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REVIEW

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High mobility group box-1: a potential therapeutic target for allergic rhinitis

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Abstract

Allergic rhinitis (AR) is a prevalent chronic inflammatory disease of the nasal mucosa primarily characterized by symptoms, such as nasal itching, sneezing, runny nose, and nasal congestion. It has a high recurrence rate and low cure rate, with a lack of effective drugs for treatment. The current approach to management focuses on symptom control. High mobility group box-1 (HMGB1) is a highly conserved non-histone protein widely present in the nucleus of eukaryotes. It is recognized as a proinflammatory agent, and recent studies have demonstrated its close association with AR. Here, we will elaborate the role and mechanism of HMGB1 in AR, so as to reveal the potential value of HMGB1 in the occurrence and development of AR, and provide a new target for clinical research on the treatment of AR.

Keywords Allergic rhinitis, High mobility group box-1, Mechanism, Target

Introduction

AR, also known as allergic rhinitis, is a type I allergic disease characterized by repeated sneezing, runny nose, nasal congestion and itching, accompanied by red eyes and watery eyes, and other manifestations include itchy palate and cough et al. [1]. AR not only diminishes patients' work efficiency and quality of life but also leads to increased consumption of medical resources, exerting a significant social and economic burden. In addition to common nasal symptoms, patients can also suffer from asthma [2–5]. Pawankar et al. [6] noted that approximately 400 million people suffer from AR, affecting 10–30% of the global population. Likewise, research has shown that the prevalence rates range between 10% and 30% among children and adults in the United States and other developed nations [7]. AR has emerged as a growing global concern in the fields of health, medicine, and economics [8]. The treatment of AR primarily encompasses drug therapy, immunotherapy, environmental control, and health education. Drug therapy and allergen-specific immunotherapy are the most commonly employed approaches, while environmental control and health education aim to prevent patient exposure to allergens or irritants [9]. Conventional treatment drugs for AR include glucocorticoids, antihistamines and antileukotrienes. Allergen-specific immunotherapy, which encompasses both subcutaneous and sublingual methods, is frequently utilized. In recent years, significant progress has been made in the prevention and treatment of allergic rhinitis. The implementation of standardized treatment measures has proven effective in controlling various symptoms and significantly enhancing patients' quality of life [10–12]. However, the long-term therapeutic efficacy remains suboptimal, highlighting the lack of effective prevention and treatment measures for AR, which contributes to the ongoing challenges in its management. Consequently, the investigation of AR pathogenesis and potential therapeutic targets has garnered increasing attention from scholars.

The high mobility group proteins were initially extracted and identified in the bovine thymus in 1973.

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They were named based on their rapid migration in polyacrylamide gel electrophoresis. Among these proteins, HMGB1 is a highly conserved non-histone protein that is widely present in the nucleus of eukaryotes [13]. It has been established to play a crucial role in various diseases as a proinflammatory factor [14, 15], including sepsis, tumors, atherosclerosis, tissue ischemia–reperfusion injury, arthritis, asthma, chronic nephritis, and systemic lupus erythematosus [16–20]. Under specific conditions, HMGB1 can be released from the cell and interact with various cytokines and chemokines, leading to the amplification and perpetuation of the inflammatory response [17, 21, 22]. This process mediates the occurrence and progression of inflammatory diseases. As for the role of HMGB1 in tumor, HMGB1 demonstrates dual functionalities in the context of cancer progression and treatment. Specifically, HMGB1 can promote tumorigenesis. Elevated production of HMGB1, often attributed to chronic inflammatory responses, is implicated in the onset of tumorigenesis [23, 24]. Conversely, HMGB1 exhibits a protective function in inhibiting tumor progression and enhancing the efficacy of tumor chemoradiotherapy and immunotherapy. Within the nucleus, HMGB1 facilitates the regulation of telomeres and ensures genome stability. A deficiency in HMGB1 precipitates genome instability, subsequently promoting tumorigenesis [25, 26]. In recent years, an increasing number of studies have focused on the role of HMGB1 in allergic diseases, such as asthma and AR et al. [27, 28]. Among these studies, HMGB1 and AR have emerged as the most frequently studied subjects. Here, we will focus on the pathogenesis of AR to clarify the role and mechanism of HMGB1 in the occurrence and development of AR, for the purposes of identifying potential targets for the treatment of AR.

