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Review

The Roles of Neuropeptide Y in Respiratory Disease Pathogenesis via the Airway Immune Response

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The lungs are very complex organs, and the respiratory system performs the dual roles of repairing tissue while protecting against infection from various environmental stimuli. Persistent external irritation disrupts the immune responses of tissues and cells in the respiratory system, ultimately leading to respiratory disease. Neuropeptide Y (NPY) is a 36-amino-acid polypeptide and a neurotransmitter that regulates homeostasis. The NPY receptor is a seven-transmembrane-domain G-protein-coupled receptor with six subtypes (Y1, Y2, Y3, Y4, Y5, and Y6). Of these receptors, Y1, Y2, Y4, and Y5 are functional in humans, and Y1 plays important roles in the immune responses of many organs, including the respiratory system. NPY and the Y1 receptor have critical roles in the pathogenesis of asthma, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis. The effects of NPY on the airway immune response and pathogenesis differ among respiratory diseases. This review focuses on the involvement of NPY in the airway immune response and pathogenesis of various respiratory diseases.

Key words: neuropeptide y, Y1 receptor, airway immune response, bronchial epithelial cells, respiratory disease

Respiratory diseases encompass a spectrum of conditions, including both acute and chronic ailments, each exhibiting a distinct pathology. Acute respiratory disease, such as infectious pneumonia, is caused by severe acute respiratory syndrome coronavirus-2 [1-3], influenza virus [4,5], and bacteria [6-8]. Chronic respiratory diseases include asthma [9-11], chronic obstructive pulmonary disease (COPD) [12-16], interstitial lung disease (*e.g.*, idiopathic pulmonary fibrosis [IPF]) [17-21], and lung cancer [22,23].

Innate and adaptive immune responses are involved in respiratory diseases [24-28]. Several studies have shown that neurotransmitters play critical roles in these immune responses. Neurotransmitters are produced by neurons and released into the synaptic cleft where they act on target cells by binding to receptors [29-31]. In addition to norepinephrine and acetylcholine [32-34], various neurotransmitters that are secreted into the lungs and airways (*e.g.*, substance P, calcitonin gene-related peptide, and vasoactive intestinal peptide) play critical roles in the respiratory system [35,36]. These neurotransmitters are responsible for the lung immune response.

Furthermore, several investigations have revealed that the neurotransmitter neuropeptide Y (NPY) plays an essential role in the lung immune response

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[32,35,37,38]. Our laboratory has reported that NPY plays critical roles in asthma [39], COPD [40], and IPF [41] via the airway immune response. However, the roles of NPY in respiratory disease pathogenesis are controversial and poorly understood. In this review, we discuss the effects of NPY on the lung immune response based on data from our laboratory and previous reports.

NPY is a 36-amino-acid polypeptide first identified in the porcine brain in 1982 [42]. NPY is expressed throughout the central and peripheral nervous systems [43,44]. The NPY receptor is a seven-transmembrane-domain G-protein-coupled receptor with six subtypes (Y1, Y2, Y3, Y4, Y5, and Y6) [45-47]. The Y1, Y2, Y4, and Y5 NPY receptors are functional in humans [48,49]. NPY maintains homeostasis by increasing appetite, controlling anxiety, regulating circadian rhythms [50-53], and regulating the immune responses of various organs and cells via multiple receptors [54-59]. These findings suggest that NPY has a critical role in the airway immune response and may be responsible for respiratory disease pathogenesis. This review focuses on the roles of NPY in various respiratory disorders in relation to the airway immune response.

