

Review article

Chronic inflammation in asthma: a contest of persistence vs resolution

Recent investigations have highlighted that endogenous anti-inflammatory mediators and immune regulating mechanisms are important for the resolution of inflammatory processes. A disruption of these mechanisms can be causally related not only to the initiation of unnecessary inflammation, but also to the persistence of several chronic inflammatory diseases. In asthma, chronic Th-2 driven eosinophilic inflammation of the airways is one of the central abnormalities. To date, elucidating the role of the different pro-inflammatory mediators involved in orchestrating the inflammatory processes in asthma has been the subject of intense research in both humans and animal models. However, the counter-regulatory mechanisms that co-determine the outcome in the contest of resolution vs persistence of the eosinophilic airway inflammation remain poorly understood. These are currently being investigated in animal models of chronic asthma. Elucidating these mechanisms is of relevance, since it can give rise to a new therapeutic approach in the treatment of chronic airway inflammation in asthmatics. This novel concept of treatment involves the stimulation of *endogenous* anti-inflammatory pathways, rather than solely antagonising the various pro-inflammatory mediators. Here, we review and discuss the current knowledge about these *endogenous* anti-inflammatory mediators in clinical and experimental asthma.

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The natural history of inflammation: 'chronicity' and resolution

Acute vs chronic inflammation

Inflammation is a response of the immune system beneficial to the host under normal circumstances. It has evolved to protect the host from potentially harmful nonself antigenic stimuli, such as micro-organisms, or in case of tissue damage. The ultimate purpose of this response is the elimination of foreign organisms or material and the restoration of tissue integrity. An acute inflammatory episode is characterized by an influx of inflammatory cells in the injured or infected tissue, followed by the release of a self-amplifying network of pro-inflammatory mediators that perpetuate leukocyte recruitment and activation, and cause leakage of the microvasculature. Together, these phenomena then result in the characteristic redness, swelling and pain of the inflamed tissue. When the stimulus has been cleared, endogenous 'stop' signals or anti-inflammatory mediators normally take over and the inflammation resolves (1–4).

In a number of conditions the state of inflammation persists for a prolonged period of time and becomes chronic. Chronic inflammation ceases to be beneficial for

the host and can lead to a loss of tissue or organ function. Since inflammation is normally a self-limiting process, 'chronicity' of inflammation can be understood as being the result of either the persistence of a stimulus, for example a micro-organism or allergen, or of a dysregulation of the endogenous anti-inflammatory mechanisms that normally coordinate resolution (1–4).

Resolution of inflammation

Resolution of inflammation is an active process, which prevents unnecessary tissue damage after clearance of the inflammatory stimulus (3, 4). It critically depends on the biological actions of several anti-inflammatory and pro-resolving mediators, expressed by various cell types, as well as on apoptosis and clearance of inflammatory cells (Fig. 1). A failure of any step in this process may lead to chronic inflammation (1–4). A schematic representation of the different phases of the resolution process in airway inflammation is depicted in Fig. 1.

The first phase in the resolution of an inflammatory episode (Fig. 1A) involves the release of endogenous anti-inflammatory mediators ('stop' signals), as well as the termination of pro-inflammatory signalling. The former

