Targeting cell signaling in allergic asthma

Seyyed Shamsadin Athari

Asthma is chronic inflammation of the airways characterized by airway hyper-responsiveness, wheezing, cough, and dyspnea. Asthma affects >350 million people worldwide. The Th2 immune response is a major contributor to the pathophysiology of asthma. Targeted therapy modulating cell signaling pathways can be a powerful strategy to design new drugs to treat asthma. The potential molecular pathways that can be targeted include IL-4/IL-13-JAK-STAT-MAP kinases, adiponectin-iNOS-NF-κB, PGD2-CRTH2, IFNs-RIG, Wnt/β-catenin-FAM13A, FOXC1-miR-P13K/AKT, JNK-Gal-7, Nrf2-ROS, Foxp3-RORyt, CysLTR, AMP, Fas-Fasl, PTTHp/PPARγ, PAI-1, FcεRI-LAT-SLP-76, Tim-3-Gal-9, TLRs-MyD88, PAR2, and Keap1/Nrf2/ARE. Therapeutic drugs can be designed to target one or more of these pathways to treat asthma.

Signal Transduction and Targeted Therapy (2019) 4:45; https://doi.org/10.1038/s41392-019-0079-0

INTRODUCTION

Asthma is a complex and chronic inflammatory disease of the airways characterized by airway hyper-responsiveness (AHR), eosinophilic infiltration, reversible airflow obstruction, airway remodeling, mucus hypersecretion, and goblet cell hyperplasia. The disease usually presents with wheezing, cough, and dyspnea. Allergy and atopy comprise the main causes of asthma. Genetic and environmental triggers modulating the activation and regulation of the immune system (i.e., Th2 immune response) are the main orchestrators in the pathophysiology of asthma.1,2 Asthma affects >350 million people worldwide. Owing to the heterogeneous nature of the disease, these patients usually encounter difficulties in their treatment course.3,4 Bronchial inflammation, smooth muscle spasm, and mucus production in allergic asthma are triggered by IL-4, IL-5, and IL-13, which are released by Th2 cells. IL-13 plays the main role in the excessive secretion of mucus and AHR. IL-5 participates in the activation and migration of eosinophils to airways triggering excessive secretion of mucus and AHR. IL-13 plays the main role in the production in allergic asthma are triggered by IL-4, IL-5, and IL-13, whereas the Th2-low subtype is characterized by neutrophilic inflammation. The Th2-high subtype is further associated with the predominance of type 2 cytokines (i.e., IL-4, IL-5, and IL-13). Accordingly, agents targeting the molecular participants in the Th2-high subtype (e.g., anti-IL-4, anti-IL-5, anti-IL-13, IgE blockers, and inhibitors of prostaglandin D2 (CRTH2) receptor) have recently been presented as potential drugs to treat asthma.11 Some of these targets are shown in Table 1.

The Th2-low (i.e., non-Th2-driven) inflammation includes either Th1 (IFN-γ, TNF, IL-1, and IL-6) or Th17 (IL-17A, IL-17E, IL-17F, and IL-22) responses. In addition to the aforementioned molecular targets, antagonists of C-X-C-chemokine receptor (CXCR2), suppressors of IFN-γ and IL-17, as well as peroxisome proliferator-activated receptor-γ and IL-8 can be applied as novel targeting adaptors.12-16 Therefore, either allergic (i.e., Th2 high or extrinsic) or nonallergic (i.e., Th2 low or intrinsic) asthma can be treated by targeting these cell signaling mediators. The following sections briefly introduce these signaling pathways and their molecular drivers.

IL-4/IL-13 SIGNALING PATHWAY

The receptors of allergic cytokines, including IL-4, IL-5, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP), trigger the JAK/STAT
This is the main route involved in the pathogenesis of asthma. IL-4, IL-5, and IL-13 are released by Th2 cells. IL-4 has a role in B-cell IgE isotype switching and upregulation of FcεRI on mast cells, which release histamine and other mediators that lead to allergic symptoms and smooth muscle spasm. IL-5 leads to activation, migration, and accumulation of eosinophils to the airway and initiates bronchial inflammation. IL-13 has a main role in mucus hypersecretion and goblet cell hyperplasia and promotes AHR. Therefore, a focus on the mechanisms of cell signaling that are related to asthma for designing new drugs and targeted molecules can be continued with the aforementioned parameters.

The IL-4/IL-13/STAT-6 pathway is a key modulator of asthma pathophysiology. The activation of STAT-6 can be blocked by interfering with the interaction of STAT-6-MAP kinase with ERK1/2 and p38, as well as by suppressing STAT-6 serine phosphorylation, preventing STAT-6 acetylation, and inhibiting the recruitment of the p300 transcriptional coactivator. ERK, p38 MAPK, JNK, and mTOR are serine kinases transactivating STAT-6 by phosphorylating its serine residues. Inhibitors of these adaptors can be

**Fig. 1** Asthma, a chronic inflammatory airway disease, is characterized by eosinophilic inflammation, mucus hypersecretion, goblet cell hyperplasia, airway hyper-responsiveness, and breathlessness. Th2 cell immune responses are dominant in the pathophysiology of asthma. IL-4, IL-5, and IL-13 are released by Th2 cells. IL-4 has a role in B-cell IgE isotype switching and upregulation of FcεRI on mast cells, which release histamine and other mediators that lead to allergic symptoms and smooth muscle spasm. IL-5 leads to activation, migration, and accumulation of eosinophils to the airway and initiates bronchial inflammation. IL-13 has a main role in mucus hypersecretion and goblet cell hyperplasia and promotes AHR. Therefore, a focus on the mechanisms of cell signaling that are related to asthma for designing new drugs and targeted molecules can be continued with the aforementioned parameters.

**Table 1.** Some of targeted therapies in control and treatment of asthma

| Target                  | Effects                                         | Th2high/low | References |
|-------------------------|-------------------------------------------------|-------------|------------|
| Cell surface protein    | Siglec-8 Apoptosis of eosinophils               | High        | 294,295    |
|                         | CD300a Activation of inhibitory receptor        | High        | 296        |
|                         | α4β1, α4β7 Increase blood eosinophils and inhibits their tissue accumulation | High        | 297        |
|                         | CCR3 Block chemokine-induced eosinophils        | High        | 298        |
|                         | CXCR2 Reduce neutrophils                        | Low         | 16         |
|                         | CD52 Deplete eosinophils                        | High        | 299        |
|                         | EMR1 Deplete primate eosinophils                | High        | 300        |
|                         | CRTH2 Reduce tissue eosinophils                 | High        | 301        |
| Transcription factor    | GATA3 Reduce IL-5                               | High        | 302        |
| Soluble mediator antagonist | Eotaxin-1 Inhibit eosinophil migration         | High        | 303,304    |
|                         | IgE Reduces allergic inflammation and exacerbations and airway obstruction | High        | 305,306    |
|                         | IL-4 Reduce allergic inflammation               | High        | 307,308    |
|                         | IL-13 Reduce airway obstruction and cough       | High        | 309,310    |
|                         | Interleukin-17RA Reduce Th17 response            | Low         | 311        |
|                         | TSLP Reduce eosinophils and allergic inflammation | High        | 312        |
|                         | PGD2 improved Lung function                     | High        | 313,314    |
considered as potential therapeutic agents in asthma. cAMP-response-element-binding protein-binding protein (CBP)/p300 also induces STAT-6 by phosphorylating the carboxyl terminal region of this molecule. The acetylation of STAT-6 and nuclear histones by CBP/p300 is further required for transcriptional activation of the 15-LOX-1 gene. In addition, the suppression of STAT-6 serine phosphorylation by inhibitors of p38 and MEK1/2 blocked the p300/Stat-6 interaction and suppressed IL-4/IL-13-induced expression of inflammatory chemokines such as CXCL1, CXCL3, CCL2, and CCL11 (etoxin-1). Several therapeutics have been introduced to interfere with the IL-4/IL-13/JAK/STAT-6 pathway. These include inhibitors of JAK, dimerization suppressors, phosphopeptides targeting the SH2 domain of STAT-6, decoy oligonucleotides, siRNAs, and finally synthetic small molecules.

ADIPONECTIN SIGNALING PATHWAY

As a risk factor of asthma, obesity has been associated with increased airway inflammation, AHR, oxidative stress, inducible nitric oxide synthase (iNOS) expression, and elevated nitric oxide (NO) levels. On the other hand, obesity is characterized by a reduced level of adipokine, which functions as an antiinflammatory and antioxidative mediator attenuating allergic asthma severity. Adiponectin activates adiponectin receptor 1 (AdipoR1), adiponectin receptor-2 (AdipoR2), T-cadherin, and calreticulin, which are all expressed on airway epithelial cells. Adiponectin directly interacts with AdipoR1 and 2 by activating AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha, respectively. AMPK, as a crucial energy sensor, regulates cellular metabolism (and obesity), as well as the inflammatory functions of macrophages.

Nuclear factor kappa-B (NF-kB) is a part of an important inflammatory signaling pathway. In mammalian cells, the NF-kB family has five members, including RelA (p65), RelB, c-Rel, p50/p105 (NF-kB1), and p52/p100 (NF-kB2). According to a study by Zhu et al. in 2019, adiponectin can mitigate obesity-related asthma, improve AMPK activity, and decrease iNOS, Bcl-2, and NF-kB p65 levels within the respiratory system. These researchers showed that the level of adiponectin significantly decreased in obesity-related asthma. They also suggested that exogenous adiponectin may inhibit airway inflammation and oxidative stress in obesity-related asthma.

In addition, adiponectin promotes inflammatory cell apoptosis by suppressing NF-kB- and tumor necrosis factor (TNF)-α-induced expression of anti-apoptotic Bcl-2 (which contains NF-kB-binding sites in its promoter region), as well as inhibiting p50 DNA binding and p65 transactivation subunits. Adiponectin can further relieve inflammation by decreasing TNF-α production through blocking TNF-α-induced iκB-α phosphorylation and subsequent NF-kB activation. Overall, adiponectin has a main role in the control of inflammation and antioxidant processes, especially in obesity-related asthma.

PROSTAGLANDIN D2 (PGD2) RECEPTOR SIGNALING PATHWAY

PGD2 is a proinflammatory mediator derived from arachidonic acid within the cyclooxygenase-2 (COX-2) pathway. PGD2 is released from activated immune cells, primarily from mast cells, during inflammatory reactions. PGD2 interacts with two receptors, PGD2 receptor 1 and 2 (DP1 and DP2), and can stimulate thromboxane receptors even at very low (µmol) concentrations. DP2 is a G-protein-coupled receptor also known as the chemoattractant receptor homologous molecule expressed on Th2 cells (CRTL2H), which is expressed on the membrane surface of Th2 cells, mast cells and eosinophils. The binding of PGD2 to the DP2 receptor induces proinflammatory downstream signaling pathways culminating in the activation and migration of Th2 cells and eosinophils to the inflammatory sites in asthma. Other metabolites of PGD2, such as DK-PGD2, Δ12PGJ2, 15-deoxy-Δ12,14PGD2 and deoxy-Δ12,14PGJ2, can also activate DP2 receptors. The activation of the DP2 receptor on Th2 cells upregulates the expression of IL-4, IL-5, and IL-13 in a dose-dependent manner and induces Th2 migration. DP2 activation on eosinophils, on the other hand, facilitates the migration of these cells and increases eosinophil degranulation.

In synergy with TNF-α, IL-4 enhances the expression of vascular cell adhesion molecule-1 and P selectin on vascular endothelial cells, facilitating the trans-endothelial passage of eosinophils from the blood into the respiratory system. IL-4 also stimulates the release of eotaxin, which is an eosinophil chemoattractant. IL-5 is involved in the maturation of eosinophils and inhibits apoptosis in these cells. Altogether, DP2 activation on immune cells leads to the release of IL-4, IL-5, and IL-13, which all have major roles in airway remodeling and structural damage of the pulmonary system. PGs also play important roles in allergic asthma, and their antagonists can become potent drugs for treating this condition.