Upper Respiratory Tract Infections

The upper respiratory tract, consisting of the nasal cavity, sinuses, pharynx, and larynx, protects against inhaled microorganisms through innate and adaptive immune responses [60,61]. The sinuses prevent lower respiratory tract infections through their epithelial mucociliary clearance function. Neuropeptides, neuropeptide receptors, and the bitter taste receptor (T2R) regulate the secretion of airway surface fluid [62,63]. Gram-negative bacteria secrete acyl homoserine lactones as quorum-sensing molecules. These bitter compounds bind to T2R (T2R38) receptors, which are expressed on sinus ciliary epithelial cells. This binding induces Ca^{2+} signaling, leading to nitric oxide (NO) production. NO, in turn, upregulates ciliary beating and promotes the mucosal ciliary clearance of pathogens in the airway surface fluid [62,63]. NPY reduces NO production and the ciliary beat frequency response in a protein kinase C-dependent manner via the NPY–Y2 receptor without T2R-induced Ca^{2+} signaling [64]. T2R initiates Ca^{2+} signaling in response to acyl homoserine lactones secreted by bacteria and swiftly generates cyclic adenosine monophosphate (cAMP), which directly kills pathogenic microbes [62,63].

The co-administration of NPY and norepinephrine increases intracellular cAMP and Ca^{2+} concentrations in human tracheal gland cells and leads to the inhibition of secretions from those cells [65]. These data suggest that NPY may negatively affect sinus clearance. To confirm this, further investigations are needed.

NPY may also be associated with the pathogenesis of cystic fibrosis (CF), based on a report showing that low serum NPY levels are correlated with poor respiratory function in CF patients [66]. CF is a disease in which an abnormality in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene results in dysfunctional epithelial clearance throughout the body, including the gastrointestinal tract and pancreas, leading to chronic refractory sinusitis and airway infection [67,68]. The signal transduction pathway comprising phospholipase C β2 (PLCβ2), inositol 1,4,5-trisphosphate receptor subtype 3 (IP_3R3), and transient receptor potential cation channel 6 (TRPC6) converts extracellular signals into a sustained Ca^{2+} response [63] and modulates the release of NPY [69]. The absence of the *CFTR* gene causes a primary dysfunction that increases the level of NPY as well as the proliferation and apoptosis of progenitor cells in the olfactory epithelium via PLCβ2/IP_3R3/TRPC6 signaling [69].

Hydrogen carbonate ion (HCO_3^-) promotes the polymerization of mucins secreted by mucous cells and crucially influences the secretion of antimicrobial peptides from serous cells [70,71]. Vasoactive intestinal peptide receptors on the plasma membrane of serous cells initiate GαS activation of adenylyl cyclase, leading to elevated cAMP levels and the efflux of chloride ions and HCO_3^- through CFTR [70,71]. NPY inhibits adenylyl cyclase and decreases vasoactive intestinal peptide-activated cAMP responses; this blunts CFTR-mediated anion and vasoactive intestinal peptide-activated cAMP secretions [71]. In CF, the absence of CFTR prevents the initiation of anion secretion, while NPY leads to persistent inflammation in human gland cells [71].

However, there is a lack of information regarding which NPY receptors participate in the pathology of CF. More detailed investigations of NPY in the upper respiratory tract, including the sinuses, are warranted because sinus clearance dysfunction, including CF, leads to infection of the lower respiratory tract and

severe pneumonia.

Viral and Bacterial Pneumonia

Influenza virus infection causes severe pneumonia, resulting in fatality due to the overproduction of cytokines [72,73]. Influenza virus infection induces the release of interferon (IFN)-α/β from alveolar macrophages. Cytokine storms also trigger IFN-α/β-induced alveolar macrophages, thereby promoting apoptosis of alveolar epithelial cells [72]. Furthermore, the influenza virus invades the alveoli, leading to epithelial cell apoptosis or necrosis and the production of proinflammatory cytokines and chemokines, including IFN-α, interleukin (IL)-6, tumor necrosis factor-α, C-C motif chemokine ligand 2, and C-X-C motif chemokine ligand (CXCL)10. These molecules recruit neutrophils and monocytes to the alveolus, resulting in lung tissue damage [72,73]. Only one report has investigated the role of NPY in the pathogenesis of influenza infection [74]. Activation of the NPY–Y1 receptor on alveolar macrophages during influenza infection suppresses the cytokine signaling-3 suppressor, thereby enhancing phosphorylated signal transducer and activator of transcription-3-mediated IFN responses. This elevated production of proinflammatory cytokines and chemokines (*e.g.*, IL-6, CXCL1, and CXCL2) contributes to the pathogenesis of influenza virus infection and pneumonia [74]. Notably, NPY is not produced by a neural source; rather, it is secreted by alveolar macrophages.