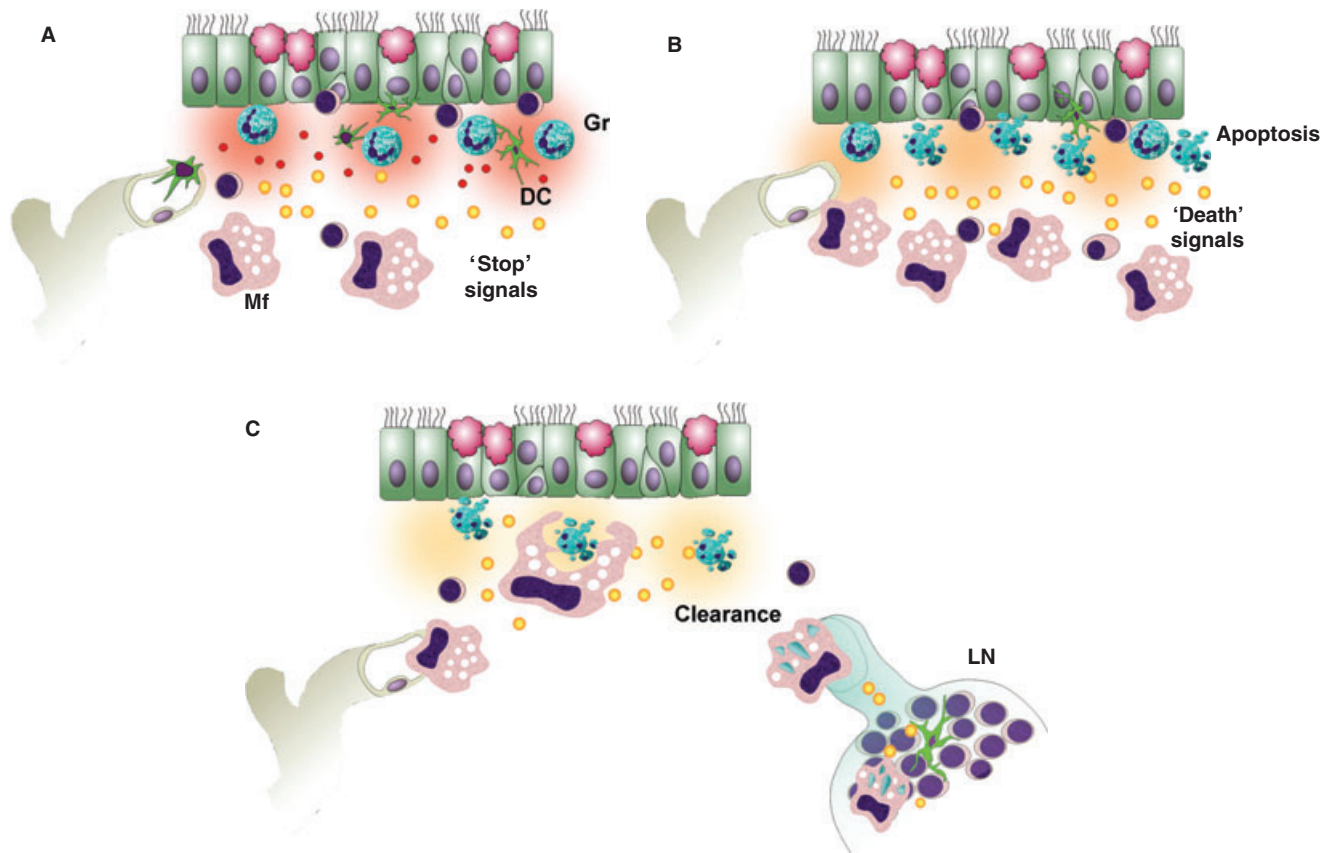


Figure 1. Schematic representation of a normal resolution process of an inflammatory episode. This figure shows a normal resolution process of an acute inflammatory episode. There are three main phases in this process. In the first phase (A), endogenous anti-inflammatory mediators or 'stop' signals are released from different cell types and pro-inflammatory signalling is terminated. This process is triggered when polymorphonuclear cells at the site undergo an 'eicosanoid class switch'. In the second phase (B) 'death signal'-induced programmed cell death or apoptosis of the inflammatory leukocytes is initiated. In the third phase (C), the apoptotic cells are phagocytosed and cleared by local macrophages that subsequently migrate to the draining lymph nodes following phagocytosis ('efferocytosis'). (red circles = pro-inflammatory mediators; yellow circles = anti-inflammatory mediators; Mf = macrophages; Gr = granulocyte; DC = dendritic cell; LN = lymph node).

include certain cytokines and growth factors, such as Interleukin-10 (IL-10) and transforming growth factor- β (TGF- β), but also various (proteolytic) enzymes and lipid mediators, such as lipoxins, resolvins and protectins, which recently have been shown to be critically involved in the resolution of inflammation (1–6). The release of these stop signals by different types of leukocytes and structural cells is a strictly regulated process. For example, when a pro-inflammatory stimulus (e.g. bacterial infection) is eliminated, the polymorphonuclear cells at the site of inflammation switch their phenotype to produce lipoxins instead of pro-inflammatory eicosanoids such as leukotrienes. This phenomenon is called the 'eicosanoid class switch'. These lipoxins then initiate the resolution sequence and also stimulate the production of a range of endogenous anti-inflammatory and pro-resolving mediators (4, 7). Notably, not all endogenous anti-inflammatory mediators are necessarily implicated in every 'normal' resolution program.

The next step (Fig. 1B) is the engagement of programmed cell death or apoptosis of the inflammatory leukocytes, as these receive 'death' signals from the altered, now anti-inflammatory environment. This phase of leukocyte apoptosis is tightly linked to the final phase, i.e. the phagocytic clearance of the apoptotic cells by local macrophages (8) (Fig. 1C). The clearance of apoptotic cells (or 'efferocytosis') may be a critical point in the control of inflammation, as secondary necrosis of the leukocytes, which could occur upon delayed clearance, leads to tissue damage and persistence of the inflammation (8). Upon phagocytosis, the macrophages down-regulate their activation status and up-regulate the release of anti-inflammatory mediators such as IL-10 and TGF- β , contributing to the local anti-inflammatory climate (9). Finally, phagocytosis triggers the macrophages to leave the site of inflammation and to migrate into the nearest lymph nodes (10), where they die by apoptosis (11).

Asthma: a disease of chronic inflammation and acute exacerbations

Chronic inflammation in asthma

Asthma is a complex syndrome in which inflammation of the conducting airways, often allergic by nature, is pivotal (12). This encompasses also recurrent exacerbations of acute inflammation in response to a variety of stimuli, such as allergen inhalation, exposure to environmental pollutants or microbial infection. Besides episodes of exacerbated acute inflammation, an underlying chronic inflammation often remains present in the asthmatic airway, even in the absence of continuous allergen exposure (13). This chronic inflammation can contribute to the decline in lung function and hyperresponsiveness observed in asthma patients.

Persistent asthma (Fig. 2) is characterized by the presence of eosinophils, mast cells and CD4⁺ T lymphocytes in the inflammatory infiltrate surrounding the bronchi (12). Important roles have also been described for more rare cells, such as dendritic cells (DC), which are essential cells for the presentation of antigen (14). These inflammatory cells, along with activated resident structural cells, such as

epithelial cells, fibroblasts and airway smooth muscle cells, perpetuate the chronic inflammation by the secretion of a vast array of pro-inflammatory mediators, such as eicosanoids, cytokines, chemokines, growth factors and proteases. These mediators can act synergistically and exert their pro-inflammatory effects by influencing the recruitment, survival and activation of inflammatory cells (13). Along with the inflammation, structural changes, also termed 'airway remodelling', are also present. Remodelling and chronic inflammation are thought to be interdependent processes (15). Whether remodelling is merely the result of (inadequate) tissue repair, or may also be protective against further asthma progression, remains a matter of debate.

Clinical (16–18) and basic (19) research has recently highlighted the critical importance of a dysregulation of endogenous inflammation-regulating mechanisms in the development of allergic immune responses and in avoiding the normal tolerogenic immune response upon allergen exposure (Fig. 2). This disruption may well be, at least in part, responsible not only for the development of allergic sensitization and acute inflammation, but also for the chronicity and severity of the inflammation in asthma (Fig. 2).