Other arachidonic acid metabolites also play a role in the pathophysiology of asthma. Increased levels of leukotriene B4 (LTB4) have been demonstrated in the BAL of asthma patients. The expression of leukotriene B4 receptor 1 (BLT1) on T cells can induce IL-13 production and promote allergic responses in airways. In accordance, asthma severity has been associated with LTB4 levels.

NF-KB-INOS-COX-2 SIGNALING PATHWAY

NF-kB is a ubiquitous transcription factor activated following the phosphorylation (catalyzed by IκB kinase) and dissociation of its inhibitor kappa-B subunit alpha (IkBa). NF-kB-induced iNOS and COX-2 are important mediators in the development of pulmonary inflammation. Furthermore, the expression of both iNOS and COX-2 is increased by activated NF-kB. On the other hand, iNOS and NF-kB themselves are involved in the activation of NF-kB, which can subsequently induce other inflammatory mediators and cells. Therefore, modulating iNOS and COX-2 is necessary for controlling inflammation in the lung and airways.

INTERFERON-VIRUS PATHWAY

Type I interferons (IFN-α and IFN-β) have essential roles in antiviral immune responses. Viral infections are sensed by innate immunity through pattern recognition receptors (PRRs), including Toll-like receptor 3 (TLR3), retinoic acid-inducible protein 1 and melanoma differentiation-associated gene 5. Zhu et al. in 2018 reported low expression of IFN-α and IFN-β in the macrophages of airway epithelium and subepithelium in asthmatic patients. In respiratory viral infections such as rhinovirus, influenza, etc., deficiencies of IFN-α and β within the macrophages of airway epithelium and subepithelium correlated with the severities of the viral infection and asthma.

WNT/B-CATENIN SIGNALING PATHWAY

The Wnt signaling pathway is categorized into the canonical (β-catenin dependent) and noncanonical (β-catenin independent) pathways. In mammals, 19 members of the Wnt family have been recognized as having critical roles in regulating biological functions.
affecting airway epithelial cells. The effects of some miRNAs small noncoding RNAs have therapeutic implications in asthma by their degradation, and ultimately inhibit their translation. These genes. miRNAs target the 3′-untranslated region of mRNAs, which are involved in the posttranscriptional regulation of MicroRNAs (miRNAs) are short (~ 22 nucleotides long) noncoding RNAs that are involved in the posttranscriptional regulation of gene expression. They are characterized by their ability to bind to complementarily base paired sequences in the 3′-untranslated region of messenger RNA (mRNA) through their 5′-carboxyl terminal. miRNAs are biologically active when bound to their target mRNAs. miRNAs are involved in a variety of biological processes, including cell proliferation, differentiation, apoptosis, and cancer. Dysregulated Wnt signaling has been linked to the pathogenesis of airway remodeling in asthmatic patients. Intracellular aggregation and nuclear transfer of Wnt/β-catenin have further been involved in lung maturity and the development of airway smooth muscle precursor cells. The activation of the Wnt signaling pathway was also shown to accelerate the proliferation of airway smooth muscle cells, which are involved in airway remodeling.

The gene encoding the family with sequence similarity 13 member A (FAM13A) has also been associated with asthma. Interestingly, FAM13A regulates β-catenin stability and augments Wnt signaling in asthma. Finally, polymorphisms in two genes related to the Wnt signaling pathway, Wnt-1-inducible-signaling pathway protein-1 and Wnt inhibitory factor-1, have been related to the Wnt signaling pathway, Wnt-1-inducible-signaling pathway protein-1 and Wnt inhibitory factor-1, have been associated with persistent asthma.

Vitamin D is involved in the regulation of innate and adaptive immune responses. Vitamin D deficiency exacerbates asthma severity and reduces glucocorticoid responsiveness. The bioactive form of vitamin D (1,25(OH)2D3) also promotes the translocation of β-catenin from the nucleus to the plasma membrane, represses β-catenin-TCF-4 transcriptional activity, and finally activates the transcription of the DICKKOPF-1 gene, which encodes an extracellular Wnt inhibitor. β-Catenin is crucial for adhesion to the cytoskeleton. Furthermore, vitamin D reduces the expression of Wnt5a and β-catenin and effectively inhibits the activity of the Wnt/β-catenin signaling pathway, preventing airway remodeling in asthma. Furthermore, 1,25(OH)2D3 also inhibits the proliferation of airway smooth muscle cells and reduces the content of α-SMA. Accordingly, elevated levels of α-SMA along with increased airway wall thickness and collagen deposition are characteristics of airway remodeling.

FOX1-MIR SIGNALING PATHWAY
MicroRNAs (miRNAs) are short (~22 nucleotides long) noncoding RNAs that are involved in the posttranscriptional regulation of gene expression. miRNAs target the 3′-untranslated region of mRNAs, trigger their degradation, and ultimately inhibit their translation. These small noncoding RNAs have therapeutic implications in asthma by affecting airway epithelial cells. The effects of some miRNAs on inflammatory responses are shown in Table 2.

The phosphoinositide 3-kinase (PI3K)/AKT signaling pathway has a regulatory role in allergic asthma and could be indirectly regulated by miR-107. Forkhead box C1 (FOXC1), a hypoxia-induced transcription factor that belongs to the FOX transcription factor family, is upregulated in hypoxic lungs. Recent studies have reported that miR-200a participates in asthma pathogenesis by targeting FOXC1 through the PI3K/AKT signaling pathway. miR-200a also inhibits lung tissue fibrosis by suppressing TGF-β1-mediated endothelial-mesenchymal transition via reducing FOXC1 expression. FOXC1 activates the PI3K/AKT signaling pathway, leading to the phosphorylation and activation of several downstream proteins, such as NF-κB and GSK3-β. Cyclin D1 is an important regulator of the cell cycle activated by PI3K/AKT signaling through inhibiting p16INK4a, the cyclin D1 suppressor. Cyclin D1 participates in G1 phase of the cell cycle and induces cyclin-dependent kinase 2 (CDK2), CDK4, or CDK6. NF-κB is also a downstream molecule of the PI3K/AKT signaling pathway. The suppression of NF-κB activity through the pentaerythritol tetranitrate-Akt-IKKβ axis reduced cyclin D1 expression and suppressed cell proliferation. The recent phenomenon has therapeutic implications related to asthma by preventing proliferation and remodeling of smooth muscle cells. Accordingly, the inhibition of the PI3K/AKT signaling pathway reduced lung inflammation by decreasing the expression of IL-4, IL-6, IL-8, TNF-α, and IgE. Overall, miRNAs can have therapeutic applications in preventing asthma inflammation by modulating FOXC1 and other signaling molecules, such as PI3K, AKT, NF-κB, cyclin D1, and TGF-β1.

JNK-GAL-7 SIGNALING PATHWAY
Damage to airway epithelial cells is an important component of asthma pathogenesis. TGF-β1 has been a mediator in cellular apoptosis and injury, as well as peribronchial fibrosis and airway remodeling in asthma.

Galectin-7 (Gal-7) is a member of the galectin family. This molecule is expressed on epithelial cells and interacts with β-galactosides. The Gal-7 gene is induced by p53 and exerts proapoptotic effects. A high expression of Gal-7 has been noted in bronchial epithelium in asthma. Silencing Gal-7 was shown...
to inhibit TGF-β1-induced apoptosis in airway epithelial cells. The inhibitory effect of Gal-7 on TGF-β1-induced apoptosis has been related to the activity of caspase-3 and the induction of Bax, Bcl-2, and PARP. Gal-7 is a mitochondrial partner that can bind and inactivate Bcl-2. On the other hand, caspase-3 and its downstream substrate PARP initiate early apoptotic events. PARP cleavage is a crucial marker of the activation of functional caspases and an indicator of apoptosis in bronchial epithelial cells in asthma. Studies have shown that Gal-7 siRNA reduced caspase-3 activity, PARP cleavage, and Bax expression while increasing Bcl-2 expression. TGF-β also affects the JNK signaling pathway. JNK, a stress-activated protein kinase and a member of the mitogen-activated protein kinase (MAPK) family, has significant roles in the apoptotic

Table 2. The relationship of miRNA and inflammation response

| miRNA             | Reaction and cell differentiate                                      | Reference |
|-------------------|-----------------------------------------------------------------------|-----------|
| miRNA-223         | Neutrophils mature and differentiate                                   | 315       |
| miRNA-146, miRNA-146a | Airway epithelium, NF-kappa-B pathway                                  | 316,317   |
| miRNA-147         | TLR signaling pathway                                                 | 318       |
| miRNA-145         | Comparable to glucocorticoid treatment                                | 319       |
| miRNA-155         | TLR signaling pathway, regulation of allergic inflammation, macrophage inflammatory response, Th2 priming of dendritic cells | 320–323   |
| miRNA-21          | TLR signaling pathway, NF-κB, IL-12p35 polarization                     | 324–326   |
| miRNA-124         | M2 phenotype of monocytic cells                                       | 327       |
| miRNA-148a, miR-148b, and miR-152 | HLA-G                                                               | 328,329   |
| miRNA-126         | Th2 response, airway hyperresponsiveness                               | 330       |
| let-7             | IL-13, regulation of allergic inflammation                            | 331–333   |
| miRNA-221         | Mast cell activity regulates the production of cytokines               | 334,335   |
| miRNA-9           | Regulates steroid-resistant airway hyper-responsiveness                | 336       |
| miRNA-672, miRNA-143 | Expression of metalloproteinase                                        | 337       |
| miR-19a           | Enhances proliferation of bronchial epithelial cells by targeting TGFβR2 gene | 338       |
| miRNA-203         | Negatively regulates c-Ab1, ERK1/2 phosphorylation, and proliferation in smooth muscle cells | 339       |
| miRNA-133, miR-133a | Upregulation of RhoA in bronchial smooth muscle cells                  | 340       |
| miR-192           | Decreased expression in peripheral blood of asthmatic individuals undergoing an allergen inhalation challenge | 341       |
| miR-212, miR-132, miR-182, miR-183 | upregulated Th17 cell differentiation                                 | 342       |
| miR-106, miR-363   | downregulated Th17 cell differentiation                                | 342       |
| miR-18b, miR-106a, and miR-363-3p | expression of retinoic-related orphan receptor c (Rorc), Rora, IL-17a, and IL-17f and abolished secretion of Th17-mediated interleukin-17α (IL-17a) have declined | 342       |
| miR-18a           | targeted Smad4, Hif1α, and Rora in the Th17 cell gene expression program | 343       |
| miRNA-34/449, let-7, miRNA-19, miRNA-21 and miRNA-455 | epithelial differentiation, mucus production, airway remodeling, and inflammation as well | 344       |
| miR-146a          | modulate T-cell immunity as well as enhance class switch and secretion of IgE in B cells | 345       |
| miR-98            | suppress the expression of TSP1 (Thrombospondin 1) in the peripheral B cells | 330       |
| miR-221           | Upregulated expression promotes IgE-mediated activation of mast cell degranulation by PI3K/Akt/PLCγ2/Ca2+ signaling pathway | 346       |
| miR-223           | Downregulation promotes degranulation via the PI3K/Akt pathway by targeting IGF-1R in mast cells  | 336       |
| miRNA-33b         | Overexpression leads the mast cell degranulation was inhibited         | 347       |
| miR-221           | Overexpression leads stimulated IL-4 secretion in mast cells through a pathway involving PTEN, p38, and NF-kappa-B | 348       |
| miR-223           | reduces IL-6 secretion in mast cells by inhibiting the IGF-1R/PI3K signaling pathway | 349       |
| miR-23b           | induces tolerogenic DC and Treg through the inhibition of the Notch1 and NF-kB signaling pathways | 350       |
| miR-21            | regulates the Th1 and Th2 balance by targeting IL-12p35 expression and overexpression promotes differentiation of Th2 | 351,352   |
| miR-139-5p, -15b-5p, 186-5p, 342-3p, 374a-5p, 409-3p, 454-3p, 660-5p, and 942-5p | lung function parameters (in males only) | 353–355   |
| miR-1290, -142-3p, and 191-5p with alone | lung function parameters (in females only) | 356       |
| miR-296-5p, -548b-5p, -138-5p, -16-5p, -1227-3p, -30d-5p, -203a-3p and -128-3p | decreasing airway hyper-responsiveness | 356       |
| miR-143-3p        | was shown to control TGF-b1-induced cell proliferation               | 357,358   |
| miR-181b-5p       | was associated with airway eosinophilic inflammation by targeting osteopontin | 152,359   |
| miR-223-3p, -142-3p and -629-3p | neutrophilic airway inflammation of the severe asthma | 360–362   |
process and airway remodeling in asthma by inducing the Wnt5a/JNK signaling pathway. TGF-β1 stimulates JNK, which phosphorylates its substrate Jun, at serine residues 63 and 73. On the other hand, silencing Gal-7 suppresses JNK activation and ameliorates bronchial epithelial cell injury, presenting a potential target for treating asthma.