Bacterial pneumonia is a respiratory illness caused by severe bacterial infection in patients with chronic respiratory disease. In Japan, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* are the primary causative organisms [75].

The neuropeptides NPY, substance P, neurokinin A, calcitonin gene-related peptide, and vasoactive intestinal peptide exhibit antibacterial activity against various bacterial infections [76]. In addition, NPY has specific receptors on human neutrophils, which moderate bacterial phagocytosis and the release of reactive oxygen species [77]. In a study examining the effects of NPY, calcitonin gene-related peptide, substance P, and somatostatin on *H. influenzae* and *M. catarrhalis*, NPY demonstrated the greatest efficacy in terms of permeabilizing and killing bacteria [78]; compared with other neurotransmitters, NPY exhibited greater bactericidal activity against *H. influenzae* and *M. catarrhalis*. In terms of bactericidal activity, the opsonin-dependent pathway is regarded as the most crucial mechanism for augmenting neuropeptide-mediated phagocytosis. NPY may exhibit higher bactericidal activity compared to other neurotransmitters by enhancing opsonin-dependent phagocytosis and reducing reactive oxygen species production [78].

However, only a few studies have examined the role of NPY in viral and bacterial pneumonia; further research is warranted.

Asthma

Bronchial asthma is a complex syndrome with multiple phenotypes, encompassing allergic and non-allergic forms as well as eosinophilic, neutrophilic, pouch-granulocytic, and obesity-related variants. Airway immune responses, including the secretion of numerous cytokines and chemokines, as well as the activation of various immune cells, are associated with asthma development [79-81]. Severe asthma pathogenesis may involve neutrophils, T helper (Th) 17 cells, group 2 innate lymphoid cells (ILC2s), and thymic stromal lymphopoietin [82-86].

Our laboratory has demonstrated several pathogenic pathways of asthma via the airway immune response [39,87-91]. Leukotriene B4 and its receptor BLT1, chemokine receptor 5, neutrophil elastase, the receptor for advanced glycation end products (RAGE), and retinoid X receptor are associated with the development of airway hyperresponsiveness (AHR) and an increase in the type-2 response [87-91]. AHR and type-2 responses are often associated with increased numbers of $CD3^+$, $CD4^+$, and $CD8^+$ T cells in the lungs [88]. RAGE induces the activation of Th2 lymphocytes; aggregation of ILC2s to the airways; and enhancement of CXCL1, CXCL2, and IL-1β levels via the IL-33–ST2 pathway [90]. The retinoid X receptor partial agonist NEt-4IB has been shown to reduce the numbers of $CD4^+$ T cells, $CD8^+$ T cells, and $CD11b^+$ cells in the lungs of an animal model of asthma [91].

Several studies have shown that NPY is essential in the pathogenesis of asthma. Specifically, NPY expression increases in the lungs, where it promotes allergic airway inflammation and the Th2 response. In contrast, NPY-deficient mice show fewer eosinophils and lower levels of immunoglobulin E in bronchoalveolar lavage fluid, resulting in diminished allergic airway inflamma-

tion [92]. NPY induces a Th1-to-Th2 cell shift and stimulates dendritic cells, suggesting its involvement in asthma pathogenesis [93]. NPY promotes the migration of immature dendritic cells and the onset of Th2 polarization via NPY–Y1 receptors, as well as the activation of extracellular signal-regulated kinase and p38 mitogen-activated protein kinase [94]. We have also shown that NPY promotes the activation of Th2 cells, the accumulation of $CD11c^+$ antigen-presenting cells in the airways, and the migration of $CD11c^+$ antigen-presenting cells into mediastinal lymph nodes after sensitization to house dust mites; notably, treatment with the NPY–Y1 receptor antagonist BIBO-3304 attenuates AHR and inflammation [39].

