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Review

Nrf2: A Promising Therapeutic Target for Glucocorticoid-Resistant Chronic Rhinosinusitis

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Chronic rhinosinusitis (CRS) presents a challenge for otolaryngologists due to its complex management and high recurrence rates. Glucocorticoids (GCs) are widely employed for their potent anti-inflammatory effects across various inflammatory conditions and play a pivotal role in treating CRS. However, some patients exhibit insensitivity to GC therapy, resulting in GC resistance (GCR). Oxidative stress is a key factor contributing to GCR development, whereas the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway functions as a vital cellular defense mechanism against oxidative stress-induced damage. Investigating the Nrf2 signaling pathway holds promise for advancing our understanding of GC sensitivity and refining its therapeutic application in CRS. This article reviews the relationship between GC sensitivity and the Nrf2 signaling pathway, as well as potential Nrf2-related drugs. Studies show that Nrf2 activators—when used alone or in combination with GCs—more effectively inhibit the release of inflammatory factors and mitigate oxidative stress damage than GC monotherapy, marking them as a promising target for CRS treatment.

Keywords. *Chronic Rhinosinusitis; Glucocorticoid-Resistant; Oxidative Stress; Nrf2 Signaling Pathway; Nrf2 Activators*

INTRODUCTION

The global prevalence of chronic rhinosinusitis (CRS) ranges from 5% to 12% [1], imposing a considerable health burden on both individuals and society. CRS, particularly CRS with nasal polyps (CRSwNP), poses a significant challenge due to difficulties in control and high recurrence rates. Recent international guidelines and expert consensus classify CRS as a chronic inflammatory disease, emphasizing that endoscopic sinus surgery is only one component of a multifaceted treatment strategy. The primary goal is to optimize conditions for local treatment, with continuous postoperative drug therapy being essential [1,2].

CRS has a complex pathogenesis, primarily involving the following mechanisms: (1) Damage to the nasal mucosal epithelial barrier coupled with an imbalance in the innate immune responses of the epithelium [3,4]. (2) Three inflammatory endotypes characterized by elevated levels of distinct lymphocyte cytokines: type 1 inflammation (represented by interferon-gamma [IFN-γ] and tumor necrosis factor-alpha [TNF-α]), type 2 inflammation (represented by interleukin [IL]-4, IL-5, IL-13, and immunoglobulin E [IgE], and type 3 inflammation [represented by IL-17A and IL-22]) [3,4]. (3) Fibrin deposition leads to tissue remodeling [3,4]. Currently, glucocorticoids (GCs) remain the first-line treatment for CRS. Both nasal and systemic GCs are recommended as level 1a treatments in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [1]. However, studies indicate that oral and nasal GCs are effective in only 50% to 80% of CRS patients, with some individuals developing GC resistance (GCR) [2,5-9].

Oxidative stress damages lipids, proteins, and nucleic acids, impairing normal cellular functions and compromising defense mechanisms, which leads to heightened inflammation. It is a significant contributor to the development of GCR [10-12] and is well evidenced in various diseases [11,13-15]. In CRSwNP, oxidative stress disrupts epithelial barrier integrity and exacerbates inflammation, including in the GCR subtype [16-19]. The nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway is one of the most crucial cellular defense mechanisms against oxi-

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dative damage [20,21] and plays a pivotal role in immune defense within the nasal mucosa [22-25]. Investigating the Nrf2 signaling pathway may reveal new drug targets for treating CRSwNP, particularly in cases with GCR. This article reviews the role of the Nrf2 pathway, its relationship with GC sensitivity, and advances in Nrf2-related drug treatments.

FACTORS INFLUENCING SENSITIVITY TO GC THERAPY IN CRS

GCs exert their anti-inflammatory effects by binding to the GC receptor (GR). Notably, elevated expression levels of GR-β, a reduced GR-α/GR-β ratio, and impaired nuclear translocation of GR-α all contribute to GCR [26-28]. Additionally, varying inflammatory profiles in airway diseases yield different responses to GC therapy [4,29-33], with increased mucosal infiltration of Th17 cells and neutrophils correlating with poor GC responsiveness [32,34]. Increased IL-17A levels further inhibit the expression of GR-α in human nasal epithelial cells (hNEpCs) via the extracellular signal-regulated kinase-NOD-like receptor thermal protein domain associated protein 3 (NLRP3)/caspase-1 signaling pathway, while simultaneously promoting GR-β expression and thus contributing to GCR [35].

Among the three inflammatory endotypes of CRS, GCs exert a more potent inhibitory effect on type 2 inflammatory cells and cytokines compared to type 1 and type 3 [4,32,36]. Conversely, excessive type 2 inflammation or an imbalance between type 1 and type 2 immune responses may result in poor GC responsiveness [33,37]. One study found that GCs dose-dependently inhibited the production of CCL11 (eotaxin) and CCL5 (RANTES) by airway smooth muscle cells in healthy donors, whereas these anti-inflammatory effects were absent even at high concentrations in patients with severe asthma [38]. This discrepancy may be due to the "impaired GR-α transactivation" in the airway smooth muscle cells of severe asthma patients [28,38]. In CRS patients, high levels of IL-8 in nasal tissue may indicate poor clinical control with topical fluticasone propionate following surgery [39]. Additionally, elevated levels of IL-25 in nasal tissue and serum, higher concentrations of Charcot-Leyden crystals in nasal secretions, and an increased 11β-hydroxysteroid dehydrogenase (HSD)1/11β-HSD2 ratio in nasal polyp tissues may predict a favorable response to GC therapy [6,7,40]. Conversely, high serum amyloid A (SAA) levels in nasal polyp tissues may indicate GC insensitivity in CRSwNP patients [41]. Moreover, the mRNA expression levels of aldehyde dehydrogenase 1 (ALDH1A1), microsomal glutathione S-transferase 1 (MGST1), and superoxide dismutase 2 (SOD2) in the sinus mucosa of CRSwNP patients were significantly lower than in controls, correlating positively with tissue neutrophilia and a poor GC response (defined as no more than a 1-point reduction in the nasal polyp score after 7 days of oral prednisone at 20 mg daily). Notably, ALDH1A1, MGST1, and SOD2 demonstrated predictive power for poor GC response in CRSwNP patients, with area under the curve values of 0.8229, 0.6333, and 0.6250, respectively (all $P<0.05$) [42]. Furthermore, Zhu et al. [43] performed transcriptomic sequencing and oxidative lipidomics on nasal polyp tissue samples obtained before and after oral corticosteroid (OCS) treatment, as well as on control nasal mucosa, and identified additional potential biomarkers. High expression of type 2 inflammatory molecules (CCL13, IGHE, CCL18, CCL23, CCR3, and CLC) along with notably low expression of *LACRT*, *PPDPFL*, *DES*, *C6*, *MUC5B*, and *SCGB3A1* correlated with a favorable therapeutic response to OCS. Factors influencing sensitivity to glucocorticoid therapy in chronic rhinosinusitis are listed in Table 1.

