¹⁹. Interestingly, the immunosuppressive drug dexamethasone was also shown to promote human and mouse naive CD4⁺ T cells to differentiate into IL-10-producing T_{Reg} cells *in vitro*, which may partly explain the protective activity of corticosteroids in allergic inflammation¹²⁰. Hence, techniques that expand T_{Reg} cell populations *in vitro* could be developed as adoptive immunotherapies for type 2-driven disease. Finally, as helminths induce multiple immunoregulatory mechanisms and can confer protection against allergies^{121–123}, helminth parasites and specific helminth antigens are also being investigated as potential therapies for a range of allergic diseases, including food allergy and asthma^{124–126}.

Type 2 inhibition by silencers of cytokine signalling. Suppressors of cytokine signalling (SOCS) are proteins that function as negative regulators of cytokine signalling and that regulate the pathogenesis of many inflammatory diseases¹²⁷. SOCS1 and SOCS3 have both been identified as important regulators of type 2 immunity. However, they have divergent activity, with SOCS1 inhibiting and SOCS3 promoting type 2-driven inflammatory disease. Although SOCS1 has a complex role in the regulation of T cell activation, studies have revealed important roles for SOCS1 in the suppression of IL-4 function *in vivo*^{128,129}. SOCS1 antagonizes IL-4–STAT6-mediated gene expression in macrophages, and mice that are deficient in SOCS1 show exacerbated T_H2 cell-driven allergic inflammation when exposed to allergens^{129,130}. SOCS1 expression is also increased in individuals with allergies, which suggests that it may function as an important negative regulator of type 2 immunity in humans as well¹³¹. Similarly to SOCS1,

***Arg1^{lox/delta}LysM–Cre* mice**
Mice that lack expression of arginase 1 (*Arg1*) specifically in monocytes and macrophages (which express lysozyme M (*LysM*)).

***Arg1^{lox/delta}Tie2–Cre* mice**
Mice that lack expression of arginase 1 (*Arg1*) specifically in endothelial cells and most haematopoietic cells, which express the receptor tyrosine kinase promoter/enhancer (which is encoded by *Tie2*; also known as *Tek*).

SOCS3 is expressed in individuals with allergies¹³¹ but rather than inhibiting type 2 immunity, SOCS3 promotes type 2 immunity by suppressing the production of the immunoregulatory cytokines TGF β 1 and IL-10 (REF. 132). Transgenic mice that overexpress SOCS3 show increased type 2 responses and pathological features that are characteristic of severe asthma when challenged with allergens¹²⁸. By contrast, transgenic mice expressing dominant-negative mutant SOCS3, as well as mice with a heterozygous deletion of SOCS3, show decreased T_H2 cell development¹²⁸. Mice lacking SOCS3 specifically in T cells also develop reduced type 2 immune responses¹³². *In vitro*, SOCS3-deficient CD4⁺ T cells produce more TGF β 1 and IL-10 but less IL-4 than wild-type T cells¹³², which confirms that SOCS3 promotes type 2 immunity by suppressing the development of IL-10- and TGF β 1-producing T_{Reg} cells. These results suggest that negative regulation of the type 2-mediated responses by dominant-negative SOCS3 could be a target for therapeutic intervention in type 2-driven disease^{133,134}.