NPY modulates macrophage function via the NPY–Y1, Y2, and Y5 receptors [95]. During the chronic phase of ovalbumin-induced allergic airway inflammation in an animal model, NPY levels are elevated within macrophages and peritracheal cells. Additionally, this phase results in the localization of NPY–Y1 and Y5 receptors to structural and inflammatory cells in the lung [96]. The roles of NPY and macrophages in asthma are unclear and require further investigation.

In a report concerning the relationship between non-Th2 asthma and NPY, the loss of forkhead box protein p1 (Foxp1) and forkhead box protein p4 (Foxp4) induced AHR without eosinophilic inflammation; the loss of Foxp1 and Foxp4 induced ectopic expression of NPY near bronchial epithelial cells. Moreover, NPY promoted AHR by inducing Rho kinase activity and phosphorylating myosin light chains [97].

NPY expression is associated with obesity; it causes obesity-related inflammation by activating macrophages in adipose tissue and increasing the expression levels of several inflammatory mediators [98, 99]. Obesity is involved in the pathogenesis of allergic and nonallergic asthma in a weight-dependent manner [100, 101]. An examination of NPY gene polymorphisms in overweight subjects (body mass index ≥ 25 kg/m^2) demonstrated an elevated prevalence of asthma in overweight subjects carrying the *NPY*-399T allele, but not the *NPY*-Pro7 allele. Overweight classification was also associated with increased atherosclerosis, as determined by carotid intima media thickness. However, total heart rate variability was higher in patients with asthma and correlated negatively with carotid intima media thickness, irrespective of the NPY genotype. This suggests that the regulation of sympathetic balance differs between asthma and atherosclerosis [102]. Moreover, another report showed that body mass index values are higher in asthma patients than in healthy individuals; NPY and IL-6 levels are positively correlated with IL-4 levels [103].

Psychological and environmental stresses exacerbate the pathophysiology of asthma [104, 105]. Physiological stress in asthma patients has a persistent enhancing effect on IL-4 and Th2 inflammatory responses. NPY mediates the association between high stress levels and IL-4 overexpression in asthma patients [106]. The stress of cold stimulation in a house dust mite-induced asthma model significantly increases the numbers of total leukocytes and eosinophils in bronchoalveolar lavage fluid, and these changes are positively correlated with NPY concentrations [107].

These findings suggest that mental and environmental stresses are associated with elevated NPY levels. However, the detailed mechanism by which the stress-induced elevation of NPY affects immune cells in asthma is unknown. NPY is involved in Th2 inflammation, non-Th2 inflammation, obesity, and stress. The results of many studies have suggested that NPY promotes asthma exacerbation, implying that NPY promotes allergic inflammation and the Th2 response, as shown in Fig. 1. However, further analyses of the roles of NPY are needed, particularly with respect to nonallergic and Th2-independent asthma.

COPD

The primary essential factor in the onset of COPD is chronic exposure to inhaled tobacco smoke, toxic gases, and pollutants, which results in airway inflammation [108, 109]. This persistent airway inflammation is responsible for the progressive lung damage in COPD, leading to alveolar wall destruction [110]. Inflammation in COPD involves macrophages, neutrophils, lymphocytes, and various proinflammatory cytokines and chemokines [110-112]. Several studies have focused on innate immune responses in COPD pathogenesis [113, 114].

Our laboratory has identified several pathogenic pathways in COPD via the airway immune response [40, 115-120]. Cysteinyl leukotriene receptor antagonists ameliorate AHR and static compliance in an asthma-COPD overlap model constructed using porcine pancreatic elastase (PPE) and ovalbumin by inhib-