HIGHLIGHTS

- Chronic rhinosinusitis (CRS) is a chronic inflammatory disease with a complex endotype, and an oxidative stress response is one causative factor in the persistence of inflammation.
- Glucocorticoids (GCs) are the first-line treatment for CRS, but GC resistance among some patients is a significant concern.
- Oxidative stress is one of the causative factors in GCR development.
- The nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway serves as a critical cellular defense mechanism against oxidative stress-induced damage.
- Studies have shown that Nrf2 activators, when used alone or in combination with GCs, more effectively inhibit the release of inflammatory factors and reduce oxidative stress damage compared to GC monotherapy, making them a promising new target for CRS treatment.

THE Nrf2 SIGNALING PATHWAY AND ITS FUNCTION

Existence and regulation of Nrf2

Nrf2 serves as a crucial protective regulatory factor in the cellular response to oxidative stress. Under normal conditions, Nrf2 resides in the cytoplasm, forming a complex with its adaptor protein Kelch-like ECH-associated protein 1 (Keap1), which anchors it to the actin cytoskeleton. In its inactive state, Nrf2 undergoes ubiquitination and degradation. However, when oxidative stress occurs, Nrf2 is phosphorylated, dissociates from Keap1, and translocates into the nucleus. There, it forms a heterodimer with a small Maf protein and binds to antioxidant response elements (AREs), initiating the transcription of downstream antioxidant genes that counteract cellular damage. These gene products include catalase (CAT), NAD(P)H:quinone oxidoreductase 1 (NQO1), various glutathione S-transferases (GSTs), glutathione

Table 1. Factors influencing sensitivity to glucocorticoid therapy in chronic rhinosinusitis

Factor/biomarker	Effect on sensitivity to GC treatment	Reference
GR-related mechanism		
High expression levels of GR-β	Decreased sensitivity	[26]
Lower GR-α/GR-β ratio	Decreased sensitivity	[27]
Impaired nuclear translocation of GR-α	Decreased sensitivity	[28]
Inflammatory endotype		
Increased Th17 cell/neutrophil infiltration	Decreased sensitivity	[32,34]
Excessive type 2 inflammation/type 1-type 2 immune imbalance	Decreased sensitivity	[33,37]
Cytokines and chemokines		
Increased IL-17A levels (inhibition of GR-α and promotion of GR-β via ERK-NLRP3/caspase-1 pathway)	Decreased sensitivity	[35]
IL-8 (high expression in nasal tissue before surgery)	Poor efficacy of postoperative topical fluticasone	[39]
High levels of IL-25 in nasal tissue and serum	Good response to GC therapy	[7]
High levels of Charcot-Leyden crystal concentration in nasal secretions	Good response to GC therapy	[6]
High ratio of 11β-HSD1/11β-HSD2 in nasal polyp tissues	Good response to GC therapy	[40]
High level of SAA in nasal polyp tissues	Decreased sensitivity	[41]
Oxidative stress molecules		
Low mRNA expression of ALDH1A1, MGST1, and SOD2	Decreased sensitivity (AUC predictive value 0.63–0.82)	[42]
Transcriptomic/lipidomic markers		
High expression: CCL13, IGHE, CCL18, CCL23, CCR3, CLC (type 2 inflammatory molecules)	Good therapeutic response to OCS	[43]
Low expression: LACRT, PPDPFL, DES, C6, MUC5B, SCGB3A1	Good therapeutic response to OCS	[43]

GC, glucocorticoid; GR, glucocorticoid receptor; IL, interleukin; HSD, hydroxysteroid dehydrogenase; SAA, serum amyloid A; ALDH1A1, aldehyde dehydrogenase 1; MGST1, microsomal glutathione S-transferase 1; SOD2, superoxide dismutase 2; AUC, area under the curve; OCS, oral corticosteroid.

peroxidase 4 (GPX4), glutamate-cysteine ligase catalytic subunit (GCLC), aldehyde oxidase 1 (AOX1), and heme oxygenase-1 (HO-1), among others [44,45].

Nrf2 is widely expressed across various tissues and cell types, exhibiting significant tissue specificity [46]. It is highly expressed in the liver, where it plays a key role in detoxification and metabolism [47,48]. In the kidneys, Nrf2 helps remove free radicals and toxins [49]. In lung tissue, it safeguards epithelial cells against inhaled pollutants, oxidative damage, and ferroptosis [50]. In the gut, Nrf2 maintains intestinal barrier function and regulates inflammatory responses [51]. Additionally, Nrf2 is present in neurons and glial cells in the central nervous system, protecting neurons from oxidative injury [52], and in cardiomyocytes where it contributes to cardiac protection [53]. Moreover, its expression in immune cells, such as macrophages and T cells, allows Nrf2 to modulate inflammation and immune responses [54,55].