NRF2-ROS SIGNALING PATHWAY

Reactive oxygen species (ROS) have been associated with airway inflammation and asthma. In airways, epithelial cells and neutrophils are the main sources of ROS. The nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor is a main regulator of oxidative stress, as well as pulmonary erythroid 2-related factor 2 (Nrf2) transcription factor is a main quinone oxidoreductase (NQO1) and hemeoxygenase (HO-1). In addition, chronic inflammation promotes Nrf2-induced TGF-β expression, which also has a main role in the progression of pulmonary fibrosis. Suppressing upstream signaling pathways leading to ROS production, therefore has potential therapeutic implications in asthma.

FOXP3-RORγT SIGNALING PATHWAY

The proportion of CD4+CD25+ Treg cells is decreased in the peripheral blood of asthmatic patients. Some studies have noted that the imbalance of Treg/Th17 correlated with the severity of asthma. Fork-like transcription factor 3 (Foxp3) is a key transcription factor regulating Treg function and development. Differentiation of Th17 cells, on the other hand, is regulated by the nuclear orphan receptor γt (RORγt). Accordingly, the balance between Foxp3 and RORγt regulates the Treg/Th17 ratio.

Long noncoding RNAs (IncRNAs) are ~200-nucleotide-long RNAs involved in the pathogenesis of airway inflammation and asthma. IncRNAs participate in posttranscriptional regulation of various target genes and proteins. IncRNAs can act as competing endogenous RNAs (ceRNAs) to bind to complementary microRNAs and prevent them from binding to their target mRNA. In asthma, IncRNAs (i.e., ceRNAs) indirectly affect the levels of Foxp3 and RORγt by targeting their specific miRNAs and therefore contribute to the Treg/Th17 imbalance, which is a hallmark of asthma pathogenesis. Although IncRNAs can regulate the Treg/Th17 balance, other potential mechanisms still need to be investigated. In conclusion, miRNAs and IncRNAs are potential regulators of immunological responses in asthma and can have potential applications in the treatment and diagnosis of this disease.

MAPK-NF-κB SIGNALING PATHWAY

The NF-κB and MAPK signaling pathways regulate inflammation and immune responses in asthma by controlling the gene expression of inflammatory factors such as TNF-α and IL-6. In asthma, the NF-κB signaling pathway, and phosphorylation of ERK, JNK, and P38 MAPK (i.e., activation of the MAPK signaling pathway) can control the production of IGE and IL-4 and inhibit inflammatory mediators in asthma.

CYSLTR SIGNALING PATHWAYS

Some evidence has shown that cysteiny1 leukotrienes (CysLTs) and their receptors are among the major contributors in allergic asthma. There are two types of CysLT receptors, namely, CysLTR1 and CysLTR2, which belong to the G-protein-coupled receptor family. CysLT C4, D4, and E4 have been reported to modulate airway inflammation and remodeling. Despite its low affinity for CysLTR1 and 2, CysLT E4 is the most potent mediator evoking the influx of eosinophils and basophils and enhancing AHR and mucus secretion. Although montelukast and pranlukast are two antagonists of CysLTR1 and 2, there are no known antagonists for CysLT E4. The 2-oxoglutarate receptor 1 or GPR99 is a novel receptor for CysLT E4, and its activation increases vascular permeability independent of the CysLTR1/CysLTR2 pathway.

P2Y12R is another modulator of CysLT E4-induced eosinophil degranulation and airway inflammation. Antagonists of P2Y12R suppress CysLT E4-induced eosinophil degranulation and inflammation in asthma and can be new candidates for managing inflammation and bronchoconstriction in this condition.

CAMP SIGNALING PATHWAYS

Cyclic 3′5′-adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are two main regulators of inflammation. Intracellular depletion of cAMP and cGMP following their hydrolysis by phosphodiesterase (PDE) enzymes augments inflammatory responses. In this regard, the suppression of PDE4, a subtype of PDE enzyme that is expressed in leukocytes, has promoted antiinflammatory effects in asthma. cAMP is also a negative regulator of T-cell activation. In this regard, PDE4 inhibitors have suppressed cytokine production by T cells, as well as biomarkers of type 2 inflammation such as perioxidin and serpinB2 in asthma. Controlling Th2-mediated responses (i.e., the production of IL-4, IL-5, and IL-13) can have a potential therapeutic role in allergic asthma.

The activation of the costimulatory receptor CD28 induces PDE4, resulting in the hydrolysis of cAMP, the induction of NF-κB, activator protein-1 (AP-1) and NFAT, as well as the activation and proliferation of T cells. In addition, some studies showed that the level of the negative regulator of glucocorticoid receptor (GR) GRβ increased in corticosteroid-resistant asthmatic patients. The attenuated function of histone deacetylase 2 (HDAC2) further decreased GR activity, providing another corticosteroid resistance mechanism in asthma. Surpassing these glucocorticoid resistance mechanisms can be helpful in treating asthma.

β2-Agonists, which are commonly used to treat asthma, act by binding to β2-adrenoceptors (β2-AR), culminating in the activation of certain G-proteins and the generation of cAMP, which promotes smooth muscle relaxation and bronchodilation in airways. Similar to G-protein-coupled receptors (GPCRs), β2-AR has seven transmembrane-spanning α-helices (i.e., hepta-helical domains). This receptor couples with the Gs as a stimulatory G-protein, which is a trimeric complex consisting of one A subunit that induces adenylyl cyclase (AC) and two B subunits transducing other signals. The A subunit further activates AC, and AC catalyzes the conversion of ATP to cAMP. Subsequently, cAMP phosphorylates protein kinase A (PKA), which in turn phosphorylates other regulatory proteins involved in airway smooth muscle spasm, regulation of intracellular calcium, and bronchodilation. Nevertheless, some studies have proposed that the relaxation effect of β2-agonists might be directly mediated through the interaction of Gs with potassium channels on the plasma membrane of airway smooth muscle cells (i.e., cAMP independent pathway).

Overall, the β2-AR pathway provides another viable therapeutic target in asthma.
patients and correlated with asthma severity. Fas has also been described to regulate Th2-mediated inflammation.178–180 Fas initiates two apoptotic and nonapoptotic signaling cascades.181,182 In the apoptosis pathway, Fas ligation changes its conformational structure, allowing signaling molecules (i.e., FADD, cFLIP, and procaspase-8) to bind to the intracellular C-terminal signaling death domain of the receptor.183 The recruitment of these proteins leads to the formation of the death-inducing signaling complex, which induces the internalization of the receptor, and apoptotic reactions ensure via either caspase- or mitochondrial-mediated cascades. The Fas-mediated nonapoptotic signaling pathway involves a variety of signaling cascades independent of the death-promoting pathway.184 Fas-mediated FADD triggers the MAPK signaling cascade, which subsequently induces NF-kB translocation, as well as cell proliferation and migration.185–187 The manipulation of the Fas signaling pathway also modulates JNK, NF-kB, p38, and nonapoptotic Fas signaling pathways via both ERK1/2 and p35.185,186 Studies have described that Th2 cells are resistant to Fas-mediated apoptosis and NF-kB activation following attachment of FasL. The resistance of Th2 cells to FasL-mediated apoptosis has been attributed to the augmented baseline activities of FLIP, TRAIL, and NF-kB in these cells.189,190

Fas-mediated nonapoptotic pathways triggered by Th2 cells may also contribute to lung inflammation. Modulating Fas signaling in Th2 cells is necessary for suppressing type 2 inflammation; however, discerning Fas signaling triggered by Th2 cells is difficult from the signaling pathway originating from other T-cell populations (Fig. 4).190 Nonetheless, using antagonists to target Fas-FasL pathways may negatively affect the function of other immune cells, and more studies are warranted to resolve this issue.
in asthma. Focusing on PAI-1 antagonists can be a viable therapeutic strategy in ECM components.\textsuperscript{193,194} PAI-1 can inhibit both t-PA and u-PA. Function and inhibit dyspnea, they can modulate the PTHrP–PPAR pathway, resulting in pulmonary dysfunction, especially in allergic asthma.\textsuperscript{191,192} Downregulation of PPAR\textsubscript{γ} further promotes downstream adipocyte differentiation-related protein and induces lipofibroblasts and ATII cells to absorb triglycerides and secrete leptin. After the binding of leptin to ATII cells, surfactant is produced to ensure normal lung function.\textsuperscript{191,192} Although PPAR\textsubscript{γ} agonists can support normal lung function and inhibit dyspnea, they can modulate the PTHrP–PPAR\textsubscript{γ} pathway, resulting in pulmonary dysfunction, especially in allergic asthma.

**PAI-1 SIGNALING PATHWAY**

Plasminogen activator inhibitor-1 (PAI-1) has been associated with asthma severity and airway remodeling. Tissue-type plasminogen activator (t-PA) or urokinase type PA (u-PA) converts plasminogen to plasmin. Plasminogen activators are involved in the dissolution of fibrin polymers and the degradation of extracellular matrix (ECM) components.\textsuperscript{193,194} PAI-1 can inhibit both t-PA and u-PA. PAI-1 deficiency prevents ECM deposition and reduces airway inflammation and remodeling, as well as AHR.\textsuperscript{195,196} Therefore, focusing on PAI-1 antagonists can be a viable therapeutic strategy in asthma.

**PTHRP/PPAR\textsubscript{γ} SIGNALING PATHWAY**

Parathyroid-hormone-related protein (PTHRP) and prostaglandin E2 are secreted by alveolar type II (ATII) cells in the physiological state. Peroxisome proliferator-activated receptor gamma (PPAR\textsubscript{γ}) (also known as glitazone receptor or nuclear receptor subfamily 3, group C, member 3- NR1C3-) is a type II nuclear receptor. The PTHrP/PPAR\textsubscript{γ} signaling pathway has been reported to participate in nicotine-induced pulmonary dysplasia in offspring.\textsuperscript{189}

Binding of PPAR\textsubscript{γ} to PTHrP induces the transformation of lung fibroblasts into lipofibroblasts by absorbing neutral lipids. This interaction also upregulates PPAR\textsubscript{γ} via activation of protein kinase A (PKA). PPAR\textsubscript{γ} further promotes downstream adipocyte differentiation-related protein and induces lipofibroblasts and ATII cells to absorb triglycerides and secrete leptin. After the binding of leptin to ATII cells, surfactant is produced to ensure normal lung function.\textsuperscript{191,192} Although PPAR\textsubscript{γ} agonists can support normal lung function and inhibit dyspnea, they can modulate the PTHrP–PPAR\textsubscript{γ} pathway, resulting in pulmonary dysfunction, especially in allergic asthma.