Disease suppression by the IL-13R α 2 decoy receptor. IL-4 and IL-13 are the major instructive cytokines of the type 2 cytokine response. They have many similar functional abilities because they share a common type 2 IL-4 receptor complex¹³⁵, but several important differences have been identified, which are probably owing to variations in their production⁴, cellular source³³ and pattern of receptor expression¹³⁶. The type 2 IL-4 receptor complex binds both IL-4 and IL-13 with fairly equal affinities and is expressed on macrophages and a wide range of non-haematopoietic tissues, which is in contrast to the type 1 IL-4 receptor that is expressed on haematopoietic cells and only binds IL-4 (REF. 137). In addition to these two receptor types that signal through STAT6, a second high-affinity decoy receptor for IL-13, IL-13R α 2, is expressed by epithelial cells, fibroblasts and smooth muscle cells. IL-13R α 2 lacks canonical Janus kinase (JAK)–STAT signalling activity and quickly internalizes IL-13, which prevents IL-13 from engaging with its signalling receptor^{138,139}. IL-13R α 2 blocks IL-13 effector function and has therefore been identified as a major suppressive mechanism in type 2-driven disease¹⁴⁰. For example, in schistosomiasis, development of IL-13-dependent fibrosis is reduced when IL-13R α 2 expression is elevated in activated myofibroblasts¹⁴¹. Granulomatous inflammation and mortality are also reduced by the expression of IL-13R α 2 in mice that are chronically infected with *S. mansoni*¹⁴². Pulmonary hypertension, which is a serious complication of chronic schistosomiasis, is similarly ameliorated by the expression of IL-13R α 2 (REF. 143). Smooth muscle cell hypercontractility in the colon is also suppressed by IL-13R α 2 both at baseline and following gastrointestinal nematode infection^{144,145}. In the lungs, IL-13 is a crucial regulator of airway inflammation, mucus production, airway hyperresponsiveness and lung remodelling, and increased expression of IL-13R α 2 by bronchiolar epithelial cells and fibroblasts has been shown to downregulate IL-13 activity in both mouse and human cells^{146–148}. Finally,

studies investigating the function of IL-13R α 2 in models of allergic lung inflammation have shown that pulmonary inflammation, mucus metaplasia, subepithelial fibrosis and airway remodelling are all significantly reduced when IL-13R α 2 expression increases^{149,150}. Thus, therapeutic strategies that augment IL-13R α 2 activity could be used to ameliorate type 2-driven disease.

Collaborating suppressive mechanisms

Cooperating inhibitory mechanisms in asthma. There is evidence that many of the suppressive mechanisms described above work together to slow the progression of type 2-driven disease. For example, although T_{Reg} cells and IL-10 inhibit type 2 immunity, studies carried out using IL-10-deficient mice have suggested that the development and effector function of T_H2 cells are differentially regulated by IL-10 (REF. 149). In the absence of IL-10, allergen-induced inflammation is exacerbated but, paradoxically, *Il10*^{−/−} mice show reduced type 2-associated airway hyperreactivity, mucus production and lung remodelling^{151–153}, which has been attributed to elevated production of the IL-13R α 2 (REF. 149). Indeed, studies carried out using IL-10- and IL-13R α 2-deficient mice showed that animals that are deficient in both mediators are much more susceptible to the development of atopic asthma¹⁴⁹. This confirms that IL-10 and IL-13R α 2 function collaboratively to suppress the cardinal features asthma, with IL-10 dampening the intensity of the inflammatory response and IL-13R α 2 blocking the downstream pathological actions of IL-13 in the lungs (FIG. 3).

Collaboration in antihelminth immunity. IL-10- and IL-13R α 2-coordinated regulation of type 2 immunity has also been observed during gastrointestinal nematode infection. In this case, IL-10 promotes type 2 immunity by actively suppressing the expression of IL-13R α 2 and IL-12 (REFS 104,154), which antagonize the downstream protective effects of IL-13 (REFS 81,138). For example, *Il10*^{−/−} mice infected with *Trichuris muris* show elevated IL-13R α 2 responses in the gut, which suppress the expression of the IL-13-inducible mediators mucin 5AC (MUC5AC) and RELM β , which are required for the expulsion of nematode parasites from the gut^{7,155}. *Il10*^{−/−} mice also quickly succumb to *T. muris* infection because they develop severe IFN γ - and IL-17A-mediated inflammation¹⁵⁴. In contrast to the severe morbidity and mortality observed in *Il10*^{−/−} mice, mice that are deficient in both IL-10 and IL-13R α 2 show little mortality when infected with *T. muris*, and they show a marked restoration of IL-13-induced MUC5AC and RELM β expression¹⁵⁴. Thus, IL-13R α 2 is a potent inhibitor of type 2 immunity in the gut as well as in the lungs. IL-12 seems to have a similar suppressive role because mice deficient for both IL-10 and IL-12p40 that are infected with *T. muris* develop substantially less morbidity and mortality than *Il10*^{−/−} mice¹⁰⁴. Similarly to mice deficient for both IL-10 and IL-13R α 2, mice lacking both IL-10 and IL-12p40 show marked increases in mucin and RELM β expression, confirming that IL-12 and IL-10 collaboratively suppress type 2 immunity during intestinal nematode infection (FIG. 3).