Antioxidant stress and anti-inflammatory effects of the Nrf2 signaling pathway

On one hand, Nrf2 induces the expression of various antioxidant enzymes to protect cells against oxidative damage [44,45]. On the other hand, it negatively regulates the activation of the nuclear factor kappa B (NF-κB) signaling pathway and suppresses NF-κB-induced pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS/NOS2), and vascular cell adhesion molecule-1 (VCAM-1) [56,57]. The interplay between Nrf2 and NF-κB is cell- and tissue-specific and warrants further investigation into its regulatory network [56,58]. One study reported that Nrf2 inhibits the expression of genes involved in inflammasome assembly—including NLRP3, Caspase-1, IL-1β, and IL-18—thus suppressing NLRP3 inflammasome activity [59]. Furthermore, the Nrf2 activator tert-butylhydroquinone (tBHQ) has been shown to induce NQO1 expression and inhibit the initiation of NLRP3 signaling in an Nrf2-ARE-dependent manner [59]. Consequently, Nrf2 appears to play a critical role in regulating pyroptosis (inflammatory necrosis) associated with NLRP3 [60,61]. The antioxidant and anti-inflammatory properties of Nrf2 have been extensively reviewed [12,58,62].

Nrf2 exerts a potent inhibitory effect on both type 2 and type 3 inflammation. For instance, soybean tar Glyteer (Gly) and coal tar activate the aryl hydrocarbon receptor (AHR)-regulated Nrf2 antioxidant stress pathway in skin inflammation. In addition, Nrf2 upregulates antioxidant enzymes such as NQO1 and HOX1, which neutralize reactive oxygen species (ROS) induced by IL-4/IL-13, while restoration of protein tyrosine phosphatase nonreceptor type 1 (PTPN1) activity downregulates signal transducer and activator of transcription (STAT)6 phosphorylation [63,64]. Moreover, tectorigenin activates the Keap1/Nrf2/HO-1 signaling pathway, thereby increasing the expression of type 1 inflammatory factors (IL-12 and T-bet) and decreasing the expression of type 2 inflammatory factors (IL-4, IL-5, IL-13, and GATA-binding protein 3) in the bronchoalveolar lavage fluid (BALF) of allergic asthma mice. It also inhibits the mesenchymal marker al-

pha smooth muscle actin while increasing the epithelial marker E-cadherin in lung tissue, thus modulating the Th1/Th2 balance and preventing epithelial-mesenchymal transition (EMT) [65]. Ramanathan et al. [66] demonstrated that disruption of the Nrf2 pathway in a murine model exacerbated eosinophilic sinusitis, as evidenced by increased goblet cell proliferation in the nasal mucosa, elevated tissue eosinophil counts, and significantly higher mucosal IL-13 levels. These findings underscore a strong anti-tissue remodeling and anti-inflammatory role for the Nrf2 pathway in type 2 CRS. Furthermore, astragalus polysaccharide reduces apoptosis, ROS, and malondialdehyde (MDA) levels in IL-13-treated hNEpCs by activating the Nrf2/HO-1 pathway, which in turn elevates levels of SOD, CAT, and glutathione peroxidase (GSH-Px) [67]. Similarly, crocin alleviates the expression of multiple inflammatory factors—including IL-5, IL-6, IL-8, IL-13, IL-25, IL-33, IFN-γ, and IL-1β—in hNEpCs treated with staphylococcal enterotoxin B or lipopolysaccharide by activating the KEAP1/Nrf2/HO-1 pathway [68]. Although direct evidence in CRS is lacking, the Nrf2 pathway has demonstrated suppression of type 3 inflammation in several disease models, including atopic dermatitis [69], psoriasis [70,71], autoimmune encephalomyelitis [72], Alzheimer disease, chronic obstructive pulmonary disease (COPD) [73], and corticosteroid-resistant mixed granulocytic asthma [74].

Functions of oxidative stress and Nrf2 signaling pathway in airway mucosa

The airway mucosa—which includes both the upper (nasal) and lower (bronchial and alveolar) regions—constitutes the primary defense against pathogenic microorganisms and harmful particles. However, continuous exposure to the external environment renders it susceptible to oxidative stress induced by pollutants, toxic substances, and airborne chemicals. This oxidative stress can trigger various respiratory diseases, such as asthma, COPD, idiopathic pulmonary fibrosis, CRS, allergic rhinitis, and obstructive sleep apnea syndrome, among others [75-80]. Numerous oxidative stress biomarkers are highly expressed in nasal polyps, including eotaxin-1, thioredoxin-interacting protein, lectin-like oxidized LDL receptor-1, NADPH oxidases (dual oxidase 1 and 2), MDA, arachidonate 15-lipoxygenase (ALOX15), and iNOS [17,18,81-90]. Notably, eotaxin-1 selectively recruits and activates eosinophils within the nasal mucosa, thereby amplifying local type 2 inflammatory responses [91]. Similarly, ALOX15 upregulates the expression of CCL26 in nasal epithelial cells, exerting a pro-inflammatory effect and contributing to tissue remodeling associated with nasal polyps [84,87,92]. Moreover, cigarette smoke promotes ROS production, which disrupts the epithelial barrier of the nasal mucosa [25]. The degree of oxidative stress in the nasal mucosa correlates positively with symptom severity, such as nasal congestion and rhinorrhea [93]. Additionally, reduced expression of antioxidant enzymes—including SOD, lactoperoxidase, peroxiredoxin-2, and the adenylyl cyclase-activating polypeptide receptor 1—diminishes the epithelium's defense against oxidative stress [83,94], thereby exacerbating inflammation and barrier damage and facilitating nasal polyp formation.

Nrf2 plays a crucial role in maintaining the integrity of the airway epithelial barrier [25,45]. In the human bronchial epithelial cell line 16HBE, knockdown of the *Nrf2* gene disrupts the epithelial barrier. Treatment with dexamethasone (DEX) increases the expression of barrier-related proteins and reduces cellular permeability in 16HBE cells, accompanied by activation of the Nrf2/AOX1 pathway. However, knockout of either the Nrf2 or AOX1 gene inhibits the accumulation of tight junction and adherens junction proteins, thereby diminishing DEX's ability to enhance barrier integrity [45]. Similarly, activation of the Nrf2 pathway can reverse barrier dysfunction induced by cigarette smoke extract in sinus epithelial cells [25]. The olfactory mucosa also expresses Nrf2; GC treatment upregulates Nrf2 expression and induces the transcription of olfactory-related genes—including cytochrome P450 (CYP450) 2A3 and 3A9, and UDP-glucuronosyltransferase (UGT) 2A1—while increasing UGT activity [95]. In a mouse model of bronchitis, GCs improved lung tissue lesions, reduced airway resistance, enhanced antioxidant enzyme activities (including SOD, GPX, and CAT), decreased levels of the lipid oxidation product MDA, and reduced apoptosis marker expression (Bach1 and Bax) via activation of the Nrf2/Keap1 pathway [96]. The Nrf2 signaling pathway and its functions are summarized in Fig. 1 and Table 2.