**FCCR\textsubscript{ε} SIGNALING PATHWAY**

Basophils express high-affinity IgE receptor (FCCR\textsubscript{ε}) on their plasma membrane. The activation of FCCR\textsubscript{ε} leads to the release of chemical mediators such as histamine. Basophils drive the differentiation of naive T cells to Th2 cells in lymph nodes by producing TSLP and IL-4 in response to protease allergens. Basophils also augment humoral memory responses through stimulation of memory B and T cells.\textsuperscript{197–200} Mast cells also play an important role in allergy by releasing histamine and other mediators after activation by IgE-allergen complexes that bind to FCCR\textsubscript{ε} on these cells. The attachment of IgE-allergen immune complexes to FCCR\textsubscript{ε} activates tyrosine kinases such as Lyn, Fyn, and Syk that subsequently phosphorylate a variety of signaling molecules such as LAT, SLP-76, and PLC-γ1 and lead to mast cell degranulation. The granules of mast cells contain a variety of highly active mediators, including histamine, prostaglandins, leukotrienes, heparin, serotonin, inflammatory cytokines (such as IL-6, TNF-α, MCP-1, etc.), and neutral proteases.\textsuperscript{201–204}

FCCR\textsubscript{ε}–mediated signaling enhances the phosphorylation of Syk, LAT, SLP-76, PLC-γ1, Akt, and ERK1/2 or p38. Following the aggregation of FCCR\textsubscript{ε}–IgE–allergen complexes and the activation of Src family kinases (such as Fyn, Lyn, and Syk), downstream signaling molecules (such as LAT and SLP-76) are phosphorylated and activated. After being phosphorylated, LAT binds to Grb2, Gads, PLC-γ1, and the guanine exchange factors, VAV and SOS, leading to the activation of PI3K and MAPK-dependent pathways and production of inflammatory cytokines (Fig. 5).\textsuperscript{201,203,205} In general, pathways involved in the activation of mast cells are potential targets to design effective drugs to control allergic asthma attacks.

The proliferation and differentiation of Th2 cells require the AP-1 transcription factor and JunB. Ap1 is activated through the MAPK pathway, whereas JunB is a part of a trimerolecular complex comprising basic leucine zipper ATF-like and interferon regulatory factor 4.\textsuperscript{206,207} Th2 cells induce the production of IgE by B cells
through the action of IL-4. IgE-mediated cross-linking of FceRI further activates mast cells. The Lyn, Fyn, and Syk kinases further phosphorylate and activate the LAT adaptor molecule following FceRI aggregation. This event results in the binding of cytosolic adaptor molecules, including SLP-76, GRB2, SOS VAV, and PLCγ1, to the LAT. The activation of these molecules then leads to the recruitment of more downstream molecules, the degranulation of mast cells, and the release of cytokines and eicosanoids. The phosphorylation of Src family kinases such as Fyn and Lyn recruits Syk kinase, which in turn phosphorylates some cellular target proteins and activates multiple signaling pathways. Syk is an intracellular tyrosine kinase and a key regulator of inflammatory cells. In accordance, Syk antagonists exude potent anti-inflammatory effects.

**TIM-3–Gal-9 SIGNALING PATHWAY**

During inflammation, macrophages differentiate into two subtypes: M1 (i.e., classically activated) and M2 (i.e., alternatively activated). M1 macrophages express CD86, secrete proinflammatory cytokines, and activate iNOS to promote inflammatory responses. M2 macrophages, on the other hand, express CD206 and are involved in immune regulation and tolerance. M2 macrophages also promote tissue repair and release anti-inflammatory cytokines, as well as Arginase-1.10,11,12

T-cell immunoglobulin mucin 3 (Tim-3) is an immunomodulatory molecule highly expressed on Th1 cells and cytotoxic T cells. Tim-3 induces apoptosis in Th1 and cytotoxic T cells and regulates the function of NK cells. M2 macrophages and macrophages. Galectin-9 (Gal-9) is a ligand of Tim-3 that activates NF-κB and regulates inflammatory cytokine genes, while the TRIF-dependent pathway leads to the production of proinflammatory cytokines, while in M2 macrophages, the recruitment of this pathway leads to the induction of anti-inflammatory cytokines. Therefore, M2 macrophages can be specifically targeted to alleviate inflammation in asthma.

In allergic diseases, eosinophils can be recruited by IL-4 and IL-10-stimulated M2 macrophages. Eosinophils in turn can reduce inflammation by accelerating the polarization of M2 cells via IL-4 and IL-13 and by inhibiting the NF-κB/P38 MAPK signaling pathway.21,22 IKK phosphorylates IkB, which subsequently undergoes ubiquitylation and degradation, inducing NF-κB and inflammatory reactions.23,24 The elevated expression levels of p-IκB and p-P38 in eosinophils shift the polarization of macrophages from M1 to M2 and decrease inflammation via reducing TNF-α, IL-6, and IL-12 levels, as well as the number of CD68-positive macrophages.25 On the other hand, eosinophils can also trigger type 2 inflammation, which is the main pathological process in allergic asthma.

Type 2 cytokines, such as IL-5 and IL-33, increase the numbers of eosinophils and M2 macrophages. In addition, eosinophils respond to these cytokines by decreasing the expression of CD68, iNOS, TNF-α, IL-6, and IL-12 and increasing CD163, Arg-1, TGF-β, IL-10, and IL-13.26-28 Therefore, attention should be dedicated to eosinophils as important contributors to the pathogenesis of allergic asthma.

The development of eosinophils requires IL-5. The receptor of IL-5 shares a common β-chain that is also expressed in IL-3 and GM-CSF receptors. In this regard, studies demonstrated that GM-CSF signaling promoted the recruitment of eosinophils to asthmatic lungs. Likewise, deficiencies of either GM-CSF or its receptor (GM-CSFR) led to pulmonary alveolar proteinosis. GM-CSF directly controls granulocyte trafficking and induces chemokines of eosinophils (such as eotaxins) within allergic lungs.29-32 Therefore, GM-CSF can be a potential factor in designing new drugs against asthma.

**TLR SIGNALING PATHWAYS**

In atopic individuals, antigen presenting cells, especially dendritic cells (DCs), recognize allergens. After migration to lymph nodes, these cells present antigens to naïve CD4 T cells and induce their differentiation into Th2 cells. The Th2 immune response is associated with the pathogenesis and progression of allergic asthma.233,234 In this process, toll-like receptors (TLRs) and NF-κB play important roles. TLRs recognize antigens through pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). TLR signaling pathways activate NF-κB (via IKKα/IKKβ), AP-1 (via MAPKs), and IRF 3 (via TBK1, IKKe, and IKKα).235-238 Genetic polymorphisms and mutations in genes related to TLR signaling pathways such as NOD1, NOD2, IL1RL1, MAP3K7IP1, and BPI have been related to the development of asthma.

Signaling pathways triggered by TLRs following antigen recognition through PAMPs or DAMPs induce cytokines, chemokines, and costimulatory molecules. The activation of TLRs causes conformational changes in the TLR domain and allows the recruitment of cytoplasmic adapter proteins such as TIR domain-containing adaptor protein (TIRAP, MAL), myeloid differentiation primary response protein MyD88 (MyD88), TIR domain-containing adapter-inducing interferon-β (TRIF, TICAM1) and TRAM that anchor the TIR domain.239,240 Based on the recruited adapter proteins, TLR signaling pathways have been classified into two distinct categories: MyD88-dependent (in all TLRs except TLR3) and MyD88-independent (also known as the TIR domain-containing adapter-inducing interferon-β (TRIF)-dependent pathway). The MyD88-dependent pathway activates NF-κB and mitogen-activated protein (MAP) kinases, inducing the expression of inflammatory cytokine genes, while the TRIF-dependent pathway activates NF-κB, IRF 3 and MAPKs inducing type I interferons and inflammatory cytokines.241

In association with Syk tyrosine kinase, the suppressor of cytokine signaling 1 and casitas B lineage lymphoma-b (Cbl-b) regulate MyD88-dependent pathways. On the other hand, sterile α- and armadillo-motif-containing protein and its splice variant TAG are regulators of the TRIF-dependent pathway.241-244 NF-κB is an important mediator involved in inflammation and can be a potent target for developing novel therapeutics to control and treat asthma.

The stimulation of TLRs in airways induces local inflammation via the recruitment of innate and adaptive immune cells. TLRs have main roles in priming cells involved in regulating innate immunity and cytokine release. Therefore, TLRs can act as novel vaccines against allergic asthma.245,246

**PAR2 SIGNALING PATHWAYS**

Protease-activated receptor-2 (PAR2) participates in bronchodilation in asthma. This molecule has been explored as a therapeutic target in asthma. Similar to β2-AR, PAR2 triggers intracellular signaling through G-protein-dependent mechanisms.247-249 Therefore, designing specific ligands to target this pathway can present therapeutic implications in asthma.
β-Arrestins are adaptor proteins recruited by GPCRs to promote receptor desensitization and internalization. These adaptor proteins can also trigger G-protein-independent signals through uncoupling GPCRs from their cognate heterotrimeric Gα subunits and decreasing their responsiveness to agonistic stimulation. Regarding β-arrestin-dependent signaling, G-protein signaling is a downstream pathway. In other words, β-arrestins can turn off G-protein-induced signal transduction. Furthermore, β-arrestins can promote inflammatory signals as well.

Inducing β2-AR using agonists recruits Gas and stimulates membrane-bound adenyl cyclase. This leads to cAMP generation and activates cAMP-dependent protein kinase (PKA), which in turn promotes the relaxation of airway smooth muscle cells through phosphorylation of cross-bridge cycling regulatory proteins. β2-AR also mediates cellular responses via Gαi-induced generation of cGMP and intracellular elevation of Ca2+. Nevertheless, the cAMP/PKA pathway remains the predominant mechanism in the relaxation of airway smooth muscle cells.