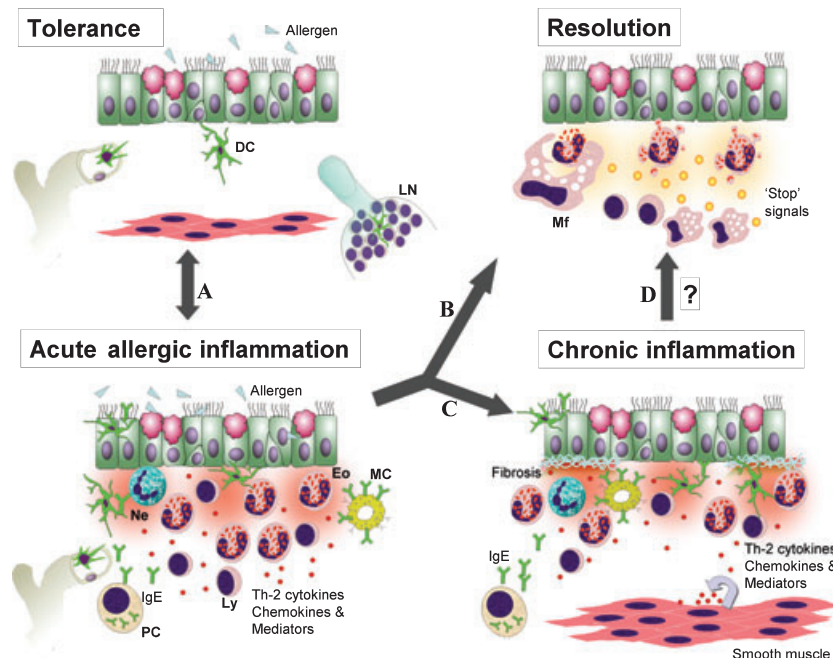


Figure 2. Tolerance, acute and chronic inflammation and resolution of inflammation in asthma. Upon encounter with a harmless airborne allergen, the immune response is normally a tolerogenic one. In contrast, in allergic individuals, an acute inflammatory response in the airways will develop (arrow A). This inflammatory response in the airways can then, in the absence of the allergen, either resolve (arrow B) or become chronic (arrow C). Chronic inflammation is accompanied by structural changes in the airways, such as sub-epithelial fibrosis and smooth muscle hyperplasia. In order to terminate a chronic inflammatory response (arrow D), endogenous anti-inflammatory mediators or 'stop' signals have to take over. These mediators can be molecules of different nature, produced by leukocytes or structural cells (red circles = pro-inflammatory mediators; yellow circles = anti-inflammatory mediators; question mark = endogenous anti-inflammatory mediator; Mf = macrophages; Eo = eosinophil; Ly = lymphocytes; Ne = neutrophil; DC = dendritic cell; MC = mast cell; PC = plasma cell).

Animal models of (chronic) asthma

Animal models of asthma have made important contributions to our current understanding of the (acute) inflammatory response in asthma (20). In order to mimic the features of chronic asthma and to elucidate potentially important immunological mechanisms, considerable efforts have been made to develop good animal models (21). Although the majority of researchers found that the inflammation in the airway wall tends to fade away over time upon prolonged inhalation of allergen in most animal models of chronic asthma (21), some groups have succeeded in developing models in which inflammation persists (22, 23). The waning of inflammation over time is not restricted to mouse models, but also appears in rat and guinea pig models of asthma (20). In this respect, several studies have been conducted that attempted to shed more light on the anti-inflammatory mechanisms responsible for this phenomenon (24, 25).

Persistent asthma and endogenous anti-inflammatory mediators

The sequence of events shown in Fig. 1 gives an account of a normal resolution process of an acute inflammatory episode. As outlined, persistent asthma can be seen as a disorder in which a dysregulation of each individual phase in this resolution process could well be an important factor contributing to chronicity. Our attention here goes to the biological effects of the various endogenous anti-inflammatory mediators that are potentially impaired in chronic asthma. A reduced biological activity of these could prevent resolution of the airway inflammation. Notably, a failure of the endogenous tolerogenic mechanisms is also thought to be responsible for the development of sensitization and acute asthmatic inflammation (16–18). Besides defects in the production of endogenous anti-inflammatory mediators, the other phases in the inflammation-resolution process can be dysregulated in asthma as well. Both a disruption of leukocyte apoptosis (26), in particular apoptosis of the eosinophils, and of the efferocytosis (8) have been implicated in the pathogenesis of chronic asthmatic inflammation.

We here give an overview and discuss interesting endogenous mediators that modulate the chronic inflammation associated with asthma, mainly based on data from animal models but also on human data, when available. In recent years, a lot of new endogenous anti-inflammatory mediators and pathways have been studied in animal models (Table 1). Some of these molecules have been studied in 'classical' animal models of acute inflammation, others in a more chronic setting. Targeting these endogenous pathways of inflammation control in humans could open up new approaches in the treatment of chronic inflammation in asthma (Table 2).

Cytokines

Interferon- γ /interleukin-12. The Th-2 mediated eosinophilic inflammation in asthma was originally believed to result from a Th-1/Th-2 imbalance. It was thought that it could be 'counterbalanced' by an augmented Th-1 activity, the more since the production of the Th-1 inducing cytokine IL-12 is impaired in asthmatics. Remarkably, it was shown that boosting the endogenous Th-1 activity by administration of *Interferon- γ* (IFN- γ) or IL-12 induced a Th-1 mediated inflammatory response resulting in an aggravation of asthma (27). In addition, clinical trials with recombinant human IFN- γ and IL-12, showed either multiple side effects or a disappointing efficacy (28).

The fact that an enhanced Th-1 activity aggravates asthma, together with other observations, such as the concurrent rise in both allergic and Th-1 mediated autoimmune diseases during the past decades, provoked that the Th-1/Th-2 paradigm gradually gave way for a new concept. A disruption of the endogenous tolerogenic mechanisms, rather a Th-1/Th-2 imbalance is now seen as central in the pathogenesis of allergic airway inflammation (16–19).

Interleukin-10. Different subtypes of regulatory T cells (Treg) producing the immunosuppressive cytokine IL-10 are now thought to be essential in the protection against asthma. In addition, IL-10 is also secreted by many other cell types, such as DC and macrophages. An impaired function of these cells could also play a role in the persistence of the disease (16, 29). Immunotherapy could function by inducing these IL-10 producing cells (30), while IL-10-dependent resolution of allergic airway inflammation in mice can be obtained by adoptive transfer of Treg (31).

Interleukin-10 exerts its anti-inflammatory effects mainly by binding to the IL-10 receptor. IL-10 receptor engagement activates the tyrosine kinases jak1 and Tyk2. Tyrosine phosphorylation subsequently activates the transcription factors STAT1, 3 and 5, that migrate to the nucleus and activate gene expression (32). There is good evidence that IL-10 secretion may be defective in atopic asthmatics, since lower concentrations of IL-10 are found in sputum and bronchoalveolar lavage fluid obtained from these patients (33), and gene polymorphisms in the IL-10 promoter were found to be associated with an asthmatic phenotype (34).