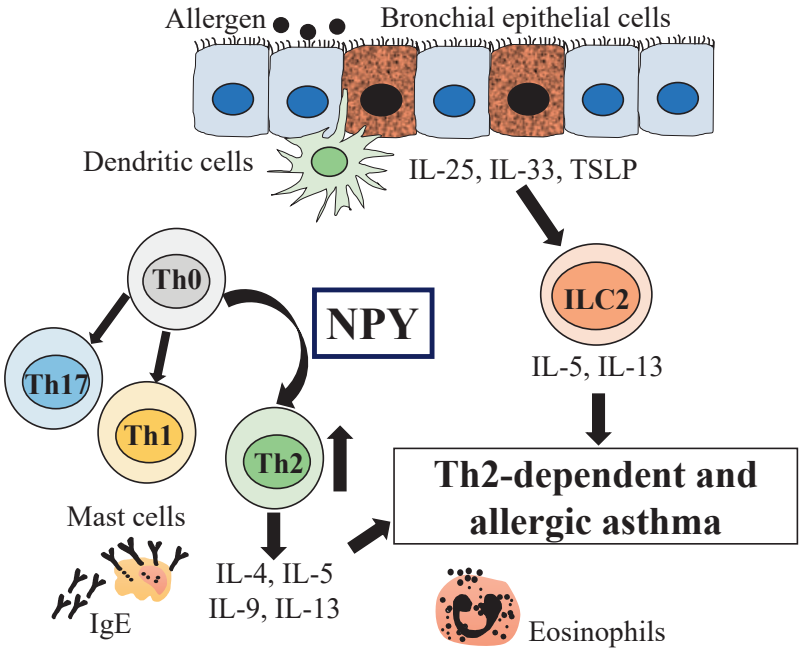

Fig. 1 The role of NPY in asthma pathogenesis. Exposure of bronchial epithelial cells to allergens stimulates dendritic cell maturation and neuropeptide Y (NPY)-induced Th2 polarization. Levels of T helper 2 (Th2) cytokines, such as IL-4, IL-5, IL-9, and IL-13, increase. Mast cells produce immunoglobulin E (IgE), and eosinophils are activated. IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) from bronchial epithelial cells induce the production of group 2 innate lymphoid cells (ILC2), which cause allergic inflammation by producing cytokines IL-5 and IL-13. NPY promotes Th2 polarization and allergic inflammation through these immune responses [39,92-94].
IgE, immunoglobulin E; ILC2, group 2 innate lymphoid cell; NPY, neuropeptide Y; Th2, T helper 2; TSLP, thymic stromal lymphopoietin.

iting type-2 cytokines, CXCL1/2 chemokines, and tumor necrosis factor-α [115]. RAGE, which exacerbates asthma pathogenesis [90], plays a critical role in promoting neutrophilic inflammation and stimulating the onset of emphysema in a PPE-induced emphysema model [116]. The retinoid X receptor partial agonist NEt-4IB, which suppresses the allergic airway response [91], also inhibits the development of emphysema [117]. IL-17A secreted from Th17 cells is essential for the development of lung inflammation and emphysema in PPE-induced pulmonary emphysema [118]. IL-23 is critical for the development of emphysema in that it exacerbates neutrophilic inflammation while elevating both the level of IL-17 and the number of Th17 cells in the lungs [119]. Although IL-33 is essential for the development of asthma [121], our laboratory showed that the loss of IL-33 promotes the development of emphysema [120].

Some studies have indicated that NPY is responsible for COPD pathogenesis. Our laboratory showed that NPY inhibits the development of emphysema by decreasing the secretion of proinflammatory chemokines, the production of IL-17A, and the number of group 3 innate lymphoid cells (ILC3). Treatment with the NPY–Y1 receptor antagonist BIBO-3304 exacerbates the development of emphysema [40].

Exposure to cigarette smoke reduces NPY levels in the paraventricular nucleus and fat mass; it also regulates adipose cytokine production [122]. A study comparing neuropeptide expression in the airways of COPD patients showed that vasoactive intestinal peptide and substance P expression levels increase in the airway epithelium, glands, and muscle fibers, whereas NPY expression levels significantly decrease [123]. NPY expression increases around nerve fibers in the tracheal epithelium but decreases with growth when mice are exposed to side-steam tobacco smoke during the early postnatal period [124]. However, the mechanisms by which NPY concentrations and expression levels decrease in COPD are unknown. Figure 2 shows the hypothetical role of NPY in the pathogenesis of COPD based on data from our laboratory and previous reports [40,123,124]. Furthermore, to our knowledge, our laboratory study is the only investigation that has demonstrated the mechanism underlying the NPY immune response in COPD [40]. Thus, further research is needed concerning the role of NPY in COPD.