KEAP1/NRF2/ARE SIGNALING PATHWAYS
As mentioned, the NF-κB, MAPK, and JAK-STAT (signal transducers and activators of transcription) signaling pathways are involved in the development of inflammation. On the other hand, the
Table 3. Signaling Pathways, related targets, and molecules are interacted in asthma pathophysiology

| Pathway       | Related molecules and actions | References |
|---------------|------------------------------|------------|
| JAK-STAT     | IL-4, IL-5, IL-13, IL-31 and TSLP | 17–21 |
| Adiponectin   | AMPK and NF-κB                | 43–45,50   |
| Prostaglandin | CRTH2 and LTB4                | 58,61,62,80,82 |
| NF-κB         | iNOS and COX-2                | 85,86,88,93 |
| Type I interferon | PRRs, TLR, RIG-1 and MDAS | 89,91,93   |
| Wnt           | WISP-1 and WIF-1              | 94,95,98,101,102 |
| PI3K/akt      | miRs                         | 111,112,114,118 |
| JNK-Gal-7     | TGF-β                         | 133,134,136,137,139 |
| Nrf2          | RO5                                | 140,142,144 |
| Foxp3- RORγt  | LncRs ceRs and miRs           | 146,147,149,152,153 |
| MAPK          | IgE and IL-4                  | 155,158   |
| CysLT         | eosinophil degranulation       | 162,164,166 |
| cAMP          | IL-4, 5, 13 and J2-AR          | 165,171,176 |
| Fas           | apoptotic Fas signaling: JNK, NF-κB, p38 | 185,186,188,189 |
| PTH/P/PPARγ   | Leptin                        | 191,192   |
| PAI-1         | t-PA, u-PA, ECM and remodeling | 193,195,196 |
| Fcr/R1        | TSLP, IL-3, IgE and mast cell degranulation | 197,199,202–204 |
| Tim-3-Gal-9   | PI3K/Akt, Th1 apoptosis and inflammation | 214,216,219,220 |
| TLRs          | NF-κB, AP-1, IRF, SOCS1 and MyD88 | 235,236,241,243,244 and 268 |
| PAR2          | b-Arrestins, cAMP/PKA         | 248,254,255 |
| Keap1/Nrf2/ARE | CHD6, CBP, ARE               | 256,258,265,268,270 |
| Ca            | PLCb, ROCK, RhoA             | 277,278,280,281 |

transcription factor Nrf2 (NF-E2 p45-related factor 2) regulates the expression of anti-inflammatory and antioxidant NADPH, NAD(P)H quinone oxidoreductase 1, glutathione peroxidase, ferritin, hemeoxygenase-1 (HO-1) and other detoxifying enzyme genes.256–259

Nrf2 belongs to the Cap ‘n’ Collar (CNC) subfamily and comprises seven functional domains: Neh (Nrf2-ECH homology) 1–7. Neh1, as a CNC-bZIP domain, permits Nrf2 to heterodimerize with the small musculoaponeurotic fibrosarcoma (Maf) protein and to form a nuclear complex with the UbcM2 ubiquitin-conjugating enzyme.260,261 The Neh2 domain contains two motifs (i.e., DLG and ETGE), which are essential for the interaction between Nrf2 and its negative regulator, Kelch-like ECH associated protein (Keap1).262,263 The carboxy-terminus of the Neh3 domain, on the other hand, has a role as the transcriptional domain and interacts with the transcription activator chromo-ATPase/helicase DNA-binding protein (CHD6). Neh4 and Neh5 are also transcriptional domains that bind to another transcriptional activator, CBP. The interaction between Neh4 and Neh5 with the nuclear cofactor RAC3/AIB1/SRC-3 enhances the expression of antioxidant response element (ARE)-containing genes. Neh5 also regulates the cellular localization of Nrf2 through a redox-sensitive nuclear-export signal motif.264–266

Keap1 is an adapter of cullin-based E3 ubiquitin ligase that suppresses the transcriptional activity of Nrf2 via inducing its ubiquitination and proteasomal degradation. The KELCH domain of the Keap1 homodimer binds to the DLG and ETGE motifs (ETGE acts as a hinge, and DLG acts as a latch) of the Neh2 domain of Nrf2 in the cytosol.267,268 Under oxidative stress conditions, Nrf2 dissociates from Keap1 following thiol modifications of its cysteine residues, preventing Nrf2 ubiquitination and proteasomal degradation. Nrf2 then translocates into the nucleus and heterodimerizes with small Maf proteins to transactivate genes containing ARE.269,270

The β-transducin repeat-containing protein (β-TrCP) presents another regulating mechanism of Nrf2. The β-TrCP binds to two motifs (i.e., DSG15 and DSAPGS) within the serine-rich Neh6 domain of Nrf2. β-TrCP is a substrate receptor of the Skp1-Cul1-Rbx1/Roc1 ubiquitin ligase complex and therefore targets Nrf2 for ubiquitination and proteasomal degradation. Glycogen synthase kinase-3, as a regulator of Nrf2, phosphorylates Nrf2 on the Neh6 domain to facilitate the attachment of β-TrCP and recognition of Nrf2 by the ubiquitin ligase complex.271,272 These pathways can be manipulated using agonists/antagonists, as well as molecular adaptors such as miRNAs to alleviate inflammatory reactions.

HO-1 is an inducible enzyme catalyzing the degradation of heme into carbon monoxide (CO) and free iron. HO-1 also promotes the degradation of biliverdin to bilirubin. The degradation of free heme as a proinflammatory mediator indicates the antioxidant effects, such as PAMPs, ROS, and DAMPs, through its PRR. The activation of the NLRP3 inflammasome mediates the cleavage of caspase-1 and the secretion of the IL-1β proinflammatory cytokine, ultimately inducing cell death through a process known as pyroptosis. Nrf2 negatively regulates the NLRP3 inflammasome through NQO1 expression. Furthermore, NQO1 inhibits the cleavage of caspase-1 and the production of IL-1β.273–276 The efficacy of Nrf2 activators in treating asthma is unclear and should be divulged in future studies.

CA2+ SIGNALING PATHWAYS

GPCR agonists and calcium (Ca2+)-dependent and -independent pathways modulate airway smooth muscle spasm. In the Ca2+-dependent pathway, phospholipase b generates the inositol trisphosphate (IP3) that binds to the IP3 receptor on the sarcoplasmic reticulum (SR) and induces Ca2+ release to the cytosol. Intracellular Ca2+ then induces calmodulin and myosin light chain kinase to phosphorylate myosin light chain and activate actin-myosin cross-bridge cycling, leading to smooth muscle spasm. In parallel with the mentioned pathway, CD38 expression evokes the generation of cyclic ADP-ribose, which binds to the ryanoide receptor and promotes the release of Ca2+ from the SR. On the other hand, the sarco/endoplasmic reticulum calcium ATPase refills the SR with cytosolic Ca2+ and inhibits smooth muscle spasm. In allergic reactions, methacholine, histamine, thrombin, and leukotriene D4 have elicited Ca2+ release to the cytosol.21

Intracellular Ca2+ plays a key role in degranulation and the secretion of the IL-1β, AP-1, IRF, SOCS1 and MyD88.275,276 The activation of the NLRP3 inflammasome mediates the cleavage of caspase-1 and the secretion of the IL-1β proinflammatory cytokine, ultimately inducing cell death through a process known as pyroptosis. Nrf2 negatively regulates the NLRP3 inflammasome through NQO1 expression. Furthermore, NQO1 inhibits the cleavage of caspase-1 and the production of IL-1β.273–276 The efficacy of Nrf2 activators in treating asthma is unclear and should be divulged in future studies.

After the release of intracellular Ca2+, cell surface channels facilitate the refilling of cytosolic stores by extracellular Ca2+. In this regard, the activation of Orai/STIM as well as store-operated Ca2+ entry pathways mediates Ca2+ influx through plasma membrane channels following the depletion of intracellular Ca2+ stores via IP3 receptor-mediated Ca2+ release from the SR.277

The Ca2+-independent pathway is mediated through the activation of RhoA and the stimulation of Rho kinase, which phosphorylates and inactivates the myosin light chain.
phosphatase target subunit. Under resting conditions, MYPT1 limits smooth muscle spasm (Fig. 6); therefore, activating MYPT1 during asthma attacks can be beneficial for controlling dyspnea.

IL-13 is overexpressed during allergic asthma attacks, augmenting canonical calcium mobilization pathways, enhancing calcium sensitization, and aggravating asthma presentation. In addition, suppression of RhoA has been reported to relax airway smooth muscles. These modulators can be useful in alleviating and treating asthma symptoms.

LIMITATIONS OF THE THERAPEUTIC TARGETING OF CELL SIGNALING PATHWAYS
There are some concerns regarding the therapeutic targeting of cell signaling pathways. First, targeting one pathway can affect the function of other signaling pathways (i.e., a pleiotropic phenomenon). On the other hand, blocking or activating a specific pathway may augment the compensatory functions of other signaling pathways, thus counteracting the therapeutic effects of the interference (i.e., redundancy function). Specifically, these problems are highlighted when targeting cytokine pathways. One solution may be targeting the last molecule within the signaling pathway.

For example, mucus secretion is mediated by the induction of the MUC5AC gene in goblet cells through several independent pathways, including the CLCA1 (a Serpin)- and 15-lipoxygenase-1-dependent pathways. These pathways are activated following the binding of IL-13 to its receptor and the phosphorylation and translocation of STAT-6 to the nucleus. The SPDEF transcription factor is another regulator of goblet cell differentiation by inhibiting FOXA2 and activating other genes in these cells. Another mechanism regulating mucus secretion through the STAT-6 pathway involves the protein calcium-activated chloride channel 1 (CLCA1). CLCA1 can induce MUC5AC gene expression via the MAP kinase pathway and MAPK13 (p38δ-MAPK). IL-13-mediated STAT-6 activation increases the expression of SAM-pointed domain-containing Ets-like factor (SPDEF), which also shares an important role in regulating mucus production. The activity of SPDEF, however, is also modulated in part by FOXM1, a member of the Forkhead box (FOX) family. This indicates that therapeutic targeting of STAT-6 affects different pathways. The complicated nature of the cellular signaling network presents a major challenge in designing new drugs to target signaling molecules.

The expression of the MUC5AC gene in airways is also regulated by signaling triggered by epidermal growth factor receptor (EGFR). Nevertheless, EGFR has multiple ligands (e.g., EGF, heparin-binding EGF, β-cellulin, amphiregulin, epiiregulin, and TGF-α). Binding of these ligands, on the other hand, activates the EGFR kinase domain and induces signaling cascades, leading to the expression of the MUC5AC gene. The EGFR signaling cascade is initiated by the activation of the PKC δ and PKC θ isoforms. EGFR ligand binding also activates the Ras–Raf–MEK1/2–ERK1/2 pathway, which ultimately leads to the expression of MUC5AC via the Sp1 transcription factor. Based on these findings, the Sp1 transcription factor represents a potential target to promote mucus production. On the other hand, blocking mucus production by silencing the IL-13 pathway can be compensated by the EGFR-dependent pathway (Fig. 7, Table 3, and Table 4). Notch is a transmembrane receptor that binds to ligands from the Delta-like and Jagged families. This interaction activates γ-secretase-mediated proteolytic cleavage of the Notch intracellular domain, which ultimately targets Hes1 and inhibits MUC5AC transcription. Nonetheless, studies have shown that Hes1 inactivation is not sufficient to induce mucus production. This fact indicates the redundant functions of various signaling pathways that limit the therapeutic efficiency of targeting signaling molecules.

Another problem with targeted therapy of signaling pathways is that these therapeutics should be designed to act locally. For example, in the case of mucus production, systemic drugs can lead to dysfunction of other organs (e.g., digestion problems because of reduced mucus production in the gastrointestinal tract).

CONCLUDING REMARKS
Cell signaling pathways can be important targets for the treatment of diseases. Designing new ligands either as agonists or antagonists for adaptor molecules of signaling pathways provides a new approach for the treatment of asthma as well. Recent knowledge about cell signaling pathways, especially within the cells that have main roles in the pathophysiology of asthma, has provided new hope for developing novel, efficient, and safe targeted therapies. Several pathways have been suggested as potential targets to design either therapeutic or prophylactic drugs against asthma. To develop highly efficient drugs, however, the interactions of these pathways with other signaling routes should be divulged in future studies.

ADDITIONAL INFORMATION
Conflict of interest: The authors declare that they have no conflict of interest.

REFERENCES
1. Athari, S. S. et al. Critical role of Toll-like receptors in pathophysiology of allergic asthma. Eur. J. Pharmacol. 808, 21–27 (2017).
2. Athari, S. S. Immune response shifting of asthma in aging. Middle-East J. Sci. Res. 13, 489–498 (2013).
3. Soriano, J. B. et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir. Med. 5, 691–706 (2017).
4. Boyman, O. et al. EAACI IG Biologicals task force paper on the use of biologic agents in allergic disorders. Allergy 70, 727–754 (2015).
5. Brightling, C., Bradding, P., Pavord, I. & Wardlaw, A. New insights into the role of the mast cell in asthma. Clin. Exp. Allergy 33, 550–556 (2003).
6. Taghavi, M. et al. Role of pattern-associated molecular patterns (PAMPs) in immune responses to fungal infections. Eur. J. Pharmacol. 808, 8–13 (2017).
7. Foster, P. S. et al. Modeling TH 2 responses and airway inflammation to understand fundamental mechanisms regulating the pathogenesis of asthma. Immunological Rev. 278, 20–40 (2017).
8. Athari, S. S. & Athari, S. M. The importance of eosinophil, platelet and dendritic cell in asthma. Asian Pac. J. Trop. Dis. 4, 541–547 (2014).