Given that IL-10 is such a prominent immunoregulatory cytokine in the human body, it has recently been tested in clinical trials to treat various chronic inflammatory diseases (35). To our knowledge, no studies have been published that evaluated the effects of recombinant human IL-10 in a randomized double-blind study in asthma patients, but clinical trials have been performed in psoriasis and Crohn's disease. Although these studies show that IL-10 is reasonable well tolerated, the results

Table 1. Endogenous anti-inflammatory mediators investigated in experimental asthma

Mediator class	Anti-inflammatory molecules
Cytokines	IL-10 (29, 31), IL-17 (49–51), IL-27 (61, 62), Opn-s (54, 55), CC10 (56, 57)
Chemokines	CCL19 (65, 66), CCL22 (65, 66), Galectins (–3, –9) (67–70)
Growth factors	TGF- β (38–44, 47), Flt3-L (72–74), KGF (75)
Lipid mediators	15-HETE (88–91), Lipoxins (77–80), PGD ₂ (83)/E ₂ (84)/I ₂ (86, 87), Protectin D1 (81), RvE1 (82)
Peptides	VIP (92–97), (A)NP101, adrenomedullin (99, 100)
Adipocytokines	Adiponectin (106–108)
Steroid hormones	Cortisol (105), sex hormones (110)
Metabolic enzymes	IDO (112–114)
Proteolytic enzymes	MMPs (2&9) (118–121), caspases (122), cathepsins (123)
Antioxidants	LMw [glutathione (128)]/enzymes [Nrf2 (129), HO-1 (127)]
Anorganic gases	CO (131), NO (130)
T cell costim. molecules	PD-1 (133), CTLA-4 (133, 134), BTLA (133)
PAR receptors	PAR-2 (117, 120)
TNF receptors	Fas (138)/4-1BB (136, 137)
Ig-like receptors	gp49B (141)
Cyclic nucleotides	cAMP (84)
Surfactant proteins	SP-A, SP-D (142)
Complement	C5a anaphylatoxin (143)
ECM components	Syndecan-1 (145), heparan sulphate (146)

The corresponding receptors of the various endogenous mediators are not mentioned in this table. Receptors are only mentioned when they can act as a mediator themselves (e.g. TNF receptors can act as co-stimulators). 15-HETE is an endogenous ligand of the PPAR (peroxisome proliferator-activated receptor).

Abbreviations: IL = interleukin; Opn-s = osteopontin-soluble; CC10 = Clara cell protein 10; CCL = CC-chemokine ligand; TGF- β = transforming growth factor- β ; Flt3-L = Fms-like tyrosine kinase-3 ligand; KGF = keratinocyte growth factor; 15-HETE = 15-hydroxyeicosatetraenoic acid; PGD₂/E₂/I₂ = prostaglandin D₂/E₂/I₂; RvE1 = resolvin E1; VIP = vasoactive intestinal peptide; (A)NP = (atrial) natriuretic peptide(s); IDO = indoleamine 2,3-dioxygenase; MMP = matrix metalloproteinase; LMw = low molecular weight; Nrf-2 = nuclear erythroid 2 p45-related factor 2; HO-1 = heme oxygenase-1; CO = carbon Monoxide; NO = nitric oxide; PD-1 = programmed death-1; CTLA-4 = cytotoxic T-lymphocyte antigen- 4; BTLA = B- and T-lymphocyte attenuator; 4-1BB = CD137; PAR = protease-activated receptor; TNF = tumor necrosis factor; Ig = immunoglobulin; Fas = CD95; gp49B = glycoprotein 49B; cAMP = cyclic adenosine monophosphate; SP = surfactant protein.

were often disappointing (36, 37). Alternative strategies for exploiting the anti-inflammatory properties of IL-10, such as drugs that stimulate the endogenous IL-10 production, might be worthwhile investigating.

Transforming growth factor- β . Another important endogenous anti-inflammatory mediator is the pluripotent cytokine and growth factor TGF- β . Transforming growth factor- β (isoforms TGF- β 1, 2 and 3) is produced by various cell types, including subsets of Treg (38). TGF- β receptor engagement activates a complex network of intracellular transduction molecules involving SMAD proteins and eventually leads to activation or inhibition of the transcription of certain genes. A detailed description of the TGF- β signalling pathway was recently reviewed elsewhere (39).

Table 2. Endogenous anti-inflammatory mediators investigated in asthma patients

Mediator class	Anti-inflammatory molecules
Cytokines	IL-10 (30, 33–37), CC10 (58, 59)
Growth factors	TGF- β (30, 38, 39, 41, 46, 48)
Lipid mediators	15-HETE (88, 89), Lipoxins (76–79), PGE ₂ (84, 85), Protectin D1 (81)
Peptides	VIP (96, 97), (A)NP (98, 101, 102)
Adipocytokines	Adiponectin (106, 107, 109)
Steroid hormones	Cortisol (105), sex hormones (111)
Metabolic enzymes	IDO (115, 116)
Proteolytic enzymes	Caspases (122)
Antioxidants	LMw (glutathione)/enzymes (SOD) (124–126)
Anorganic gases	NO, CO (132)
T cell costim. molecules	CTLA-4 (134, 135)
TNF receptors	Fas (121, 139)
Cyclic nucleotides	cAMP (144)
ECM components	Heparin (147)

The corresponding receptors of the various endogenous mediators are not mentioned in this table. Receptors are only mentioned when they can act as a mediator themselves (e.g. TNF receptors can act as co-stimulators). 15-HETE is an endogenous ligand of PPAR.

Abbreviations: IL = interleukin; TGF- β = transforming growth factor β ; 15-HETE = 15-hydroxyeicosatetraenoic acid; PGE₂ = prostaglandin E₂; VIP = vasoactive intestinal peptide; ANP = (atrial) natriuretic peptide(s); LMw = low molecular weight; SOD = superoxide dismutase; CO = carbon monoxide; NO = nitric oxide; CTLA-4 = cytotoxic T-lymphocyte antigen- 4; Fas = CD95; cAMP = cyclic adenosine monophosphate; PPAR = peroxisome proliferator-activated receptors.

TGF- β has immunosuppressive activities in both humans and mice (40) and is involved in the induction of Foxp3⁺ Treg (41), which can suppress effector T cell functions in asthma (42). A dysregulation of either TGF- β activity or Foxp3⁺ 'naturally occurring' Treg leads to various immune-pathologies among which Th-2 driven allergy (38). This is illustrated by the fact that a reduced expression and/or activity of TGF- β or TGF- β signalling pathways in experimental asthma consistently results in exacerbations (43, 44), as do TGF- β blocking antibodies (45). Moreover, gene polymorphisms in the TGF- β promoter have been associated with asthma development (34, 46).

Besides IL-10, specific immunotherapy can induce TGF- β (30), and both mediators are thought to collaborate in regulating inflammatory immune responses (47). TGF- β is also a potent pro-fibrotic factor (48), which may limit its therapeutic potential. It has been suggested that the combination of TGF- β and IL-10 may enhance the regulatory function while reducing the TGF- β -dependent fibrosis (47).