Portal hypertension

An increase in the pressure within the portal vein (the vein that carries blood from the digestive organs to the liver). The increase in pressure is caused by a blockage in the blood flow through the liver, which is commonly associated with cirrhosis or scarring of the liver.

Ascites

Abdominal fluid that accumulates as a result of high pressure in the blood vessels of the liver, often a result of chronic liver injury.

Redundancy in the suppression of type 2 fibrosis. IL-10, IL-12 and IL-13R α 2 have also been shown to collaboratively suppress the progression of liver fibrosis in schistosomiasis by limiting the production and function of the profibrotic cytokine IL-13 (REF. 156). Although the development of IL-13-dependent fibrosis increases when any one of the mediators is targeted individually^{81,141,149}, a substantial acceleration of liver fibrosis is observed when all three inhibitory mechanisms are simultaneously blocked, which indicates that they function as both redundant and collaborative inhibitors of wound healing and fibrosis¹⁵⁶. Indeed, in contrast to infected wild-type mice, in which lethal cirrhosis can take several months to develop, mice with a combined deficiency of IL-10, IL-12p40 and IL-13R α 2 develop lethal IL-13-dependent cirrhosis as soon as 3–4 weeks following the establishment of a patent infection. However, many of the serious complications that are associated with advanced liver

cirrhosis — including portal hypertension, ascites, variceal bleeding and mortality — are reduced when the triple-deficient mice are treated with a neutralizing monoclonal antibody specific for IL-13. This confirms that IL-10, IL-12 and IL-13R α 2 suppress type 2-driven fibrosis by inhibiting the expansion and activity of the IL-13-producing lymphocyte population in the liver (FIG. 3).

Therapies targeting type 2 immunity

Targeting IL-4 and/or IL-13 signalling. As the maintenance and the progression of type 2-driven inflammatory disease is greatly influenced by the cytokines IL-4 and IL-13, it is not surprising that many of the therapeutic strategies currently under development for type 2-driven diseases are focused on disrupting the activity of one or both of these cytokines (FIG. 4). Although there is a great deal of functional overlap between these cytokines¹³⁵, there is substantial