Pulmonary Fibrosis

There are several types and classifications of pulmonary fibrosis, including IPF [125-127]. IPF is a disease with poor prognosis, characterized by progressive

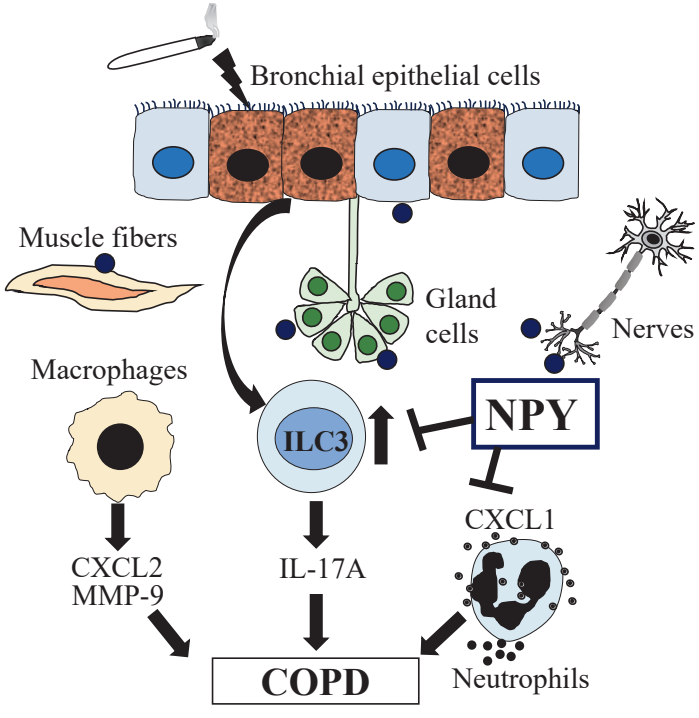

Fig. 2 The hypothetical role of NPY in the pathogenesis of chronic obstructive pulmonary disease (COPD). Cigarette smoking damages bronchial epithelial cells and reduces the uptake of NPY, presumably released from nerves [124] into bronchial epithelial cells, glandular cells, and muscle fibers [123]. Airway inflammation induces the production of ILC3s, which stimulate IL-17A release. C-X-C motif chemokine ligand 1 (CXCL1) recruits and activates neutrophils; macrophage-derived CXCL2 and matrix metalloproteinase-9 (MMP-9) promote COPD onset. NPY protects against the development of COPD by inhibiting airway inflammation caused by ILC3-derived IL-17A [40].
COPD, chronic obstructive pulmonary disease; CXCL1, C-X-C motif chemokine ligand 1; CXCL2, C-X-C motif chemokine ligand 2; ILC3, group 3 innate lymphoid cell; MMP-9, matrix metalloproteinase-9; NPY, neuropeptide Y.

pulmonary fibrosis and respiratory failure [17, 128, 129]. It is fatal when complicated by acute exacerbations [130-132]. Pirfenidone and nintedanib are the only anti-fibrotic agents used to treat IPF [133-138]; new therapeutic agents for IPF are needed.

The epithelial–mesenchymal transition (EMT) plays a critical role in IPF progression [139-142]. Although many mechanisms of IPF pathogenesis have been elucidated using mouse models of bleomycin (BLM)-induced pulmonary fibrosis [143-146] and *in vitro* experiments with human lung epithelial A549 cells [147-149], IPF pathogenesis is particularly complex and remains poorly understood.

IL-1β is a proinflammatory cytokine in the IL-1 family; its release from airway epithelial cells and alveolar macrophages promotes the development of fibrosis in IPF [144, 150-154]. IL-1β stimulates Th17 cells, increases the level of IL-17A, and promotes the EMT, leading to the progression of pulmonary fibrosis [142, 155, 156]. IL-1β and Th17 cells are also involved in the pathologies of various organs and cells [157-160].