THE RELATIONSHIP BETWEEN THE Nrf2 SIGNALING PATHWAY AND GC SENSITIVITY

The impact of GCs on the Nrf2 signaling pathway

Low doses of GCs have been shown to activate the Nrf2/HO-1 signaling pathway, upregulate HO-1 expression, and restore both cell viability and antioxidant enzyme levels in an H_2O_2-induced myocardial infarction cell model [97]. In contrast, excessive doses of GCs may inhibit the Nrf2 pathway, thereby reducing cellular defense against oxidative stress [98,99]. In the HEK-293 cell model, even physiological concentrations of GCs can suppress Nrf2 function [100]. Furthermore, different GC formulations exert heterogeneous effects on the regulation of the Nrf2 pathway in various animal and cell models [100-105], indicating that the regulatory effects of GCs on the Nrf2 pathway must be analyzed in a context-specific manner.

The Nrf2 pathway and the GR

The biological effects of GCs are primarily mediated by the GR. The classical GR pathway entails forming a complex between GR and chaperone proteins (e.g., Hsp90, Hsp70, and p23) along with FK506-binding proteins (FKBP51 and FKBP52) in the cytoplasm in the absence of ligands. This complex stabilizes the GR

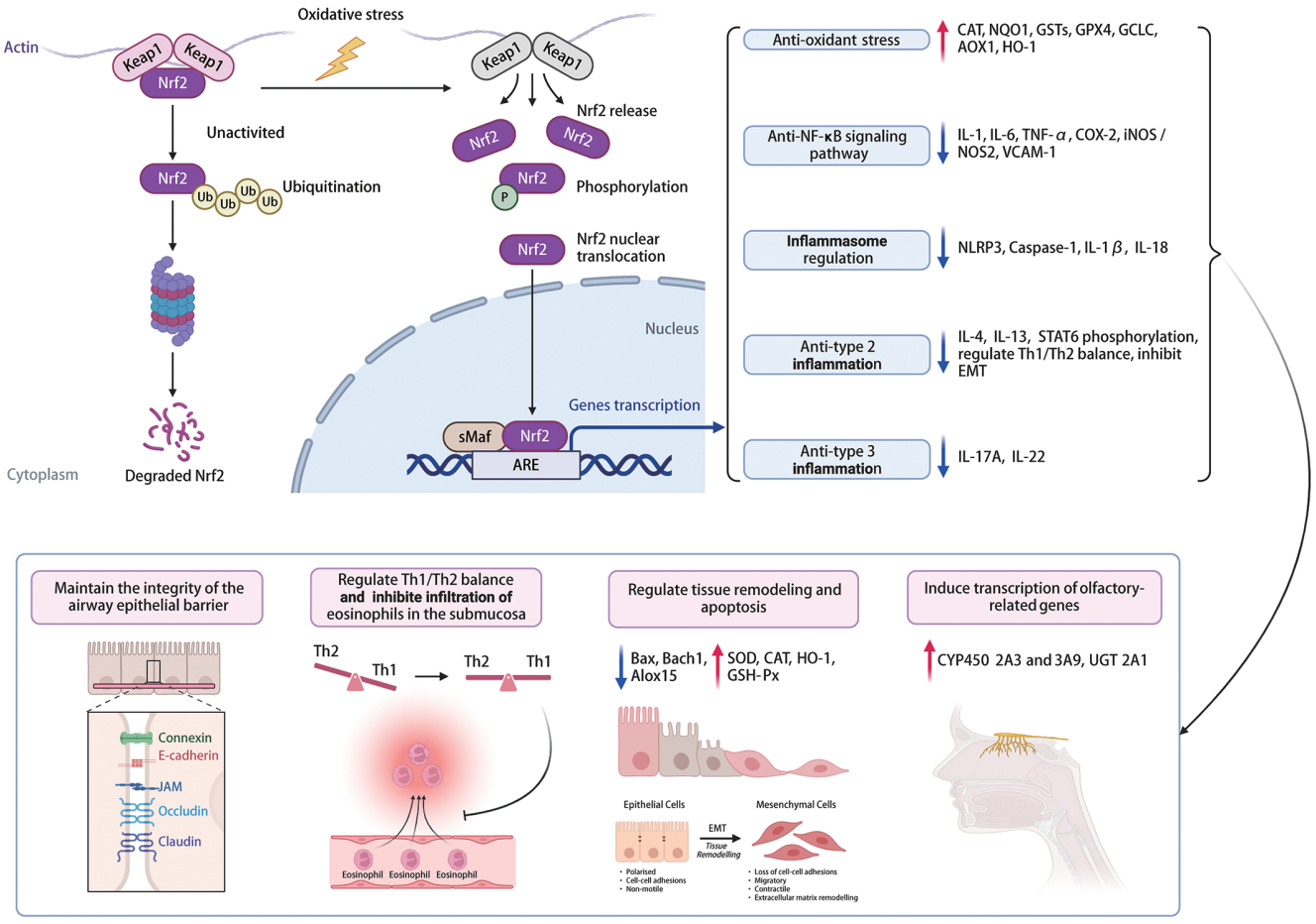

Fig. 1. The nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway and its function. Under normal physiological conditions, Nrf2 is localized in the cytoplasm where it forms a complex with Kelch-like ECH-associated protein 1 (Keap1). If Nrf2 remains inactive, it undergoes ubiquitination and degradation. However, when oxidative stress occurs, Nrf2 is phosphorylated and dissociates from Keap1 before translocating into the nucleus. Once in the nucleus, it forms a heterodimer with a small Maf (sMaf) protein and binds to antioxidant response elements (ARE), thereby initiating the transcription of downstream genes (see text). Ub, ubiquitination; P, phosphorylation; CAT, catalase; NQO1, NAD(P)H:quinone oxidoreductase 1; GST, glutathione S-transferase; GPX4, glutathione peroxidase 4; GCLC, glutamate cysteine ligase catalytic subunit; AOX1, aldehyde oxidase 1; HO-1, heme oxygenase-1; NF-κB, nuclear factor kappa B; IL, interleukin; TNF-α, tumor necrosis factor alpha; COX-2, cyclooxygenase-2; iNOS/NOS2, inducible nitric oxide synthase; VCAM-1, vascular cell adhesion molecule; NLRP3, NOD-like receptor thermal protein domain associated protein 3; STAT6, signal transducer and activator of transcription 6; EMT, epithelial-mesenchymal transition; SOD, superoxide dismutase; UGT, UDP-glucuronosyltransferase. Created with BioRender.com.