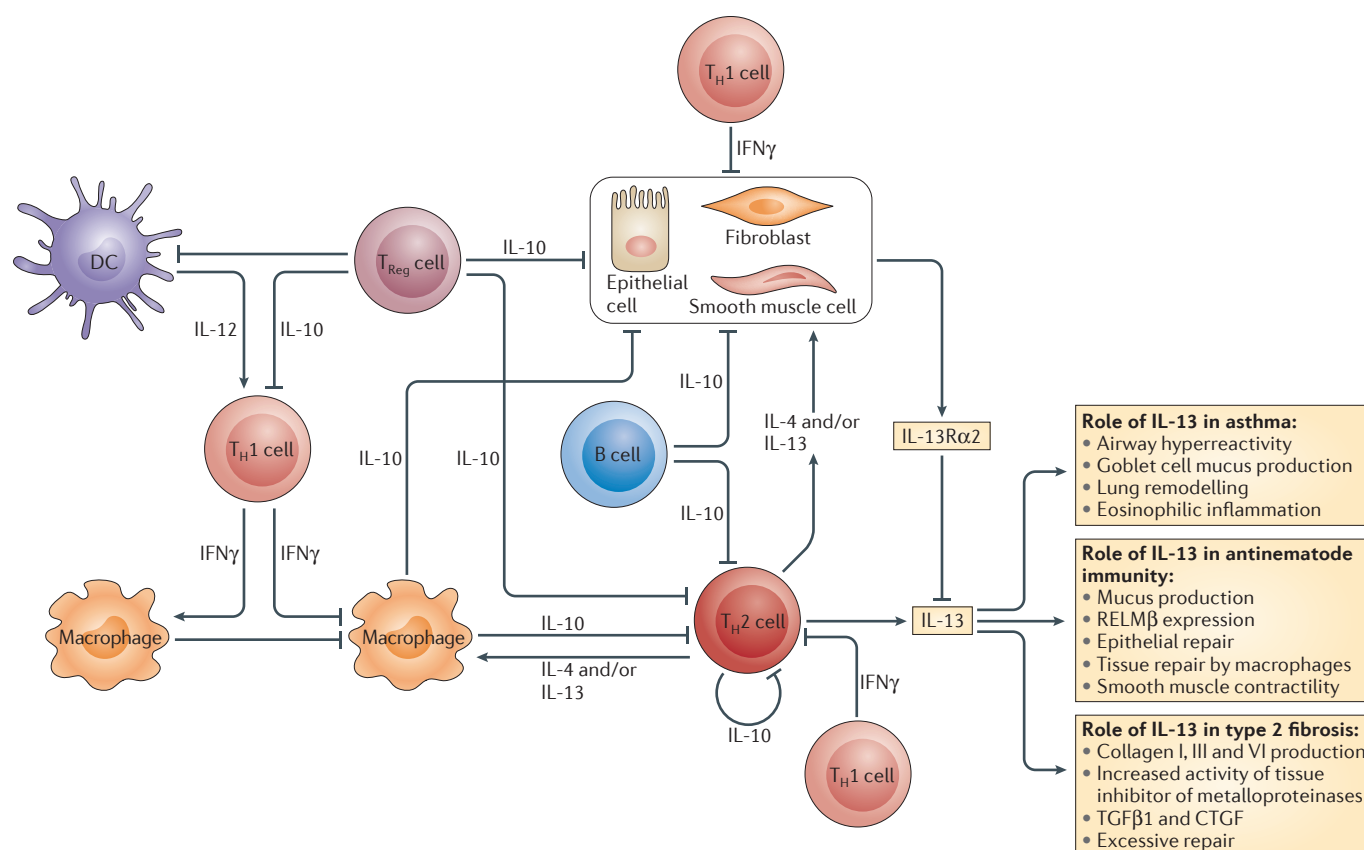


Figure 3 | Collaboration between interleukin-10, the IL-13 decoy receptor and type 1 immunity in the suppression of type 2 immunity. Interleukin-13 (IL-13) is crucial to the pathogenesis of asthma as it stimulates mucus production, airway hyperreactivity and lung remodelling. In the absence of the suppressive cytokine IL-10, which is produced by multiple cell types, the frequency of T helper 2 (T_H2) cells increases, which leads to exacerbated type 2-driven eosinophilic inflammation but also to increased expression of the IL-13 decoy receptor IL-13R α 2 by fibroblasts, smooth muscle cells and epithelial cells. Despite the increased IL-13 response, airway hyperreactivity, mucus production and airway remodelling are reduced in *IL10*^{-/-} mice because of the increased IL-13R α 2 activity. Therefore, IL-10 and IL-13R α 2 are both involved in the suppression of IL-13-driven asthma.

IL-13-dependent antinematode immunity is tightly regulated by the combined inhibitory activities of IL-10, IL-12 and IL-13R α 2. In the absence of IL-10, the production of IL-13R α 2 and IL-12 increases, which results in reduced IL-13 effector function during helminth infection. However, if type 1 immunity or IL-13R α 2 expression is suppressed, IL-13-dependent immunity is restored. IL-10, IL-12 and IL-13R α 2 have similar cross-regulatory and suppressive activity during the development of IL-13-dependent fibrosis. If all three inhibitory mediators are knocked out or simultaneously blocked, IL-13-dependent liver fibrosis in chronic schistosomiasis progresses to lethal cirrhosis much more rapidly. CTGF, connective tissue growth factor; DC, dendritic cell; IFN γ , interferon- γ ; RELM β , resistin-like molecule- β ; TGF β 1, transforming growth factor- β 1; T_{Reg} cell, regulatory T cell.