Interleukin-17. Interleukin-17 (or IL-17A) is a pleiotropic cytokine produced primarily by Th-17 cells. It has recently been reported that IL-17 possesses potent anti-inflammatory properties during established asthma in a murine model (49). The authors of this study showed that IL-17 had a dual role. While IL-17 appeared an essential factor to obtain allergic sensitization, IL-17 attenuated the eosinophilic inflammation in sensitized mice by its

effects on DC. In contrast, pro-inflammatory roles for IL-17 in allergic airway disease have also been described, in particular by enhancing neutrophilic inflammation and macrophage activation in severe neutrophilic asthma (50), as well as in mouse models (51). This is in line with the potent pro-inflammatory role of this cytokine in autoimmune diseases (52). Therefore, the precise role of IL-17 and Th-17 cells during the different stages of chronic allergic airway disease has to be delineated further (53), but one has to keep in mind its potential divergent roles in severe neutrophilic asthma compared with eosinophil-dominated forms of this disease.

Osteopontin. Osteopontin is an extracellular-matrix protein that supports adhesion and migration of inflammatory cells. It has recently been recognized as an immunoregulatory T-helper-1-type cytokine. The soluble form of this protein, Opn-s (soluble) is another cytokine with dual roles in experimental asthma, i.e. pro-inflammatory during primary sensitization and anti-inflammatory during secondary antigenic challenge. Opn-s is secreted by activated T cells and exerts its anti-inflammatory effects by influencing the DC subsets in the different stages of allergic airway disease (54). Opn-s could be an interesting therapeutic target, but its precise role in chronic human asthma will have to be investigated further. One problem with therapeutic administration of Opn-s is that this molecule has been implicated in airway remodelling and fibrosis (55).

Clara cell protein 10. The secretory Clara Cell protein 10 (CC10, also called CC16 or uteroglobin in humans) is a 10 kDa peptide secreted by the nonciliated clara cells in the airway epithelium with anti-inflammatory properties in experimental asthma. Clara Cell protein 10-deficient mice showed an aggravated pulmonary inflammation, which could be reversed by reconstitution of CC10 in these mice (56, 57). In humans, polymorphisms in the CC10 gene and lower CC10 levels have been correlated to infant wheezing (58) and increased risk of asthma (59). Moreover, it is tempting to speculate that the high-dose tolerance observed in patients allergic to the cat allergen Fel d1 could be related to the structural homology of this environmental protein with the endogenously produced CC10 molecule (60). Consequently, CC10 appears a relevant modulator of immune function in bronchial asthma.

Other cytokines. Finally, there are more cytokines with potential anti-asthma effects (Table 1). In the past, studies with interferons, IL-18 and IL-1R α had limited success (28). Moreover, IL-27 has potent anti-Th-2 effects (61) and can induce IL-10 in mice (62). Other recently identified cytokines such as IL-35 might also be promising in asthma, since it contributes to Treg function (63). These mediators all deserve further investigation before they can be coined as interesting new therapeutic agents.

Chemokines and growth factors

Chemokines. In asthma, several chemoattractants that control the migration and the activation of inflammatory cells and propagate the allergic response have been described (64). Examples are eotaxin (CCL11), RANTES (CCL5) and TARC (CCL17). Few studies have investigated the chemokines critically involved in the resolution process of an inflammatory episode. One study showed that CCL21 (CC-Chemokine Ligand 21 or Secondary Lymphoid tissue Chemokine), which is key to attract DC and T cells into the lung draining lymph nodes, and CCL19 (CC-Chemokine Ligand 19 or Epstein-Barr Ligand Chemokine), which promote DC-T cell interactions in the lymph nodes, are critically involved in the resolution murine asthma (65). These chemokines are produced in the high endothelial venules in the lung-draining lymph nodes and can bind CCR7, a receptor expressed on DC and T cells. In this manner, these chemokines direct the migration of DC and (regulatory) T cells to the lymph nodes, and this CCR7-directed migration of immune cells is crucial for the induction of tolerance (66). Therefore, modulating this chemokine pathway could open up a new strategy for asthma immunotherapy.

Galectins. One particular family of chemoattractant proteins with immune regulating properties has recently caught the attention, namely the galectins. Galectins constitute a family of β -galactoside binding lectin proteins that are secreted by various cell types, especially circulating leukocytes. Recent studies have highlighted the immunomodulatory roles of several galectins in experimental models of several diseases featuring chronic inflammation (67). In experimental asthma, both pro- and anti-inflammatory effects have been described for galectin-3 (68, 69) and galectin-9 (70, 71). In addition, these galectins also affected airway obstruction and remodelling. In spite of the conflicting results, these studies show that galectins can be important modulators of the eosinophilic airway inflammation, although little is known in humans.

Growth factors. Several growth factors modulate the allergic airway inflammation and could represent interesting therapeutic targets. Transforming growth factor- β has been discussed above. Another growth factor that reverses inflammation *in vivo* in a mouse asthma model is Fms-Like Tyrosine kinase-3 Ligand or Flt3-L (72). Administration of Flt3-L plasmid reversed hyperresponsiveness and fibrosis in a model of chronic asthma (73). Moreover, treatment of mice with Flt3-L and GM-CSF induced the tolerogenic 'plasmacytoid' or pDC in mice (74). No data are available about the effects of Flt3-L in asthma patients, but the studies in experimental models certainly warrant more research. Finally, growth factors that influence the epithelium, such as epidermal growth

factor (EGF) or keratinocyte growth factor (KGF), are molecules of interest in asthma, since the epithelial barrier function in asthma is impaired as a consequence of defective tight junction assembly. In a rat model of chronic asthma, topical administration of KGF reduced lung permeability and airway inflammation in association with a restoration of the epithelial integrity (75).

Lipid mediators

The role of endogenous lipid mediators in the resolution of inflammatory processes has recently become the focus of intense research. Anti-inflammatory properties have been described for several lipoxins, protectins, resolvins and cyclopentone prostaglandins (4–7, 76). These mediators are secreted by immune and structural cell types and can give rise to 'stop' signals during the course of an inflammatory process. Studying these lipid mediators is a research area that can lead to new treatment opportunities for asthma (77, 78).