and facilitates ligand binding. Upon GC binding, the chaperone proteins dissociate, allowing GR to bind to GC-responsive elements in the nucleus and effect transcriptional activation or repression. Additionally, GR interacts with NF-κB and activator protein 1, thereby inhibiting the transcription of downstream inflammatory factors [106].

Simultaneously, GCs modulate Nrf2 activity through GR-Nrf2 interactions. Nuclear accumulation of GR does not impede Nrf2's nuclear translocation [99,107]. However, excessive GR signaling can counteract Nrf2 transcriptional activity by reducing Nrf2-dependent histone acetylation around AREs, which impairs cellular antioxidant capacity [107-109]. Melatonin, secreted by the pineal gland, has been shown to inhibit GC-induced GR nuclear translocation, enhance Nrf2 and HO-1 expression, and provide protection against GC-induced oxidative stress [110,111]. While some studies indicate that GR signaling activation negatively regulates the Nrf2 pathway, other findings from various disease models reveal that inhibition or knockout of GR expression is often accompanied by decreased Nrf2 expression, and vice versa [10,112-115]. These observations suggest that the effect of GR on Nrf2 may be bidirectional, warranting further investigation into the underlying mechanisms.

Inhibition of the Nrf2 pathway and GCR

Inhibition of the Nrf2 pathway may contribute to GCR [13,116-118]. For example, Adenuga et al. [118] found that Nrf2 knockout mice exhibited more severe oxidative stress responses—including increased neutrophil influx in the lungs following ciga-

Table 2. Nrf2 signaling pathway effects

Effects	Mechanism	Specific function	Reference
Antioxidant stress	Upregulates the expression of various antioxidant enzymes, including CAT, NQO1, GSTs, GPX4, GCLC, AOX1, and HO-1. These enzymes neutralize ROS, thereby protecting cells from oxidative stress.	By activating the Nrf2 signaling pathway, cells can increase their antioxidant defense capacity, reduce oxidative stress damage to DNA, proteins, and lipids, and then maintain the normal function of cells.	[44,45]
Anti-NF-κB signaling pathway	NF-κB is an important pro-inflammatory transcription factor that can induce the expression of a variety of pro-inflammatory cytokines, such as IL-1, IL-6, TNF-α, COX-2, iNOS, and VCAM-1.	By inhibiting the activity of NF-κB, Nrf2 can reduce the expression of these proinflammatory cytokines, thereby alleviating the inflammatory response. The interaction between Nrf2 and NF-κB is cell and tissue-specific.	[56,57]
Inflammasome regulation	Nrf2 inhibited the expression of genes involved in inflammasome assembly, including NLRP3, Caspase-1, IL-1β and IL-18. Nrf2 activator tBHQ can induce the expression of NQO1 in an Nrf2-ARE-dependent manner and inhibit the initiation of the NLRP3 signaling pathway.	Nrf2 plays a key role in inflammatory necrosis by inhibiting the activity of the NLRP3 inflammasome and reducing pyroptosis.	[59-61]
Anti-type 2 inflammation	Nrf2 can upregulate the expression of antioxidant enzymes, such as NQO1 and HOX1, by activating the antioxidant stress pathway regulated by the AHR, neutralize ROS induced by IL-4/IL-13, and down-regulate STAT6 phosphorylation by restoring the activity of PTPN1. In addition, Nrf2 can regulate Th1/Th2 balance and inhibit EMT by activating the Keap1/Nrf2/HO-1 signaling pathway.	Nrf2 has potent anti-inflammatory effects in type 2 inflammation, such as allergic asthma, chronic sinusitis, and atopic dermatitis.	[63-68]
Anti-type 3 inflammation	Nrf2 can inhibit the expression of IL-17A and IL-22 and inhibit the differentiation and function of Th17 cells.	No direct evidence exists for CRS, but the Nrf2 pathway has shown suppression of type 3 inflammation in several disease models: atopic dermatitis, psoriasis, autoimmune encephalomyelitis, Alzheimer disease, COPD, and corticosteroid-resistant mixed granulocytic asthma.	[69-74]
Protection of airway mucosa	Nrf2 can reduce oxidative stress damage to epithelial cells by regulating the integrity of the epithelial barrier in airway mucosa (including nasal and bronchial mucosa). *Nrf2* gene knockout leads to impaired epithelial barrier function, while drugs such as DEX can enhance the integrity of the epithelial barrier by activating the Nrf2/AOX1 pathway.	Nrf2 protects the airway mucosa from oxidative stress and inflammatory damage by upregulating the activity of antioxidant enzymes, such as SOD, GPX, and CAT, and reducing the production of lipid peroxidation products such as MDA.	[25,45,96]
Regulation of tissue remodeling and apoptosis	Nrf2 reduces apoptosis and the expression of oxidative stress markers (such as Bax and Bach1) while increasing the activity of antioxidant enzymes (such as SOD, CAT, and GSH-Px) by activating the Keap1/Nrf2 pathway.	Nrf2 can inhibit tissue remodeling and apoptosis, reducing airway inflammation and fibrosis in inflammatory diseases.	[67,96]
Role in olfactory mucosa	Nrf2 enhances olfactory mucosa's antioxidant and detoxification ability by upregulating the expression of CYP450 and UDP-glucuronosyltransferase.	Nrf2 protects olfactory mucosa from oxidative stress and inflammatory damage by activating the expression of downstream genes.	[95]