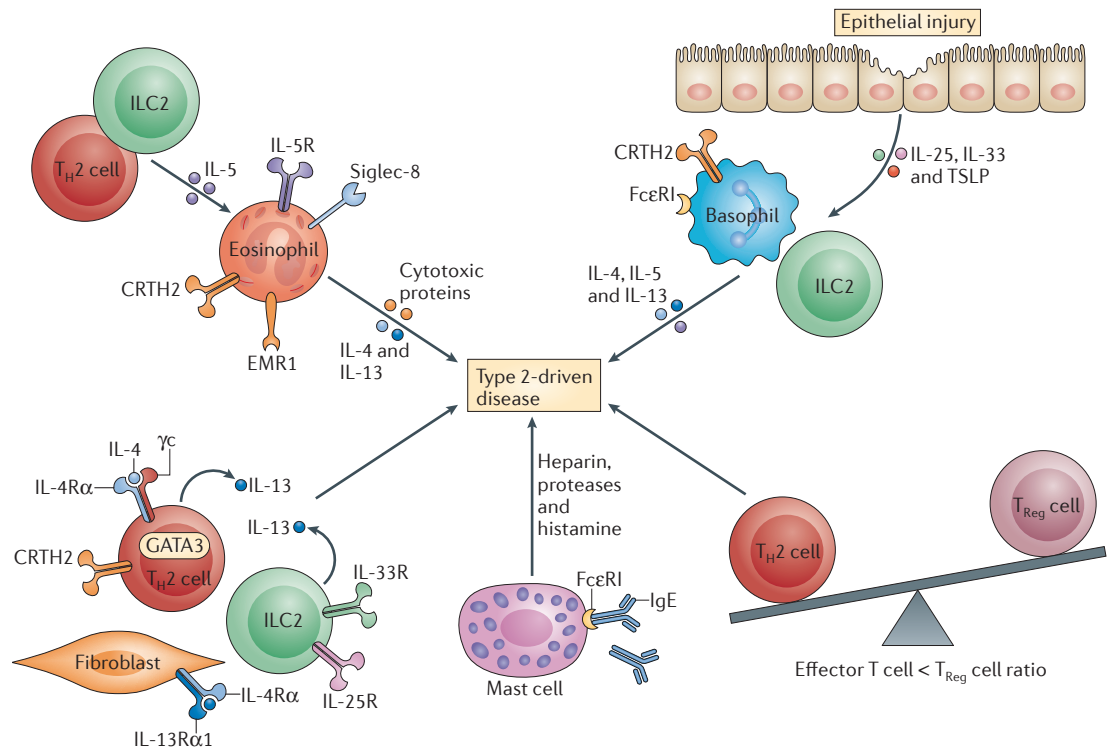


Figure 4 | Novel targeted therapies for type 2-driven disease. Several novel therapeutic strategies targeting type 2 cytokine signalling pathways, eosinophil development and recruitment, epithelial cell-derived alarmins, prostaglandins and regulatory T (T_{Reg}) cell activity are at various stages of development for type 2-driven disease. γc , common γ -chain; CRTH2, prostaglandin D2 receptor 2; EMR1, EGF-like module receptor 1 (also known as F4/80); FcεRI, high-affinity Fc receptor for IgE; GATA3, GATA-binding protein 3; IL, interleukin; IL-4Rα, IL-4R α -chain; IL-5R, IL-5 receptor; ILC2, group 2 innate lymphoid cell; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; $T_{\text{H}}2$ cell, T helper 2 cell; TSLP, thymic stromal lymphopoietin.