NPY exhibits anti-inflammatory effects by suppressing IL-1β and other inflammatory cytokines and chemokines [161-163]. Thus, we explored whether NPY could protect against pulmonary fibrosis in IPF via the suppression of IL-1β. We found that NPY protected against fibrosis onset in IPF by inhibiting IL-1β through the NPY–Y1R axis [41]. To our knowledge, that report was the first to show that NPY has a critical role in IPF pathogenesis.

In the same study, we established a BLM-induced pulmonary fibrosis model using NPY-deficient ($NPY^{-/-}$) and wild-type (WT) mice *in vivo* [41]. Using this model, we found a significant exacerbation of lung fibrosis and worsened airway inflammation in BLM-exposed $NPY^{-/-}$ mice compared to WT mice. Both the level of IL-1β and the number of Th17 cells in the airway were significantly greater in $NPY^{-/-}$ mice than in WT mice at the acute phase of BLM exposure. NPY treatment significantly reduced the fibrotic area and significantly lowered the levels of IL-1β in both WT and $NPY^{-/-}$ mice that had BLM-induced lung fibrosis. These findings suggested that NPY ameliorates the development of lung fibrosis by suppressing the production of IL-1β and the number of Th17 cells. Our *in vitro* experiments in the same study showed that A549 cells exposed to BLM exhibited significantly greater IL-1β release and EMT promotion; NPY reduced IL-1β release from BLM-exposed A549 cells and suppressed the EMT [41]. Under steady-state conditions, Y1 was the most highly

expressed NPY receptor in A549 cells. Concurrent treatment of BLM-exposed A549 cells with the Y1 receptor antagonist BIBP3226 and NPY led to enhanced IL-1β production and EMT promotion. These *in vivo* and *in vitro* results suggest that NPY suppresses pulmonary fibrosis progression by regulating IL-1β production and the EMT through the NPY–Y1 receptor axis [41].

We also assessed the numbers of NPY-positive cells in mice and humans in the same study [41]. In animals with BLM-induced lung fibrosis, NPY-positive cells were mainly expressed in bronchial epithelial cells and epithelial cell adhesion molecule (EpCAM)-positive cells, as the studies [96,97] that previously demonstrated NPY-positive cell expression in asthma models. We also evaluated the expression of NPY-positive cells using tissue from transplanted human lungs. We found that NPY-positive cells were expressed around bronchial epithelial cells, EpCAM-positive cells, and pro-surfactant protein C-positive cells in samples from a healthy lung donor. The number of NPY-positive bronchial epithelial cells was decreased in IPF, consistent with prior findings [123] that demonstrated reduced NPY-positive cell expression in COPD lung tissue. We detected IL-1β-positive cells among EpCAM-positive cells and alveolar macrophages in samples from IPF patients [41]. These findings indicate that NPY produced by bronchial epithelial cells suppresses the development of pulmonary fibrosis by inhibiting IL-1β secretion from bronchial epithelial cells and alveolar macrophages (Fig. 3). Compared to healthy lung tissue, IPF lung tissue contains fewer NPY-positive cells, presumably because NPY production from bronchial epithelial cells is suppressed in IPF. However, the sample size in that study [41] was small; further research is needed. Another limitation of that study was that its design did not allow evaluation of the associations among NPY, alveolar macrophages, and nervous tissue. To our knowledge, however, our laboratory is the first to describe the critical role of NPY in IPF pathogenesis.