Nrf2, nuclear factor erythroid 2-related factor 2; CAT, catalase; NQO1, NAD(P)H:quinone oxidoreductase 1; GST, glutathione S-transferase; GPX4, glutathione peroxidase 4; GCLC, glutamate-cysteine ligase catalytic subunit; AOX1, aldehyde oxidase 1; HO-1, heme oxygenase-1; ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; IL, interleukin; TNF-α, tumor necrosis factor alpha; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; VCAM-1, vascular cell adhesion molecule-1; NLRP3, NOD-like receptor protein 3; tBHQ, tert-butylhydroquinone; Nrf2-ARE, Nrf2-antioxidant response element; HOX1, heme oxygenase 1; AHR, aryl hydrocarbon receptor; STAT6, signal transducer and activator of transcription 6; PTPN1, protein tyrosine phosphatase nonreceptor type 1; Th1, T helper type 1; Th2, T helper type 2; EMT, epithelial-mesenchymal transition; Keap1, Kelch-like ECH-associated protein 1; Th17, T helper type 17; CRS, chronic rhinosinusitis; COPD, chronic obstructive pulmonary disease; DEX, dexamethasone; SOD, superoxide dismutase; MDA, malondialdehyde; Bax, Bcl-2-associated X protein; Bach1, BTB and CNC homology 1; GSH-Px, glutathione peroxidase; CYP450, cytochrome P450.

rette smoke exposure—compared to wild-type mice. These knockout mice also showed diminished or absent anti-inflammatory responses to budesonide treatment [118]. In another mouse model of steroid-resistant chronic asthma, suppressed Nrf2 expression in lung tissue and reduced downstream CAT activity were accompanied by increased lipid oxidation damage following intranasal allergen stimulation, effects that were not mitigated by budesonide treatment [13]. In a clinical study, Qi et al. [117] treated 44 patients with significant sensorineural hearing loss (SSNHL) using intratympanic GC injections and divided them into GC-sensitive (IGCS) and GC-insensitive (IGCI) groups based on hearing improvement. Peripheral blood mononuclear cells collected from patients and healthy volunteers both before and after treatment showed that baseline Nrf2 mRNA levels in patients were lower than those in

controls. After treatment, the IGCS group exhibited increased Nrf2 and histone deacetylase 2 (HDAC2) mRNA and protein levels, whereas the IGCI group showed no significant changes. These findings suggest that a low Nrf2/HDAC2 protein response to GC treatment is associated with GC insensitivity in SSNHL, and that activation of the Nrf2-HDAC2 pathway may underlie differences in GC sensitivity among SSNHL patients [117].

POTENTIAL DRUG TARGETS ASSOCIATED WITH THE Nrf2 SIGNALING PATHWAY

Nrf2 activators have demonstrated stronger anti-inflammatory and organ-protective effects than GCs in numerous diseases [10,13,102,105,119-124]. Consequently, Nrf2 activators represent potential therapeutic targets for GCR diseases [105]. In the