Table 4. Role of the cytokines in pathophysiology of asthma and related signaling molecules

| Cytokine | Function | Signaling pathway | References |
|----------|----------|-------------------|------------|
| IL-4     | AHR      | JAK-STAT, ERK, p38 MAPK, JNK and mTOR | 17–21,154,158,186,188,197,199,202,204 |
| IL-5     | Eosinophilic inflammation |                      |            |
| IL-13    | Mucus production |                      |            |
| IL-13    | Goblet cell hyperplasia |                  |            |

Signal Transduction and Targeted Therapy (2019)4:45
38. André, D. M. et al. Therapy with resveratrol attenuates obesity-associated asthma. *Am. J. Respir. Cell Mol. Biol.* 50, 980–986 (2014).

39. Tigli, H. & Moschen, A. R. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat. Rev. Immunol.* 6, 772 (2006).

40. Shore, S. A. et al. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. *J. Allergy Clin. Immunol.* 118, 389–395 (2006).

41. Miller, M. et al. Adiponectin and functional adiponectin receptor 1 are expressed by airway epithelial cells in chronic obstructive pulmonary disease. *J. Immunol.* 182, 659–668 (2009).

42. Williams, A. S. et al. Role of the adiponectin binding protein, T-cadherin (Cdh13), in allergic airways responses in mice. *PloS ONE* 7, e41088 (2012).

43. Hardie, D. G., Ross, F. A. & Hawley, S. A. AMPK—a nutrient and energy sensor that maintains energy homeostasis. *Nat. Rev. Mol. Cell Biol.* 13, 251 (2012).

44. Yamauchi, T. et al. Targeted disruption of AdipoR1 and AdipoR2 causes aberrant glucose metabolism and insulin sensitivity. *Nat. Med.* 13, 332 (2007).

45. Sag, D., Carlng, D., Stout, R. D. & Sattles, J. Adenosine 5′-monophosphate-activated protein kinase promotes macrophage polarization to an anti-inflammatory functional phenotype. *J. Immunol.* 181, 8633–8641 (2008).

46. Gilmore, T. D. Introduction to NF-κB players, pathways, perspectives. *Oncogene* 25, 6680 (2006).

47. Mishra, V., Banga, J. & Silveira, P. Oxidative stress and cellular pathways of asthma and inflammation: therapeutic strategies and pharmacological targets. *Pharmacol. Ther.* 181, 169–182 (2018).

48. Zhu, L. et al. Adiponectin alleviates exacerbation of airway inflammation and oxidative stress in obesity-related asthma mice partly through AMPK signaling pathway. *Int. Immunopharmacol.* 67, 396–407 (2019).

49. Cazt, S. D. & Johnson, J. L. Transcriptional regulation of β2 by nuclear factor κB and its significance in prostate cancer. *Oncogene* 20, 7342 (2001).

50. Viator, P. et al. NF-κB2/p100 induces Bcl-2 expression. *Leukemia* 17, 1349 (2003).

51. Akita, K., Kawata, S. & Shimotohno, K. p21WAF1 modulates NF-κB signaling and induces anti-apoptotic protein Bcl-2 in Tax-expressing rat fibroblast. *Virology* 332, 249–257 (2005).

52. Ajuwon, K. M. & Spurlock, M. E. Adiponectin inhibits LPS-induced NF-κB activation and IL-6 production and increases PPARγ2 expression in adipocytes. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 288, R1220–R1225 (2005).

53. Ouchi, N. et al. Obesity, adiponectin and vascular inflammatory disease. *Curr. Opin. Lipidol.* 14, 561–566 (2003).

54. Lovren, F. et al. Adiponectin primes human monocytes into alternative anti-inflammatory M2 macrophages. *Am. J. Physiol. Heart Circ. Physiol.* 299, H656–H663 (2010).

55. Masaki, T. et al. Adiponectin protects LPS-induced liver injury through modulation of TNF-α in KK-Ay obese mice. *Hepatology* 40, 177–184 (2004).

56. Ouchi, N. et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-κB signaling through a cAMP-dependent pathway. *Circulation* 102, 1296–1301 (2000).

57. Xue, L. et al. Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. *J. Allergy Clin. Immunol.* 133, 1184–1194 (2014), e1187.

58. Domingo, C. et al. The prostaglandin D2 receptor 2 pathway in asthma: a key player in airway inflammation. *Respir. Res.* 19, 189 (2018).

59. Matsuda, K. et al. Monomeric IgE enhances human mast cell chemokine production: IL-4 augments and dexamethasone suppresses the response. *J. Allergy Clin. Immunol.* 116, 1357–1363 (2005).

60. Townley, R. G. & Agrawal, S. CRTH2 antagonists in the treatment of allergic asthma. *Expert Opin. Investig. Drugs* 18, S191–S201 (2009).

61. Sykes, D. A. et al. FcεRII, a slowly dissociating CRTh2 antagonist with enhanced efficacy, induces apoptosis and the unmet need in asthma. *Am. J. Respir. Crit. Care Med.* 185, 651–663 (2012).

62. Meezan, C. et al. FcεRII agonist and causes activation of human eosinophils and Th2 lymphocytes. *Prostaglandins Other Lipid Mediat.* 75, 153–167 (2005).

63. Savery, N. et al. Molecular pharmacology of the human prostaglandin D2 receptor, CRTH2. *Br. J. Pharmacol.* 137, 1163–1172 (2002).
69. Sandham, D. A. et al. Discovery of fevipivaptan (NVP-QAW039), a potent and selective DP2 receptor antagonist for treatment of asthma. ACS Med. Chem. Lett. 8, 582–586 (2017).

70. Xue, L. et al. Leukotriene E4 activates human Th2 cells for exaggerated proinflammatory cytokine production in response to prostaglandin D2. J. Immunol. 188, 694–702 (2012).

71. Cornett, F. G. et al. Selective modulation of chemokinesis, degranulation, and apoptosis in eosinophils through the PGD2 receptors CRTH2 and DP. J. Allergy Clin. Immunol. 108, 982–988 (2001).

72. Xue, L. et al. Prostaglandin D2 causes preferential induction of proinflammatory Th2 cytokine production through an action on chemotractant-receptor like molecule expressed on Th2 cells. J. Immunol. 175, 6531–6536 (2005).

73. Patel, K. D. Eosinophil tethering to interleukin-4–activated endothelial cells requires both P-selectin and vascular cell adhesion molecule-1. Blood 92, 3904–3911 (1998).

74. Moore, P. E. et al. IL-13 and IL-4 cause eotaxin release in human airway smooth muscle cells: a role for ERK. Am. J. Physiol.Lung Cell. Mol. Physiol. 282, L847–L853 (2002).

75. Farne, H., Jackson, D. J. & Johnston, S. L. Are emerging PGD2 antagonists a logical targets.

76. Aceves, S. S. & Ackerman, S. J. Relationships between eosinophilic in

77. Yurt, M. et al. Vitamin D supplementation blocks pulmonary structural and asthmatic airway remodeling. Chinese. J. Pathophysiol. 33, 1683–1689 (2017).

78. Roemer, N. et al. A novel antagonist of prostaglandin D2 blocks the locomotion of eosinophils and basophils, Eur. J. Clin. Investig. 38, 663–671 (2008).

79. Vatrella, A. et al. Dupilumab: a novel treatment for asthma. J. Allergy Allergy 17, 123 (2014).

80. Kuna, P., Bjermer, L. & Tornling, G. Two phase II randomized trials on the CRTH2 antagonist AZD1981 in adults with asthma. Drug Des. Dev. Ther. 10, 2759 (2016).

81. Tromp, I. I. et al. 25-Hydroxyvitamin D concentrations, asthma and eczema in childhood: the generation R study. Clin. Nutr. 37, 169–176 (2018).

82. Brehm, M. J. et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. J. Allergy Clin. Immunol. 126, 52–58 (2010).

83. Supyniewska, G. et al. 25-Hydroxvitamin D, biomarkers of eosinophilic inflammation, and airway remodeling in children with newly diagnosed untreated asthma. Allergy Asthma Proc. 38, 29–36 (2017).

84. Palmer, H. G. et al. Vitamin D3 promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of β-catenin signaling. J. Cell Biol. 154, 369–388 (2001).

85. Solberg, O. D. et al. Airway epithelial miRNA expression is altered in asthma. Am. J. Respir. Crit. Care Med. 186, 965–974 (2012).

86. Pua, H. H. & Ansel, K. M. MicroRNA regulation of allergic inflammation and asthma. Curr. Opin. Immunol. 36, 101–108 (2015).

87. Auch, J. et al. Resveratrol attenuates experimental allergic asthma in mice by restoring inositol polyphosphate 4 phosphatase (INPP4A). Int. Immunopharmacol. 68, 88–94 (2019).

88. Schuliga, M. NF-kB signalling in chronic inflammatory airway disease. Bio-molecules 5, 1266–1283 (2015).

89. Chen, G. G. et al. Increased inducible nitric oxide synthase in lung carcinoma of smokers. Cancer 112, 372–381 (2008).

90. Anto, R. J. et al. Cigarette smoke condensate activates nuclear transcription factor-κB through phosphorylation and degradation of IkBα: correlation with induction of cyclooxygenase-2. Carcinogenesis 23, 1511–1518 (2002).

91. Kim, J.-B. et al. Inhibition of LP5-induced INOS, COX-2 and cytokines expression by poncirin through the NF-κB inactivation in RAW 264.7 macrophage cells. Biol. Pharm. Bull. 30, 2345–2351 (2007).

92. Shin, N.-R. et al. Galgeun-tang attenuates cigarette smoke and lipopolysaccharide induced pulmonary inflammation via lkoB/NF-κB signaling. Molecules 23, 2489 (2018).

93. Contoli, M. et al. Role of deficient type III interferon-λ production in asthma exacerbations. Nat. Med. 12, 1023 (2006).

94. Edwards, M. et al. Impaired innate interferon induction in severe therapy resistant atopic asthma children. Mucosal Immuno. 6, 797 (2013).

95. Kato, H. et al. Differential roles of MDAS and RIG-1 helicases in the recognition of RNA viruses. Nature 441, 101 (2006).

96. Yamamoto, M. et al. Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. Science 301, 640–643 (2003).

97. Zhu, J. et al. Bronchial mucosal iNOS expression and pattern recognition receptor expression in patients with experimental rinoavirus-induced asthma exacerbations: IL-10 and its receptor. J. Allergy Clin. Immunol. 143, 114–125 (2019), e114.

98. Sharma, R. & Chopra, V. Effect of the Wingless (wg1) mutation on wing and haltere development in Drosophila melanogaster. Dev. Biol. 48, 461–465 (1976).

99. Yurt, M. et al. Vitamin D supplementation blocks pulmonary structural and functional changes in a rat model of perinatal vitamin D deficiency. Am. J. Physiol. Lung Cell. Mol. Physiol. 307, L1599–L1607 (2014).

100. Baarsma, H. A., Königshoff, M. & Goesen, R. The WNT signaling pathway from ligand secretion to gene transcription: molecular mechanisms and pharmacological targets. Pharmacol. Ther. 138, 66–83 (2013).

101. Hussain, M. et al. Wnt/β-catenin signaling links embryonic lung development and asthmatic airway remodeling. Biochem. Biophys. Acta 1863, 3226–3242 (2017).

102. Huo, Y. et al. Tiotropium inhibits methacholine-induced extracellular matrix production via β-catenin signaling in human airway smooth muscle cells. Int. J. Chron. Obstr. Pulm. Dis. 13, 1469 (2018).