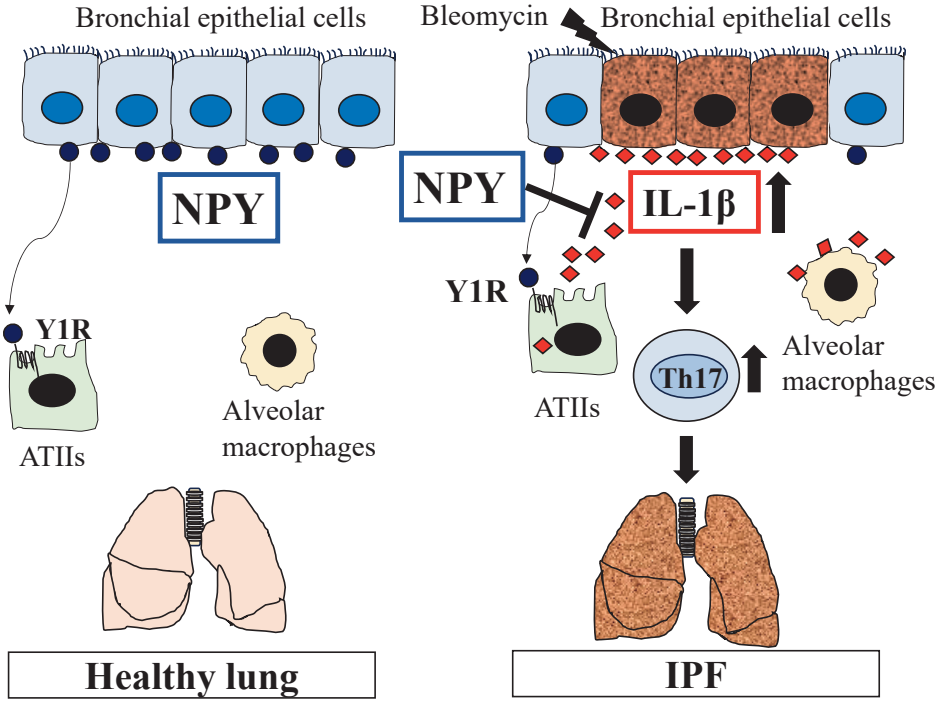

Fig. 3 The role of NPY in the pathogenesis of idiopathic pulmonary fibrosis (IPF). In healthy lungs, neuropeptide Y (NPY) is secreted from bronchial epithelial cells and maintains lung homeostasis via the Y1 receptor (Y1R) on type II alveolar epithelial cells (ATIIs). Stimuli (*e.g.*, bleomycin) damage bronchial epithelial cells, and NPY expression is lower in damaged bronchial epithelial tissue than in healthy lung tissue. IL-1β secretion, mainly from bronchial epithelial cells, ATIIs, and alveolar macrophages, is significantly enhanced. NPY may protect against the development of IPF by inhibiting IL-1β secretion and T helper 17 (Th17) cell migration via the NPY–Y1R axis [41].
ATIIs, type II alveolar epithelial cells; IPF, idiopathic pulmonary fibrosis; NPY, neuropeptide Y; Y1R, NPY–Y1 receptor; Th17, T helper 17.

Despite its limitations, our study highlights the need for further investigation of NPY in IPF pathogenesis.

Conclusions and Future Perspectives

In this review, we have discussed the roles of NPY and the airway immune responses in several respiratory diseases. Notably, our laboratory showed that NPY acts via the Y1 receptor in respiratory diseases, but that the effects of NPY and corresponding immune responses differed among asthma, COPD, and IPF [39-41]. Our laboratory and others have shown that NPY affects Th cells in a manner that is distinct among respiratory diseases [39,41,92,93,106]. NPY regulates the Th1/Th2 balance, and a nervous tissue-derived decrease in NPY levels results in a shift toward Th1 cells [164]. Moreover, NPY promotes Th2 polarization by inducing dendritic cell migration [94]. In an animal model of experimental autoimmune encephalomyelitis, NPY decreases the levels of cytokines derived from Th1 and Th17 cells while increasing the levels of cytokines derived from Th2 cells [165]. Therefore, NPY may exert distinct effects on Th cells, potentially exacerbating asthma pathogenesis in Th2-dependent asthma, while inhibiting the onset of lung fibrosis by regulating Th17 cells in IPF. NPY in the lungs may moderate respiratory disease pathogenesis via the airway immune response. Further studies are needed to confirm this hypothesis.

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