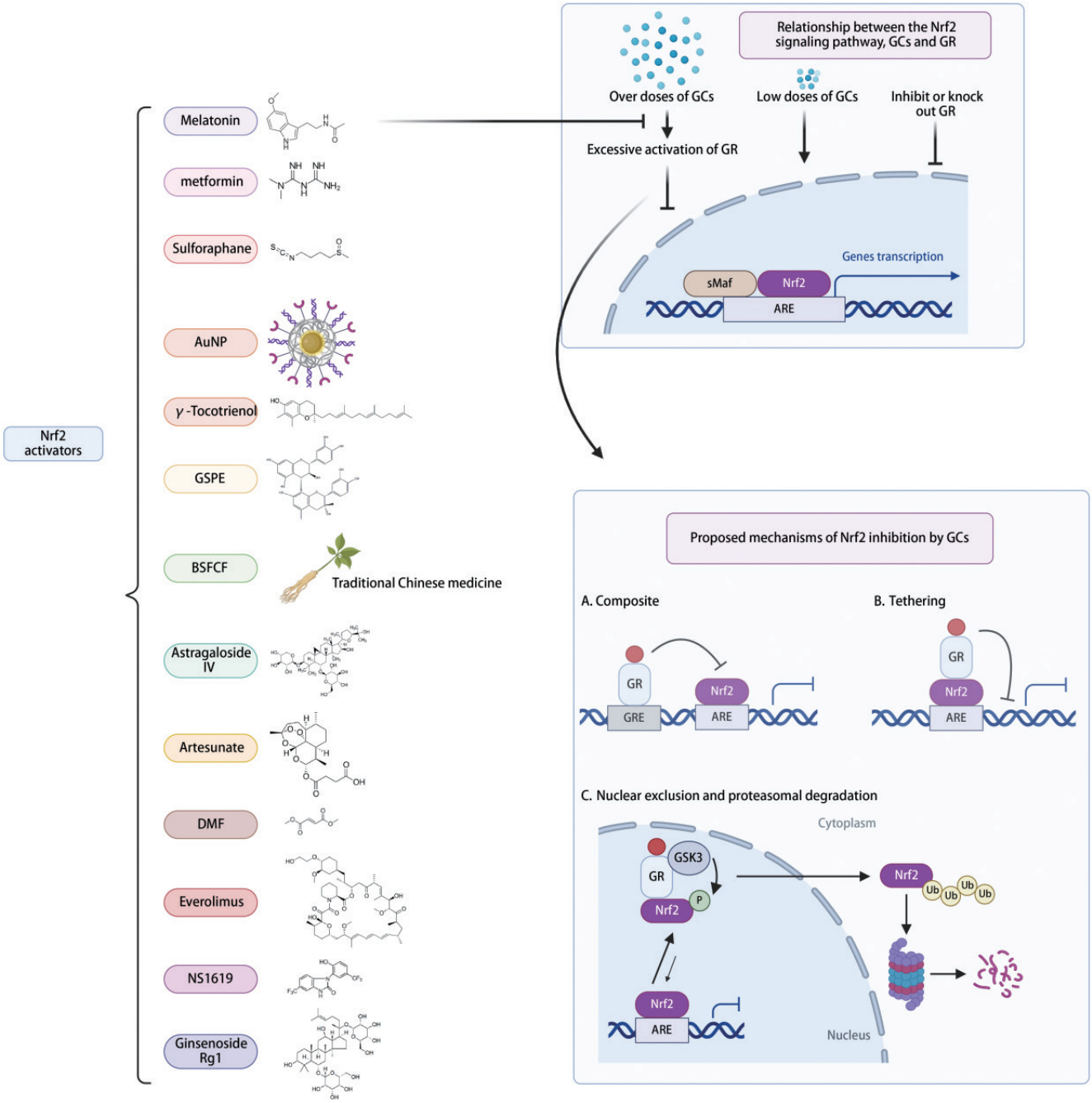

Fig. 2. The relationship between the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, glucocorticoids (GCs), glucocorticoid receptor (GR) [109], and associated drug targets. sMaf, small Maf; ARE, antioxidant response elements; AuNP, gold nanoparticles; GSPE, grape seed proanthocyanidin extract; BSFCF, Bu-Shen-Fang-Chuan formula; DMF, dimethyl fumarate; NS1619, a mitochondrial ROS scavenger; GRE, glucocorticoid-responsive elements; GSK3, glycogen synthase kinase 3. Created with BioRender.com.

field of chronic airway inflammatory diseases, Tao et al. [119] discovered that metformin inhibits IL-8 secretion in a GCR model using human bronchial epithelial cells exposed to cigarette smoke and upregulates the expression of Nrf2 and HO-1. Similarly, Sakurai et al. [120] observed that sulforaphane improves GC insensitivity in asthmatic mice exposed to cigarette smoke via an Nrf2-dependent pathway. As noted earlier, in a GCR chronic asthma mouse model, Nrf2 expression in lung tissue is suppressed after nasal allergen stimulation; moreover, budesonide treatment does not attenuate this oxidative response [13].

Another potential therapeutic agent, gold nanoparticles, exhibits significant anti-inflammatory and antioxidant properties and can partially restore Nrf2 expression along with CAT activity [13]. Furthermore, γ-tocotrienol, an isomer of vitamin E, has been reported to upregulate nuclear Nrf2 expression in a mouse model of asthma while reducing cytokine and chemokine levels in BALF, total ROS, oxidative damage biomarkers, and serum IgE levels [122]. In addition, the research team reported that γ-tocotrienol ameliorates bronchial epithelial thickening and alveolar sac destruction in a mouse model of COPD by inhibiting the nuclear translocation of STAT3 and NF-κB, while concurrently enhancing Nrf2 activation in the lungs; its anti-inflammatory and antioxidant effects exceed those of GCs [123]. Zhou et al. [125] and Qian et al. [126] documented the protective effects of grape seed proanthocyanidin extract (GSPE) in mouse models of asthma and GC-resistant asthma. GSPE has been shown to inhibit iNOS expression in lung tissue, reduce eosinophil infiltration and airway epithelial goblet cell production, and decrease serum levels of type 2 inflammatory factors such as IL-4, IL-13, and IgE. In a GCR asthma mouse model, GSPE activates the Nrf2-miR-29b axis to improve GCR. Furthermore, when combined with DEX, GSPE more effectively suppresses the production of IL-4, IL-13, and TGF-β1 in BALF while increasing IFN-γ expression compared to DEX monotherapy [126]. As noted ear-

Table 3. Therapeutic role of Nrf2 activators in related diseases

Nrf2 activator	Model organism	Effect and outcome	Reference
Melatonin	Peripheral blood mononuclear cells, Indian palm squirrel *Funambulus pennanti*	Inhibits GC-induced GR nuclear translocation, enhances Nrf2 and HO-1 expression, and exerts protective effects in GC-induced oxidative stress	[110,111]
Metformin	COPD rat model	Inhibits IL-8 secretion and upregulates the expression of Nrf2 and HO-1	[119]
Sulforaphane	Asthma mouse model	Improves GC insensitivity	[120]
AuNP	Murine model of GCR asthma	Restores the expression of Nrf2 and the activity of the antioxidant enzyme CAT	[13]
γ-Tocotrienol	Asthma mouse model	Blocks nuclear NF-κB levels and enhance nuclear Nrf2 levels in lung lysates to greater extents than prednisolone, markedly suppressed. Methacholine-induced airway hyperresponsiveness in experimental asthma	[122]
GSPE	Asthma mouse model, steroid-insensitive asthma mouse model, human peripheral blood mononuclear cells	Inhibits iNOS, lung eosinophil infiltration, and production of airway epithelial goblet cells; reduces IL-4, IL-13, and IgE in serum and BALF; reduces TGF-β1 while increasing IFN-γ in BALF. Activates the Nrf2-miR-29b axis to improve GCR	[125,126]
BSFCF	COPD rat model	Inhibits inflammatory reactions in a COPD rat model through the PI3K/Akt-Nrf2 and NF-κB signaling pathways	[124]
Astragaloside IV	Sprague-Dawley rats	Improves lung injury by activating the Nrf2/Keap1 pathway	[96]
Artesunate	Mouse model of allergic asthma, BEAS-2B cell line	Inhibits neutrophil recruitment, reduces 3-nitrotyrosine, and decreases pro-oxidants iNOS and NADPH oxidase (NOX1, 2, 3, and 4) in lung tissue	[127]
DMF	Human renal mesangial cells, lupus nephritis mice	Upregulates HO-1 and NQO1, inhibits MCP-1 and IL-6, and inhibits renal fibronectin expression	[105]
Everolimus	T-ALL cell lines and CG-resistant patient-derived T-ALL xenografts	Overcomes resistance to GCs under conditions of high tumor burden	[102]
NS1619	T-ALL cell lines, patient-derived xenografts, and primary cells from patients with refractory T-ALL	Reduces the growth of T-ALL xenografts derived from GCR patients	[121]
Ginsenoside Rg1	Human keratinocytes cells	Weakens UVB-induced GCR in keratinocytes through the Nrf2/HDAC2 signaling pathway	[10]