103. Jia, X. X., Zheng, Y. R. & Huang, Y. Effects of Wnt/β-catenin signal pathway on asthma airway remodeling. Chinese. J. Pathophysiol. 33, 1683–1689 (2017).

104. Royer, J. et al. A novel antagonist of prostaglandin D2 blocks the locomotion of eosinophils and basophils, Eur. J. Clin. Investig. 38, 663–671 (2008).

105. Chagani, T. et al. Fas (CD95) and FasL (CD95L) expression in airway epithelium of smokers. Cancer Sci. 98, 271–280 (2007).

106. Aguilera, O. et al. The Wnt antagonist DICKKOPF-1 gene is induced by 1α, 25-dihydroxyvitamin D 3 associated to the differentiation of human colon cancer cells. Carcinogenesis 28, 1877–1884 (2007).

107. Palmé, H. G. et al. Vitamin D alleviates airway remodeling in asthma by down-regulating the activity of Wnt/β-catenin signaling pathway. Int. Immunopharmacol. 68, 88–94 (2019).

108. Contoli, M. et al. Role of dectin-1 in Th2 cell proliferation and chemoresponses in MCF7 and MDA-MB231 cells. J. Carcinog. 11, C281–C291 (2004).

109. Feng, X.-J. et al. The PTEN/Pik3Ak signaling pathway mediates HMGB1–induced cell proliferation by regulating the NF-κB/Cyclin D1 pathway in mouse mesangial cells. Am. J. Physiol. Cell Physiol. 306, C1119–C1128 (2014).

110. Li, C. et al. Involvement of cyclin D1/Cdk4 and pRb mediated by Pik3Ak pathway activation in P2b–induced neuronal death in cultured hippocampal neurons. Toxicol. Appl. Pharmacol. 229, 351–361 (2008).

111. Sun, Y., Luo, D. & Liao, K. Cyclin D1 and protein λ plays different roles in modulating chemoresponses in MCF7 and MDA-MB231 cells. J. Carcinog. 11, 12 (2012).

112. Gao, N. et al. G1 cell cycle progression and the expression of G1 cyclins are regulated by Pik3Ak/mtOR/p70S6K1 signaling in human ovarian cancer cells. Am. J. Physiol.Cell Physiol. 287, C281–C291 (2004).

113. Wu, H. et al. A negative feedback loop between miR-200b and the nuclear factor-κB pathway via IKKβ and IκBα in breast cancer cells. FEBS J. 283, 2259–2271 (2016).

114. Bera, A. et al. Nfkb-mediated cyclin D1 expression by microRNA-21 influences renal cancer cell proliferation. Cell. Signal. 25, 2575–2586 (2013).

115. Signal Transduction and Targeted Therapy (2019)4:45
184. Park, S.-M., Schickel, R. & Peter, M. E. Nonapoptotic functions of FADD-binding death receptors and their signaling molecules. Curr. Opin. Cell Biol. 17, 610–616 (2005).
185. Desbarats, J. et al. Fas engagement induces neurite growth through ERK activation and p35 upregulation. Nat. Cell Biol. 5, 118 (2003).
186. Neumann, L. et al. Dynamics within the CD95 death-inducing signaling complex decide life and death of cells. Mol. Cell. Biol. 6 (2010).
187. Kleber, S. et al. Yes and Pikh bind CD95 to signal invasion of glioblastoma. Cancer Cell 13, 235–248 (2008).
188. Wisniewski, P., Ellert-Miklaszewska, A., Kwiatkowska, A. & Kaminska, B. Non-apoptotic Fas signaling regulates invasiveness of glioma cells and modulates MMP-2 activity via NFkB-TIMP-2 pathway. Cell Signal. 22, 212–220 (2010).
189. Fournier, Y. et al. Comparison of sensitivity of Th1, Th2, and Th17 cells to Fas-mediated apoptosis. J. Leukoc. Biol. 87, 1019–1028 (2010).
190. Williams, J. W. et al. Non-apoptotic Fas (CD95) signaling on T cells regulates the resolution of Th2-mediated inflammation. Front. Immunol. 9, 2521 (2018).
191. Liu, Y. et al. Protective effect of electro-acupuncture at maternal different points on perinatal nicotine exposure-induced pulmonary dysplasia in offspring based on HPA axis and signal transduction pathway. Biochem. Biophys. Res. Commun. 505, 586–592 (2018).
192. Rehan, V. K. & Torday, J. S. PPAR signaling mediates the evolution, development, homeostasis, and repair of the lung. PPAR Res. 2012 (2012).
193. Rijken, D. & Sakharov, D. Basic principles in thrombolysis: regulatory role of plasminogen. Exp. Biol. Med. 229, 138–146 (2004).
194. Lee, S. H. et al. A plasminogen activator inhibitor-1 inhibitor reduces airway inflammation by the immune receptor Tim-3 and Tim-3 ligand regulates T helper type 2 responses and induction of peripheral tolerance. Nat. Immunol. 4, 1102 (2003).
195. Toshchakov, V. et al. TLR4, but not TLR2, mediates IFN-γ production induced by LPS in human monocytes. Nat. Immunol. 13, 1303–1324 (2012).
196. Broome, C. A. et al. Fas engagement induces neurite growth through ERK activation and p35 upregulation. Nat. Cell Biol. 5, 118 (2003).
197. Anderson, A. C. et al. Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells. Science 318, 1114–1115 (2007).
198. Gil, J. M. & Mackman, N. The phosphatidylinositol 3-kinase-Akt pathway limits lipopolysaccharide activation of signaling pathways and expression of inflammatory mediators in human monocytes. J. Biol. Chem. 277, 32124–32132 (2002).
199. Kleber, S. et al. Yes and PI3K bind CD95 to signal invasion of glioblastoma. Cancer Cell 13, 235–248 (2008).
200. Prussin, C. & Metcalfe, D. D. IgE, mast cells, basophils, and eosinophils. J. Leukoc. Biol. 69, 1019–1028 (2006).
201. Kitaura, J. et al. Regulation of highly cytokinergic IgE-induced mast cell adhesion through the adaptor protein LAX. Cell Signal. 22, 212–220 (2010).
202. Weinblatt, M. E. et al. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis biomarker. Ann. Rheum. Dis. 71, 647–647 (2013).
203. Liu, L. et al. Eosinophils attenuate arthritis by inducing M2 macrophage polarization. J. Clin. Invest. 129, 535–549 (2019).
204. Aggarwal, N. R., King, L. S. & D’Alessio, F. R. Diverse macrophage populations are induced by IL-4 and IL-13 and lack eosinophilia but have normal antibody and cytotoxic T cell responses. J. Immunol. 177, 1531–1532 (2001).
205. Rosenkranz, C. A. et al. Interaction of Tim-3 and Tim-3 ligand regulates T helper type 1 responses and induction of peripheral tolerance. Nat. Immunol. 4, 449 (2013).
206. Molosky, A. B. et al. Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages associated with glucose homeostasis. Science 332, 243–247 (2011).
207. Aderem, A. & Ulevitch, R. J. Toll-like receptors in the induction of the innate immune response. Nature 406, 780–785 (2000).
208. Casanova, J.-L., Abel, L. & Quintana-Murci, L. Human TLRs and IL-1Rs in host defense: natural insights from evolutionary, epidemiological, and clinical genetics. Annu. Rev. Immunol. 29, 447–491 (2011).
209. Lopez-Santalla, M. et al. AB0176 P38 MAPK phosphorylation as a rheumatoid arthritis biomarker. Ann. Rheum. Dis. 71, 647–647 (2013).
210. Toshchakov, V. et al. Toll-like receptor 2 as a major gene for asthma in children of atopic European ancestry. J. Immunol. 185, 1411–1416 (2010).
211. Takeda, K. & Akira, S. Toll-like receptors in innate immunity. J. Biol. Chem. 281, 248–250 (2006).
212. Mansell, A. et al. Suppressor of cytokine signaling 1 negatively regulates Toll-like receptor signaling via inhibition of the MyD88-TRIF pathway. Biochem. Biophys. Res. Commun. 508, 894–901 (2019).
213. Schneider, C. et al. Alveolar macrophages are essential for protection from respiratory failure and associated morbidity following influenza virus infection. PLoS Pathog. 10, e1004053 (2014).
214. Kopf, M. et al. IL-5-deficient mice have a developmental defect in CD8+ T-cell responses. J. Immunol. 160, 928–937 (1998).
215. Gaurav, R. & Agrawal, D. K. Clinical view on the importance of dendritic cells in asthma. Expert Rev. Clin. Immunol. 9, 899–919 (2013).
216. Chen, K. & Kolls, J. K. T Cell–mediated host defense mechanisms and development efforts. J. Exp. Med. 210, 1203–1212 (2011).
217. Aggarwal, N. R., King, L. S. & D’Alessio, F. R. Diverse macrophage populations are induced by IL-4 and IL-13 and lack eosinophilia but have normal antibody and cytotoxic T cell responses. J. Immunol. 177, 1531–1532 (2001).
218. Brown, S. et al. Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages associated with glucose homeostasis. Science 332, 243–247 (2011).
219. Molosky, A. B. et al. Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. J. Exp. Med. 210, 535–549 (2019).
220. Schneider, C. et al. Frontline science: coincidental null mutation of Csf2r in a colony of P38Ky/– mice causes alveolar macrophage deficiency and fatal respiratory viral infection. J. Leukoc. Biol. 101, 367–376 (2017).
221. Nobs, S. P., Kayhan, M. & Kopf, M. GM-CSF intrinsically controls eosinophil accumulation in the setting of allergic airway inflammation. J. Allergy Clin. Immunol. 134, 1513–1524 (2019).
222. Akira, S. et al. Alveolar macrophages are essential for protection from respiratory failure and associated morbidity following influenza virus infection. J. Exp. Med. 210, 1203–1212 (2011).
223. Eder, W. et al. Toll-like receptor 2 as a major gene for asthma in children of European farmers. J. Allergy Clin. Immunol. 113, 482–488 (2004).
224. Casanova, J.-L., Abel, L. & Quintana-Murci, L. Human TLRs and IL-1Rs in host defense: natural insights from evolutionary, epidemiological, and clinical genetics. Annu. Rev. Immunol. 29, 447–491 (2011).
225. Takeda, K. & Akira, S. Toll-like receptors in innate immunity. Int. Immunol. 17, 1–14 (2005).
226. Akira, S., Uematsu, S. & Takeuchi, O. Pattern recognition and innate immunity. Cell 124, 783–801 (2006).
227. Mansell, A. et al. Suppressor of cytokine signaling 1 negatively regulates Toll-like receptor signaling by mediating Malt degradation. Nat. Immunol. 7, 148 (2006).
228. Han, C. et al. Integrin CD11b negatively regulates TLR-triggered inflammatory responses by activating Syk and promoting degradation of MyD88 and TRIF via Caspase-1. Nat. Immunol. 14, 1738–1747 (2013).
229. Palsson-McDermott, E. M. et al. TAG, a splice variant of the adaptor TRAM, negatively regulates the adaptor MyD88-independent TLR4 pathway. Nat. Immunol. 10, 579 (2009).
230. Zakeri, A. & Yazdi, F. G. Toll-like receptor-mediated involvement of innate immune cells in asthma disease. Biochim. Biophys. Acta Gen. Subj. 1861, 3270–3277 (2017).
Targeting cell signaling in allergic asthma

Athari

217

249. Walker, J. K. & DeFea, K. A. Role for antioxidant-responsive elements (ARE). Mol. Biol. Cell 37, 273–290 (2007).

250. Shenoy, S. K. et al. β-Arrestin-2 regulates the development of allergic asthma. J. Clin. Investig. 112, 566–574 (2003).