evidence that IL-13 functions as a primary disease-inducing effector cytokine, whereas IL-4 functions as a key amplifier of type 2 immunity by facilitating the expansion of the $CD4^+$ $T_{\text{H}}2$ cell population in secondary lymphoid organs³⁵. Although there are situations in which the disruption of both cytokines would probably be more efficacious, some studies have suggested that it might be better, and perhaps safer, to only disrupt IL-13 signalling¹⁵⁷. This is certainly the case in chronic schistosomiasis, in which combined depletion of IL-4 and IL-13 results in the development of a highly skewed and lethal type 1-driven inflammatory response in the liver and intestines^{157,158}. By contrast, IL-13 blockade preserves some features of the protective type 2 immune response but greatly diminishes the development of pathological fibrosis, which results in less morbidity and mortality during chronic infection^{4,142}. Several antagonists, antisense oligonucleotides, micro-RNAs and humanized monoclonal antibodies targeting IL-4Rα, IL-13Rα1, GATA-binding protein 3 (GATA3) and IL-13 are being evaluated in clinical trials¹⁵⁹. Cytokine-specific vaccinations directed against IL-4, IL-13 or other type 2 cytokines might also prove efficacious in some settings^{160,161}. Thus, as new results are published^{162–164}, we should have a greater understanding of the importance of targeting IL-13 or both IL-4 and IL-13 signalling in several type 2-driven diseases.

Targeting IL-5 and eosinophils. Therapeutic strategies that block the development, activation, recruitment or maintenance of eosinophils in diseased tissues are also being actively investigated as treatments for type 2-associated disease (FIG. 4). Eosinophils are present in high numbers in many type 2-driven diseases, are important sources of IL-4 and IL-13, and have crucial roles in the pathophysiology of asthma, eosinophilic oesophagitis and hypereosinophilic disorders¹⁶⁵. Eosinophils are released into the blood as mature cells and are quickly recruited to sites of inflammation, at least partly, by the actions of the epithelial alarmins thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, which stimulate the production of large quantities of IL-5 from ILC2s¹⁶⁶; IL-5 produced by $CD4^+$ $T_{\text{H}}2$ cells amplifies the response during the development of an adaptive immune response¹⁶⁵. As IL-5, together with eosinophil-attracting chemokines, regulates the development, recruitment and survival of eosinophils in tissues, several humanized monoclonal antibodies that block the binding of IL-5 to IL-5Rα are being investigated in Phase II and Phase III clinical trials¹⁶⁵. An IL-5Rα-specific monoclonal antibody that eliminates eosinophils by an antibody-dependent cellular cytotoxicity mechanism is also being examined. Although preliminary findings look encouraging¹⁶⁷, it will be interesting to learn whether other cell types — such as

ILC2s, basophils, mast cells and T_H2 cells — will compensate for the reduction in eosinophils, as has been observed in some preclinical studies^{168,169}, or whether lasting protection can be conferred by targeting IL-5 and eosinophils.

Targeting TSLP, IL-25, IL-33 and ILC2s. The epithelial cell-derived alarmins TSLP, IL-25 and IL-33 are important initiators of type 2 immunity^{170–172}. They are released when the epithelium is damaged by allergens or pathogens and they trigger the production of the canonical type 2 cytokines IL-5, IL-9 and IL-13 by cells of the innate immune system¹⁶⁶. TSLP targets DCs, basophils, mast cells, monocytes and natural killer T cells, and has been shown to be crucial to the initiation of $CD4^+$ T_H2 cell responses in some settings¹⁷³. IL-25 and IL-33 have similar T_H2 cell-inducing activity but also promote type 2 immunity by targeting ILC2s¹⁶⁶. Although TSLP, IL-25 and IL-33 have all been shown to promote type 2 immunity when overexpressed in mice^{170–172}, the requirement for these cytokines in the initiation and maintenance of type 2 immunity in response to allergens and helminth parasites has been more variable, with some studies identifying little or no role for TSLP, IL-25 or IL-33 when they are targeted individually^{174–178}. Nevertheless, functional roles for TSLP, IL-25, IL-33 and ILC2s in type 2 immunity are inferred from the observation that type 2 inflammation can develop in mice that are deficient in B cells and T cells³³. Therefore, it will be important to investigate the contribution of ILC2s in established models of chronic type 2-driven disease. It will also be important to test the contributions of TSLP, IL-25 and IL-33 in patients with asthma and other persistent type 2 cytokine-driven disorders. Humanized monoclonal antibodies targeting IL-25 and IL-33 have been developed and are currently being tested in preclinical studies, whereas antibodies specific for TSLP have been shown to reduce allergen-induced bronchoconstriction and airway eosinophilia in individuals with allergies both before and after allergen challenge¹⁷⁹. However, whether blockade of TSLP, IL-25 or IL-33 will have clinical value remains unknown (FIG. 4).