Lipoxins. The anti-inflammatory actions of the lipoxins, a group of endogenously produced bioactive eicosanoids derived from arachidonic acid, have been described (77, 78). Lipoxin biosynthesis results from the interaction between the enzymes 5-lipoxygenase (5-LO) and 15-lipoxygenase (15-LO) and interact with a recently identified receptor, termed ALX. ALX is a G-protein coupled receptor, expressed on leukocytes and epithelial cells that transduces counter-regulatory signals. This induces intracellular presqualene diphosphate (PSDP), an inhibitory molecule that can prevent cell activation and pro-inflammatory signalling (77, 78). In patients with aspirine-sensitive and severe asthma, lipoxin synthesis is deficient (79). Moreover, inhibition of *in vitro* chemokine release by lipoxins is more effective in cells from severe asthmatics than from mild asthmatics (79). Endogenously produced lipoxins (LXA₄/LXB₄) have a very short half-life, so that stable analogues have been designed for *in vivo* testing. In experimental asthma, these analogues can reduce allergic responses (80). Thus, small molecule analogues of lipoxins, as well as PSDP, are likely to have potential as anti-asthmatic agents.

Resolvins and protectins. Recent research has also focussed on two other families of lipid agonists that control the magnitude and duration of inflammation, namely the resolvins and protectins (4–7, 76). These mediators are locally produced from omega-3 polyunsaturated fatty acids during the course of an inflammation-resolution process initiated by lipoxins and function among others by facilitating chemokine removal and proteolysis. The main sources remain to be established, but presumably they are secreted by epithelial cells and polymorphonuclear leukocytes. In asthma, it has recently been demonstrated that a prominent member of the protectin family, protectin D1, is present in lower levels in

exhaled breath condensates of patients with exacerbated asthma compared with healthy subjects. Administration of protectin D1 dampens the allergic airway inflammation and hyperresponsiveness in murine asthma models (81). Likewise, it was recently reported that intra-peritoneal administration of the anti-inflammatory and resolution phase molecule resolvin E1 (RvE1) resulted in similar effects. Taken together, these studies show that protectin D1 and RvE1 are pivotal counter-regulatory signals in allergic inflammation, making these molecules worthwhile for further investigation. Designing drugs that stimulate the receptors of these molecules, such as agonists for the RvE1-receptors chemerin receptor 23 (chemR23) and leukotriene B₄ receptor (LTB₄) (82), could be a feasible approach for future asthma treatment.

Prostaglandins. Besides the lipoxins and the resolvin/protectin family, anti-inflammatory properties have been acknowledged for a third group of lipid mediators, namely the COX-2 derived cyclopentone prostaglandins. The first prostaglandin of interest is PGD₂. Although it is well-documented that PGD₂ is a strong bronchoconstrictor and works pro-inflammatory in asthma via binding the DP2 prostanoid receptor, selective engagement of the other receptor for PGD₂, the DP1 prostanoid receptor, with a synthetic agonist in a mouse model resulted in anti-inflammatory effects (83). Whether selective stimulation of the DP1 receptor could be an interesting approach to treat asthma, is currently unknown.

A second prostaglandin of interest is PGE₂. This mediator works pro-inflammatory in various diseases in other organs. However, evidence suggests that PGE₂ limits pulmonary inflammation and controls tissue repair and fibrosis (84). The activities of PGE₂ in the lung are mediated by four prostanoid receptors (EP1–EP4), two of which (EP2 and EP4) function by augmenting the intracellular cAMP concentrations. In asthma patients, it has been shown that inhaled PGE₂ inhibits both the early and late asthmatic response (85). However, more research is needed to determine the validity of this approach.

Finally, PGI₂, also named prostacyclin, is a potent vasodilator. It possesses anti-inflammatory properties in animal models (86) via binding to the PGI₂ prostanoid receptor (IP), which is expressed on Th-2 cells. PGI₂ then acts as an anti-inflammatory substance by controlling recruitment of Th-2 cells into the inflammatory site. Moreover, PGI₂ stable analogues have been developed and can suppresses the cardinal features of asthma via inhibition of the DC function (87). 15d(deoxy)-PGI₂ is also one of the endogenous ligands for peroxisome proliferator-activated receptor (PPAR)- γ , a ligand-activated transcription factor belonging to the nuclear hormone receptor superfamily. Activation of this receptor appears a promising therapeutic approach to treat chronic inflammatory disorders (88). In general, PPAR receptors ($-\alpha$, $-\beta$, $-\gamma$, and $-\delta$) exert anti-inflammatory

actions in various inflammatory diseases when they are activated by endogenous or synthetic ligands *in vivo* (89). Stimulation of these receptors can also reduce many of the features of allergic airway inflammation in animal models (90). In addition, PPAR- γ stimulation can inhibit airway wall remodelling as well, as has recently been demonstrated in a mouse model of occupational asthma (91). Besides PGI₂, other endogenous ligands of PPAR subtypes are usually of lipoid nature and include unsaturated and saturated fatty acids, components of very low density lipoprotein (vLDL) and 15-HETE (15-hydroxyeicosatetraenoic acid). Synthetic ligands of PPAR receptors, such as the thiazolidinediones rosiglitazone and pioglitazone (PPAR- γ agonists) to treat diabetes or fenofibrate (PPAR- α agonist) to reduce cholesterol levels, have been developed and seem to have promising potential to treat chronic inflammatory conditions such as asthma as well (88).

Peptides

Neuropeptides. Vasoactive intestinal peptide (VIP) is one of the major peptide neurotransmitters abundant in the respiratory tract, where it is localized in cholinergic and sensory nerves. Upon release, it can bind to G-coupled VIP receptors (VPAC1-2 and PAC1) expressed on various cell types in the airways, including immune cells, which can ultimately lead to an increase in intracellular cAMP and an inhibitory effect on the target cell. Vasoactive intestinal peptide induces dilatation of the airways and pulmonary vessels, but its anti-inflammatory activities remain debatable (92). Nevertheless, it was recently shown that mice lacking the VIP gene developed airway hyperresponsiveness and airway inflammation which were partially reversible by VIP (93, 94). Synthetic VIP analogues also inhibit neutrophil recruitment in the rat airways *in vivo* (95). Vasoactive intestinal peptide-based long-acting synthetic compounds are tested in clinical trials (96, 97). This approach may well show to be beneficial not just for bronchodilatation, but also to treat chronic inflammation.

In addition to VIP, several other endogenous neuropeptides with anti-inflammatory properties have recently emerged as factors participating in the maintenance of immune tolerance, and their receptors could become therapeutic targets to treat various immune disorders (98). The therapeutic potential of these neuropeptides or their receptors in asthma has not yet become entirely clear.

Other peptides. Adrenomedullin, an ubiquitous anti-inflammatory peptide secreted by multiple cell types, including alveolar macrophages. Adrenomedullin is expressed in the human lung and can inhibit microvascular leakage and bronchoconstriction in animal models (99). Moreover, adrenomedullin deficiency in transgenic mice increases airway hyperresponsiveness

(100). However, little is known about the effects of adrenomedullin on chronic allergic inflammation.