251. Hollingsworth, J. W. et al. Both hematopoietic-derived and non-hematopoietic-derived β-arrestin-2 regulates murine allergic disease. Am. J. Respir. Cell Mol. Biol. 43, 269–275 (2010).

252. Billington, C. K. & Penn, R. B. Signaling and regulation of G protein-coupled receptor action which regulates gene expression and inflammation. Am. J. Physiol. Heart Circ. Physiol. 290, H1162–H11870 (2006).

253. Kaulmann, A. B. & Bohn, T. Carotenoids, inflammation, and oxidative stress—implications of cellular signaling pathways and relation to chronic disease prevention. Nutr. Res. 34, 907–929 (2014).

254. Shenoy, S. K. et al. β-Arrestin-dependent, G protein-independent ERK1/2 activation by the β2 adrenergic receptor. J. Biol. Chem. 281, 1261–1273 (2006).

255. Billingston, C. K. & Penn, R. B. Signal and regulation of β-arrestin-2-mediated protein interactions with G protein-coupled receptors in airway smooth muscle. Respir. Res. 4, 4 (2003).

256. Huang, C.-Y. et al. Activation of Nrf2/ARE pathway protects endothelial cells from oxidant injury and inhibits inflammatory gene expression. Am. J. Physiol. Heart Circ. Physiol. 290, H1162–H11870 (2006).

257. Kaplan, M. H. STAT signaling in inflammation. JAKSTAT 2, e24198 (2013).

258. Brown, S. et al. NF-κB transcription factor, a novel target of ketamine cytochrome growth factor action which regulates gene expression and inflammation in the healing skin wound. Mol. Cell. Biol. 22, 5492–5505 (2002).

259. Wang, H. et al. XRh inhibits the NRF2-ARE signaling pathway through a direct interaction with the Neh7 domain of NRF2. Cancer Res. 73, 3097–3108 (2013).

260. Pfirker, K. et al. The ubiquitin-conjugating enzyme Ubcm2 can regulate the stability and activity of the antioxidant transcription factor Nrf2. J. Biol. Chem. 285, 23064–23074 (2010).

261. Wang, X. J. et al. Oxaiplatin activates the Keap1/Nrf2 antioxidant system conferring protection against the cytotoxicity of anticancer drugs. Free Radic. Biol. Med. 70, 68–77 (2014).

262. Canning, P., Sorrell, F. J. & Bullock, A. N. Structural basis of Keap1 interactions with Nrf2. Free Radic. Biol. Med. 88, 101–107 (2015).

263. Kim, J.-H., Yu, S., Chen, J. D. & Kong, A.-N. The nuclear cofactor RAC3/A1B3/SRC3 enhances Nrf2 signaling by interacting with transactivation domains. Oncogene 32, 514 (2013).

264. Nol, P., Nguyen, T., Shennatt, P. J. & Pickett, C. B. The carboxyl-terminal Neh3 domain of Nrf2 is required for transcriptional activation. Mol. Cell. Biol. 25, 10985–10996 (2005).

265. Li, W., Yu, S.-W. & Kong, A.-N. T. Nrf2 possesses a redox-sensitive nuclear exporting signal in the Neh5 transactivation domain. J. Biol. Chem. 281, 27251–27263 (2006).

266. Tong, K. I. et al. Different electrotactic potentials define ETGE and DLG motifs as hinge and latch in oxidative stress response. Mol. Cell. Biol. 27, 7511–7521 (2007).

267. Cullinan, S. B. et al. The Keap1-BTB protein is an adaptor that bridges Nrf2 to a Cu3-based E3 ligase: oxidative stress sensing by a Cu3-Keap1 ligase. Mol. Cell. Biol. 24, 8477–8486 (2004).

268. Hayes, J. D., McMahon, M., Chowdhry, S. & Dinkova-Kostova, A. T. Cancer chemoprevention mechanisms mediated through the Keap1–Nrf2 pathway. Anti-cancer drugs 17, 1713–1748 (2010).

269. Ahmed, S. M. U. et al. Nrf2 signaling pathway: pivotal roles in inflammation. Biochim. Biophys. Acta 1863, 585–597 (2017).

270. Rada, P. et al. SCL/β3-TCP promotes glycylin synthase kinase 3-dependent degradation of the Nrf2 transcription factor in a Keap1-independent manner. Mol. Cell. Biol. 31, 1121–1133 (2011).

271. Chowdhry, S. et al. Nrf2 is controlled by two distinct β-TCP recognition motifs in its Neh7 domain, one of which can be modulated by GSK-3 activity. Oncogene 32, 3765 (2013).

272. Prestera, T. et al. Parallel induction of heme oxygenase-1 and chemoprotective phase 2 enzymes by electrophiles and antioxidants: regulation by upstream antioxidant-responsive elements (ARE). Mol. Med. 1, 827–837 (1995).

273. Wunder, C. & Potter, R. F. The heme oxygenase system: its role in liver inflammation. Curr. Drug Targets Cardiovasc. Hematol. Drug. 3, 199–208 (2003).

274. Bauermeister, C. & Flavell, R. Induction of heme oxygenase-1 and chemoprotective phase 2 enzymes by electrophiles and antioxidants: regulation by upstream antioxidant-responsive elements (ARE). Mol. Med. 1, 827–837 (1995).
Targeting cell signaling in allergic asthma

Athari

303. Ding, C., Li, J. & Zhang, X. Bertilimumab (Cambridge Antibody Technology Group). Curr. Opin. Investig. Drugs. 5, 1213–1218 (2004).
304. Ricketts, H. C. & Cowan, D. C. Asthma, obesity and targeted interventions: an update. Curr. Opin. Allergy Clin. Immunol. 19, 68–74 (2019).
305. Detoraki, A. et al. Omalizumab in patients with eosinophilic granulomatosis with polyangiitis: a 36-month follow-up study. J. Asthma 53, 201–206 (2016).
306. Pelaul, G. et al. Targeted therapy in severe asthma today: focus on immuno-noglobulin E Drug Des. Dev. Ther. 11, 79 (2017).
307. Borish, L. C. et al. Interleukin-4 receptor in moderate atopic asthma: a phase III randomized, placebo-controlled trial. Am. J. Respir. Crit. Care Med. 160, 1816–1823 (1999).
308. Hart, T. et al. Preclinical efficacy and safety of pascolizumab (SB 240683): a randomized, placebo-controlled trial of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. Am. J. Respir. Crit. Care Med. 188, 1294–1302 (2013).
309. Gauvreau, G. M. et al. Effects of an anti-TSLP antibody on allergen-induced respiratory inflammation and eosinophilic inflammation by anti-human-interleukin-13 antibody (CAT-354). Clin. Exp. Allergy 35, 1096–1103 (2005).
310. Maselli, D. J., Keyt, H. & Rogers, L. Profile of lebrikizumab and its potential in the treatment of asthma. J. Asthma Allergy 8, 87 (2015).
311. Busse, W. W. et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. Am. J. Respir. Crit. Care Med. 188, 1294–1302 (2013).
312. O’Connell, R. M. et al. MicroRNA-155 is induced during the macrophage inactivation of MyD88 as a novel target of miR-155, involved in extracellular matrix production in airway smooth muscle via negative regulation of histone deacetylase 2. J. Biol. Chem. 285, 642–650 (2010).
313. Bhattacharya, C. et al. Interleukin-17 receptor monoclonal antibody, in moderate to severe asthma. J. Asthma Allergy 8, 87 (2015).
314. Kim, R. Y. et al. MicroRNA-21 drives severe, steroid-insensitive experimental asthma by amplifying phosphoinositide 3-kinase activation and ERK 1/2 phosphorylation, and proliferation in smooth muscle cells. Physiol. Rep. 3, e12541 (2015).
315. polifex, E. et al. MicroRNA-9 regulates steroid-resistant airway hyperresponsiveness by reducing protein phosphatase 2A activity. J. Allergy Clin. Immunol. 136, 462–473 (2015).
316. Liao, G., Panettieri, R. A. & Tang, D. D. Micro RNA-203 negatively regulates c-Abl ERK 1/2 phosphorylation, and proliferation in smooth muscle cells. Physiol. Rep. 3, e12541 (2015).
317. Di Valentin, E. et al. New asthma biomarkers: lessons from murine models of acute and chronic asthma. Am. J. Physiol. Lung Cell Mol. Physiol. 296, L185–L197 (2009).
318. Liu, X. et al. MicroRNA-146a modulates human bronchial epithelial cell survival in response to the cytokine-induced apoptosis. Biochem. Biophys.Res. Commun. 380, 177–182 (2009).
319. Tang, B. et al. Identification of MyD88 as a novel target of miR-155, involved in negative regulation of Helicobacter pylori-induced inflammation. FEBS Lett. 584, 1481–1486 (2010).
320. Zago, V. jet al. Negative regulation of TLR4 via targeting of the pro-inflammatory tumor suppressor PDCD4 by the microRNA miR-21. Nat. Immunol. 11, 141 (2010).
321. Sawant, V. D. et al. Serum microRNA-21 as a biomarker for allergic inflammation in children. MicroRNA 4, 36–40 (2013).
322. Sinha, V. et al. Nuclear factor of activated T cells 1 cell. Mol. Immunol. 78, 133–139 (2016).
323. Spurlock, C. F. et al. Expression and functions of long noncoding RNAs during human T helper cell differentiation. Nat. Commun. 6, 6932 (2015).
324. Kho, A. T. et al. Circulating microRNAs and association with methacholine PC20 in the Childhood Asthma Management Program (CAMP) cohort. PloS ONE 5, e10854 (2010).
325. Williams, A. E. et al. Maternally imprinted microRNAs are differentially expressed during mouse and human lung development. Dev. Dyn. 236, 572–580 (2007).
326. Bhaskaran, M. et al. MicroRNA-127 modulates fetal lung development. Physiol. Genomics. 37, 268-278 (2009).
327. Lu, T. et al. MicroRNA-21 limits in vivo immune response-mediated activation of the IL-12/IFN-y pathway, Th1 polarization, and the severity of delayed-type hypersensitivity. J. Immunol. 187, 3362–3373 (2011).
328. Weidner, J., Malmhall, C. & Radinger, M. MicroRNAs in asthma pathogenesis. Transl. Genet. Genom. 3, 2 (2019).
329. Davis, J. S. et al. Circulating microRNAs and association with methacholine PC20 in the Childhood Asthma Management Program (CAMP) cohort. PloS ONE 5, e108329 (2017).
330. Xie, Y. & Merkel, O. M. Pulmonary delivery of siRNA via polymeric vectors as therapies of asthma. Arch. der Pharmazie 348, 681–688 (2015).
331. Zafr, M. P. et al. Gene silencing of SOCS3 by siRNA intranasal delivery inhibits asthma phenotype in mice. PloS ONE 9, e91996 (2014).
332. Xo, A. T. et al. Circulating microRNAs and prediction of asthma exacerbation in childhood asthma. Respiratory Res. 19, 128 (2018).
333. Cheng, W. et al. MicroRNA-379-3p promotes TGF-beta-induced cell proliferation and extracellular matrix production in airway smooth muscle via negative regulation of the Wnt/beta-catenin pathway. J. Cell. Physiol. 233, 3164–3172 (2018).
334. Spurlock, C. F. et al. Expression and functions of long noncoding RNAs during human T helper cell differentiation. Nat. Commun. 6, 6932 (2015).
335. Zhao, X. et al. MicroRNA-21 regulates steroid-resistant airway hyperresponsiveness by reducing protein phosphatase 2A activity. J. Allergy Clin. Immunol. 136, 462–473 (2015).
336. Heffler, E. et al. MicroRNA profiling in asthma: potential biomarkers and therapeutic approaches. Am. J. Respir. Crit. Care Med. 157, 642–650 (2017).