Nrf2, nuclear factor erythroid 2-related factor 2; GC, glucocorticoid; GR, glucocorticoid receptor; HO-1, heme oxygenase-1; COPD, chronic obstructive pulmonary disease; IL, interleukin; AuNP, gold nanoparticles; GCR, glucocorticoid resistance; CAT, catalase; NF-κB, nuclear factor kappa B; GSPE, grape seed proanthocyanidin extract; iNOS, inducible nitric oxide synthase; IgE, immunoglobulin E; BALF, bronchoalveolar lavage fluid; TGF-β1, transforming growth factor-beta 1; IFN-γ, interferon gamma; BSFCF, Bu-Shen-Fang-Chuan formula; PI3K/Akt, phosphatidylinositol 3-kinase/protein kinase B pathway; KEAP1, Kelch-like ECH-associated protein 1; BEAS-2B, human bronchial epithelial cell line; DMF, dimethyl fumarate; NQO1, NAD(P)H:quinone oxidoreductase 1; MCP-1, monocyte chemoattractant protein-1; T-ALL, T-cell acute lymphoblastic leukemia; UVB, ultraviolet B; HDAC2, histone deacetylase 2.

lier, Nrf2 activators such as Gly, coal tar, tectorigenin, *Astragalus* polysaccharide, and crocin can inhibit type 2 inflammation and restore Th1/Th2 balance in airway inflammatory diseases.

Some traditional Chinese medicine formulations and domestically developed drugs have been reported to activate the Nrf2 signaling pathway in airway inflammatory diseases. For instance, the traditional Chinese medicine formula Bu-Shen-Fang-Chuan formula (BSFCF) has been shown to inhibit inflammatory reactions in a COPD rat model by modulating the PI3K/Akt-Nrf2 and NF-κB signaling pathways [124]. Additionally, a combination of astragaloside IV and budesonide has demonstrated the ability to ameliorate lung injury in a rat model of bronchitis by activating the Nrf2/Keap1 pathway, counteracting oxidative stress, and providing a protective effect [96]. Furthermore, artesunate—a domestically developed antimalarial drug—has been found to improve oxidative lung injury in an ovalbumin-induced mouse model of allergic asthma. Artesunate is more effective than DEX at inhibiting neutrophil recruitment, reducing the formation of the oxidative damage marker 3-nitrotyrosine, and decreasing the production of pro-oxidants such as iNOS and NADPH oxidases (NOX1, 2, 3, and 4) in lung tissue, while concurrently upregulating nuclear Nrf2 levels [127].

Similar studies have been reported in other disease areas. For example, dimethyl fumarate (DMF) has been shown to exert effects similar to those of sulforaphane, improving inflammatory lesions in a lupus nephritis mouse model through activation of the Nrf2 pathway. Both DMF and sulforaphane demonstrate superior anti-inflammatory and organ-protective effects compared to GCs [105]. In a mouse study of GC-resistant T-cell acute lymphoblastic leukemia (T-ALL), the mTOR inhibitor everolimus was found to overcome GCR, a response accompanied by upregulation of the *Nrf2* gene [102]. In a subsequent study using a T-ALL cell model, the same research team observed that combining DEX with NS1619, a mitochondrial ROS scavenger, significantly reduced the growth of T-ALL xenografts derived from GCR patients while activating Nrf2 [121]. Following ultraviolet (UV) radiation, GCR and subsequent skin inflammation may develop; in this context, ginsenoside Rg1 mitigates UVB-induced GCR in keratinocytes through modulation of the Nrf2/HDAC2 signaling pathway [10]. Fig. 2 and Table 3 summarize the relationship between the Nrf2 signaling pathway, GCs, GR, and related drug targets.

THE POTENTIAL APPLICATION OF Nrf2 ACTIVATORS IN CRS TREATMENT

Notably, CRS, as a chronic inflammatory disease, exhibits a complex endotype [1,4,29-31,128-132]. The release of multiple inflammatory factors triggers and sustains an oxidative stress response, which constitutes a critical pathological process that perpetuates and exacerbates inflammation [14,16,19,42,83,94,133]. Therefore, controlling the oxidative stress response is conducive to breaking the vicious cycle of inflammation in CRS.

Although GCs are the first-line treatment for CRS, their anti-inflammatory effects are both time- and dose-dependent [7,134-137]. Upon reduction or cessation of GC therapy, CRS—especially type 2 CRS—tends to relapse rapidly. Even in some CRSwNP patients who initially respond well to treatment, the anti-inflammatory efficacy is diminished if GCs are reintroduced after a short interval. In addition, GCR may develop at the onset of treatment in non–type 2 CRS patients. Numerous research teams worldwide are dedicated to identifying complementary therapies to GCs, and the recent emergence of targeted biological agents is beginning to fill this gap. Currently, the targets of emerging biological agents for refractory CRS include anti-IgE, anti-IL-4, anti-IL-5, and anti-TSLP [138,139], all of which aim to suppress the Th2 inflammatory response in CRS. However, biological agents for non–type 2 CRS have not yet been commercialized. Moreover, excessive suppression of the Th2 inflammatory reaction may lead to immune imbalances—such as reduced immune surveillance against tumors—which could potentially promote tumor development [140,141]. Consequently, the clinical use of these biological agents entails certain risks. Having been employed to treat CRS for less than a decade, the long-term complications of biological agents remain to be fully elucidated. Therefore, developing targeted biological agents for non–type 2 and GCR-type CRS is urgently needed for refractory cases.

Activating the Nrf2 signaling pathway plays a crucial role in immune defense. This pathway is tightly regulated, and the transcription of multiple downstream genes confers potent antioxidant and anti-inflammatory effects. Numerous studies indicate that the use of Nrf2 activators alone, or in combination with GCs, offers superior inhibition of inflammatory factor release and oxidative stress damage compared to GCs alone. Thus, Nrf2 activators hold potential value as an adjunctive therapy to GCs. Encouragingly, many Nrf2 activators have already been applied clinically in other disease fields—with favorable efficacy and safety profiles, as exemplified by metformin in type 2 diabetes. Consequently, expanding the clinical applications of Nrf2 activators in CRS may help fill the therapeutic gap for non–type 2 and GCR-type CRS.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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