Atrial natriuretic peptide (ANP) is a peptide belonging to the group of the Natriuretic Peptides (NPs). Atrial natriuretic peptide was studied in the past primarily for its cardiovascular effects. The lung is a direct site of ANP synthesis and immune cells in the lung express natriuretic peptide receptor A (NPRA). In animal models, ANP can counter-act airway hyperresponsiveness, but its effects on the Th-2 driven immune response remain a matter of debate (101). Earlier studies with inhaled ANP have also been conducted in humans, and it was found that ANP possessed bronchodilating properties, but its effects on the airway inflammation were not evaluated (102). More research is needed to assess the therapeutic relevance of modulating the system by which ANP or other NPs exert their effects.

Immune responses in asthma also generate heat-shock proteins (HSPs). Heat-shock proteins are intracellular peptides that carry out crucial housekeeping functions within a cell. They are cytoprotective molecular chaperones that ensure correct folding of proteins. Heat-shock proteins can prevent or arrest inflammatory damage when they are released from the cell under conditions of stress, such as microbial infection. Heat-shock protein-derived peptides possess immuno-regulatory properties in clinical trials in patients with rheumatoid arthritis and type I diabetes (103). Little is known about the role of the endogenous HSPs in chronic asthma, but some studies have documented anti-inflammatory properties of microbial HSP-derived peptides (exogenous HSPs) (104).

In conclusion, peptide-based treatments for bronchial asthma appear both relevant and feasible. The further development of this field can lead to new therapeutic opportunities.

Hormones and serum proteins

Hormones can regulate inflammation. One example is the beneficial effect on both Th-2 driven airway inflammation and lung function of the endogenous steroid hormone cortisol (105).

Nowadays, new interest has risen in some groups of (protein) hormones produced by fat cells, called adipocytokines. In general, the adipose tissue can profoundly influence immune responses in vertebrates, as the metabolic system and immune system are closely intertwined. In light of the epidemiologic association between asthma and obesity, the attention goes primarily to the adipocytokines adiponectin and leptin (106). The secretion of these mediators is altered in obesity, presumably contributing to decreased immune tolerance and allergy (107). While the secretion of the pro-inflammatory mediators leptin and TNF- α by fat cells is increased in obesity, the plasma concentration of adiponectin decreases. The negative correlation between adiponectin and markers of inflammation indicates an anti-inflammatory role for

adiponectin in these diseases. Moreover, adiponectin decreases airway hyperresponsiveness and inflammation in murine asthma (108) and can increase IL-10 mRNA expression and IL-10 production of human macrophages (109). Therefore, targetting the pathway by which adiponectin exerts its effects, for example its two specific receptors AdipoR1 and AdipoR2, represents an interesting novel therapeutic approach, especially in obese asthmatics.

Conflicting data exist about impact of sex hormones on the allergic airway inflammation. In animal models, it has been reported that androgens suppress the immune system, while conflicting results were obtained for progesterone and estrogens (110). Also in humans, a role for the various sex hormones in modulating the inflammation has been documented, but a straightforward interpretation about the effects of each hormone is lacking. Modulation of the actions of the various sex hormones could improve our ability to manage asthma (111), but interference with the actions of these hormones is unlikely to become a major therapeutic approach because of their obvious side effects.

Proteases and enzymes

Several enzymes belonging to different families have been implicated in tolerance induction and resolution of inflammation in experimental and clinical asthma. First of all, there are the metabolically active enzymes, such as indoleamine 2,3-dioxygenase (IDO), which is implicated in the tryptophan catabolism. Indoleamine 2,3-dioxygenase can be expressed on the surface of the tolerogenic 'plasmacytoid' or pDC in both mice and humans (112). These play a role in controlling the balance of inflammation vs tolerance either by generating regulatory T cell activity (113), inducing deletion of Ag-reactive T cells or by controlling the potential of myeloid DC to stimulate Th-2 effector cells (114). An increase in IDO activity in sputum of asthmatics using inhaled corticosteroids was recently found (115). Nevertheless, the supposed immunoregulatory role of IDO-producing DC in humans has recently been called into question and definitive proof is lacking (116).

A second group of enzymes with modulatory effects on the asthmatic response are the proteases. Stimulating or inhibiting particular protease pathways could be an interesting approach to treat chronic inflammation and remodelling, as proteases can play a role in the initiation and progression of an inflammatory response as well as in fibrosis and remodelling (117, 118). They can modulate inflammation through proteolytic (in)activation of cytokines, chemokines, growth factors and matrix components (119) and activation of PARs. These are a family of G-protein-coupled receptors activated by proteolysis that are widely expressed on leukocytes and structural cells involved in asthma and can modulate inflammation (117, 120). Activation of PAR2, for example, can suppress

eosinophilic inflammation in a rabbit model (120). Proteases can also influence the resolution of an inflammatory response. Matrix metalloproteinases 2 and 9 (gelatinases A and B) play a role in the clearance of apoptotic inflammatory cells *in vivo* (121), while the intracellular caspases regulate the apoptotic process itself. Defects of caspase-induced apoptosis in eosinophils from steroid-resistant patients may contribute to the persistence of inflammation (122). Finally, proteases could also play a role in the induction of tolerance to allergens (123).

Antioxidants

Aberrations in the oxidant/antioxidant balance in the airways can play a role in the pathogenesis of a variety of airway diseases, among which asthma and COPD (124). Oxidative stress by reactive oxygen species has been recognized as contributing to the chronic inflammation in asthma (125). In the human lung and airways, antioxidant defences include enzymatic antioxidants such as superoxide dismutase (SOD), catalase, glutathione S-transferase (GST), heme oxygenase-1 (HO-1) and thioredoxin. Nonenzymatic antioxidants include glutathione, ascorbate, α -tocopherol, uric acid and bilirubin. Individuals with asthma have decreased levels of ascorbate and α -tocopherol in bronchoalveolar lavage fluid, diminished activities of SOD and elevated oxidized glutathione disulfide/glutathione ratios, which indicates both increased oxidative stress and reduced antioxidant capacity (126). Nevertheless, the anti-inflammatory role of these molecules in the chronic eosinophilic inflammation in humans is difficult to prove. In mouse models, HO-1 (127) and glutathione (128) attenuate ovalbumin-induced airway inflammation, while disruption of the transcription factor Nrf-2 (nuclear erythroid 2 p45-related factor 2), which regulates transcription of various antioxidants, leads to the development of severe allergen-driven airway inflammation and hyperresponsiveness (129). Taken together, these studies suggest that modulating the oxidant/antioxidant balance could be a relevant adjuvant therapeutic approach in the asthma treatment.