Restoring effector cell and T_{Reg} cell homeostasis. The balance between type 2 effector cells and T_{Reg} cells tightly controls the development of type 2-driven allergic disease¹⁸⁰. Therefore, several preclinical and clinical studies are underway to determine whether modifying the ratio of T_{Reg} cells to effector T cells might represent a viable therapeutic strategy for asthma and other type 2-driven allergic diseases. Allergen immunotherapy is a well-established procedure that desensitizes individuals with allergies to specific allergens¹⁸¹. Clinical studies are underway to determine whether the decrease in allergy-related disease achieved by allergen immunotherapy is associated with increases in the number of IL-10-producing FOXP3-expressing T_{Reg} cells ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01028560) identifier NCT01028560). Another study is investigating whether a specific type of immune-tolerizing DC can induce T cell tolerance in allergic individuals. This study is examining whether *in vitro*-generated immune-tolerizing DCs can induce antigen-specific T_{Reg} cells and can suppress

allergen-specific T cell function *in vitro* ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01711593) identifier NCT01711593). A related study is investigating the immunomodulatory potential of plasmacytoid DCs (pDCs), which also control T_{Reg} cell development. As airway inflammation in asthma is associated with increases in the number of activated $CD25^+$ T cells, IL-2 and soluble IL-2 receptors, a humanized monoclonal antibody against the IL-2 receptor α -chain (CD25) is being examined as a potential therapy for patients with moderate to severe asthma. Preliminary results have shown that CD25-directed therapy improves pulmonary function in patients whose disease is not well controlled with corticosteroids¹⁸². The authors concluded that protection probably results from the decreased production of pro-inflammatory cytokines by activated effector T cells. However, CD25-directed therapy may also diminish the number of ILC2s. Inhibitors targeting products of the arachidonic acid pathway may also help to restore the ratio of effector T cells to T_{Reg} cells in allergy and asthma¹⁸³. Finally, a Phase I clinical study recently assessed whether the eggs of the parasite *Trichuris suis* can be safely delivered to adults and children with peanut or tree nut allergy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT0170498) identifier NCT0170498). The ultimate goal of these studies is to determine whether a harmless helminth parasite can be used to restore the balance of T_{Reg} cells and effector T cells in the intestines¹⁸⁴. Thus, immunotherapeutic approaches that expand the T_{Reg} cell population and/or that reduce the number of effector T cells in tissues hold promise for type 2-driven disease (FIG. 4).

Conclusion and future directions

Although the type 2 response has important protective activity as it suppresses type 1 inflammation, neutralizes toxins, controls key metabolic functions and augments tissue repair pathways, this Review discusses how a dysregulated type 2 response can also quickly evolve into a disease-promoting mechanism. Consequently, there is a range of endogenous regulatory mechanisms that primarily function to reduce the intensity, duration and pathogenesis of type 2 immunity. As highlighted above, many of these regulatory mechanisms are being actively investigated as novel therapeutic strategies for a range of type 2-driven diseases. Therefore, it will be important to identify patients who might benefit from a specific strategy, as was recently shown in a study using lebrikizumab, which is a humanized monoclonal antibody specific for IL-13 (REF. 164). In this clinical study, patients with asthma who showed the most improvement in lung function following IL-13-directed therapy had the highest pretreatment levels of the IL-13-inducible serum biomarker periostin. Thus, the discovery of unique biomarkers that can identify important pathological mechanisms will probably be key to the successful implementation of novel immunotherapies for type 2-driven diseases¹⁸⁵. As type 2 immunity helps to maintain immune homeostasis and to regulate key metabolic functions^{17,186}, it will also be important to fine tune these therapies so that unwanted side effects — such as metabolic syndrome, obesity and type 1 inflammation — are avoided.

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Competing interests statement

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