Anorganic gases

Endogenously produced anorganic gases can modulate the allergic airway inflammation. The two most important of these gases are nitric oxide (NO) and carbon monoxide (CO). In mouse asthma models, conflicting results were obtained about the effects of NO, the nitric oxide synthase (NOS) enzymes, and the arginase enzymes (130). Endogenous NO has been reported to increase or decrease inflammation, while it is presumably a protective factor against bronchoconstriction. Nitric oxide's precise effects in asthma remains a matter of debate, and clinical trials are being performed presently testing these apparently conflicting results. Carbon monoxide attenuates aeroallergen-induced inflammation in mice (131), and is

believed to possess similar effects in humans, but because of the obvious side effects, clinical application of CO-based therapy is not a valid option (132).

Co-stimulatory molecules and cell-surface receptors

The interactions between DC and T cells take place in what has become known as the 'immunological synapse', and these interactions are crucial for both the initiation and maintenance of the allergic responses. Besides through soluble mediators, cell-cell communication takes place through cell surface molecules called co-stimulatory molecules. Some of these molecules can give a negative signal to the T cell upon ligation, resulting in a down-regulation of the Th-2 mediated inflammatory response to the allergen, tolerance induction and Treg formation or apoptosis of the T cells. These negative regulators belong either to the CD28 superfamily or to other families, such as the TNF receptor or the immunoglobulin (Ig)-like receptor superfamilies and often bear immunoreceptor tyrosine-based inhibitory (ITIM) motifs. Ligand engagement of these receptors results in an intracellular cascade that ultimately leads to a decrease in cell activation.

CD28 receptors. Negative co-stimulators belonging to the CD28 superfamily include PD-1, CTLA-4 and BTLA (133). CTLA-4 and PD-1 expression on T cells are related to tolerance induction and resolution of airway inflammation in mice (27). In humans, Treg also can express these molecules, and the potential impaired role of subpopulations of these cells in chronic inflammation in asthmatics is currently being investigated (18). Modulating these pathways of negative regulation in several ways appears a relevant therapeutic strategy. For example, intranasal delivery of the cytoplasmic domain of CTLA-4 prevents allergic inflammation in experimental asthma (134). In humans, little is known about the therapeutic effects of interfering with these pathways, although some of these molecules have been studied in clinical samples from patients (135).

TNF and Ig-like receptors. Negative regulators belonging to the TNF-receptors include 4-1BB(CD137) and the death receptor Fas(CD95) (133). In experimental asthma, 4-1BB stimulation inhibited IgE production, hyperreactivity and eosinophilia (136), while injection of agonistic anti-CD137mAb could completely reverse established allergic airway disease (137). Moreover, Fas-positive T cells regulate the resolution of inflammation in experimental asthma (138), indicating that deregulation of death receptors on human T cells could be important in the chronic nature of asthma. Therefore, immunotherapy directed at these pathways could be beneficial in the treatment of chronic Th-2 mediated disease. Of note, steroid treatment in patients can also induce apoptosis and Fas expression on peripheral leukocytes (122, 139).

Other inhibitory cell-surface receptors belong to the Ig-like receptor superfamily. The immune-inhibiting effects of members of this class of receptors in allergy are well-known (140), but few studies have assessed the effects of these receptors in classical mouse asthma models. One of these ITIM-bearing Ig-like receptors, gp49B(LILRB4), possesses anti-inflammatory effects in a mouse model of ragweed sensitization and challenge during an infection with the nematode *Ascaris suum* (141). In summary, stimulating these endogenous pathways could be a promising therapeutic approach, especially in the context of immunotherapy, but not enough is known about the safety and efficacy of interfering with these in humans.

Other

Finally, there are a number of other endogenous molecules where some early data suggest on anti-inflammatory activity in asthma, and the list (Tables 1 and 2) continues to grow. A detailed discussion about the actions and therapeutic potential of each of these molecules lies beyond the scope of this review and we will mention these only briefly. Relevant molecules include surfactant proteins (the collectins surfactant protein A and D or SP-A and SP-D) (142), intracellular cAMP, and complement factor C5a (143). Increasing the intracellular 'second messenger' cAMP levels by administration of PDE₄-inhibitors is also a potentially relevant therapeutic approach, and clinical trials are being conducted today to treat asthma patients with these drugs (144). Here, it is interesting to note that some of the mediators discussed above, such as PGE₂ and VIP, can also exert their inhibitory actions on the target cells by augmenting the intracellular cAMP concentrations.

In addition, extracellular matrix components can have anti-inflammatory effects in allergic lung disease. This has been shown in animal models for proteoglycans (syndecan-1) (145) and some of their glycosaminoglycan side chains (heparane sulphate) (146). In particular heparin (related to heparane sulphate) treatment is believed to have therapeutic potential as a future adjuvant asthma treatment (147). However, more basic research is needed about the actions of these molecules before a conclusion can be reached if these are realistic targets warranting further clinical testing.

Concluding remarks

Resolution of inflammation is, under physiological conditions, a complex process initiated by 'stop' signals. These 'stop' signals are related to the production of endogenous anti-inflammatory mediators that are reviewed here. These mediators can be produced by various cell types, including Treg, macrophages (148), structural cells such as smooth muscle cells and

fibroblasts (149), and even eosinophils (150). In chronic inflammatory conditions such as persistent asthma, the sequence of events leading to the resolution of inflammation is dysregulated. Exploiting the various endogenous anti-inflammatory pathways that exist in the human body opens up a window of opportunity for the development of new therapies for these chronic inflammatory diseases. As shown in this review (Tables 1 and 2), numerous endogenous anti-inflammatory mediators with therapeutic potential have been identified in animal models, but far less is known about these pathways in humans, and very few drugs interfering with these pathways have reached the stage of a clinical trial. Traditionally, the treatment of persistent asthma has relied on corticosteroids and has focussed on counter-acting the pro-inflammatory cellular and molecular mediators that drive the chronic inflammatory

response. Hence, the therapeutic potential of drugs that stimulate the endogenous anti-inflammatory pathways in the body to achieve better control of inflammation has been overlooked. This novel approach could therefore lead to the development of drugs that can aid in the treatment of asthma. Potentially, some of these drugs could have fewer side effects, as they rely on the body's own ability to repair.

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