The pathogenesis of AR

AR is a type I allergic inflammation mediated by immunoglobulin E (IgE) [29]. Several factors contribute to the pathogenesis of AR. Multiple signal transduction pathways involved in the occurrence of AR are all related to the imbalance of Th1/Th2 cytokines, or are closely related to AR-related inflammation and immune cells, or are simultaneously associated with several factors [11, 30, 31]. Here, we will specifically clarify the pathogenesis of AR from the following three aspects.

Nasal mucosal epithelial barrier injury

The nasal mucosa is the first line of defense of the nasal cavity against the factors of airborne infection, the dysfunction of the nasal microflora has a significant impact on the occurrence and development of nasal inflammation. Impaired epithelial barrier function facilitates allergen penetration into the lower mucosa, resulting in monocyte activation and triggering a cascade of allergic reactions [32–34]. When mucosal integrity is compromised, the mucosal epithelia produces and releases injury-related molecules that chemotaxis and activate antigen-presenting cells, thereby activating and promoting innate and adaptive immunity. Histone deacetylase (HDAC) is considered a crucial factor in allergic inflammation and tight junction dysfunction. For instance, when the nasal mucosal epithelial barrier is damaged, HDAC activates mucosal repair mechanisms and triggers a protective inflammatory response [35–37]. Furthermore, local epithelial damage to the skin and mucosal barrier can result in the release of epithelial cytokines, such as IL-25 and IL-33, which can trigger allergic reactions and contribute to the development of AR [38, 39]. Therefore, safeguarding and restoring the integrity of the epithelial barrier play a crucial role in the pathogenesis of AR.

Antigen presentation and sensitization

AR is a chronic inflammatory disease mediated by a diverse range of immune inflammatory cells. Currently, the widely recognized immune theory posits that an imbalance in the mechanism of helper T lymphocytes (Th) plays a prominent role [40–42]. Normally, the proliferation of Th1 and Th2 cells maintains a relatively balanced state. When viruses and bacteria enter the mucosa, the body initiates a Th1 reaction, prompting Th1 cells to secrete IL-2 and IFN-γ, which mediate cellular immunity against infections. Stimulation of the airway mucosa by allergens results in excessive polarization of Th2 cells, leading to the overexpression of Th2 effector factors (IL-4, IL-5, IL-13), which mediate humoral immunity. Th2 cytokines act on B cells, inducing their transformation into plasma cells that produce and secrete specific IgE, thereby further mediating the occurrence of allergic reactions [43, 44].

The onset of symptoms and inflammation

AR symptoms occur when a patient, who has been sensitized by previous exposure to an allergen, encounters the pathogenic agent again. The allergen binds to allergen-specific IgE on mast cells present in the nasal mucosa, leading to the cross-linking of IgE with FcεRI. This activation of mast cells triggers the release of both pre-stored and newly synthesized mediators, including histamine, thiopeptide leukotrienes (leukotriene C4 and leukotriene D4), prostaglandin D2, and other substances [45–47]. These active mediators bind to their respective receptors, resulting in local and systemic changes. For instance, histamine activates H1 receptors in sensory nerve endings, leading to itching, systemic reflexes, and triggering of paroxysmal sneezing. The accumulation of inflammatory

mediators can result in severe allergic reaction symptoms. Furthermore, leukotrienes, vascular endothelial growth factor, prostaglandin D2, and other mediators can induce plasma exudation in blood vessels, leading to edema, blood deposition in the venous sinusoids, and increased secretion of glandular mucus. These effects can contribute to nasal congestion and the early manifestation of acute AR symptoms [6, 12, 48]. The pathogenesis, symptoms and treatment of AR were summarized, as shown in Fig. 1.

Overview of HMGB1

High mobility group protein was first isolated from calf breast gland chromatin by Goodwin et al. Because of its solubility in 10% trichloroacetic acid, rapid migration in the polyacrylamide gel electrophoresis system, and absence of aggregation, the protein is referred to as the "high mobility group protein" or HMG protein [49]. HMGB1 belongs to the HMG subfamily. The structure of HMGB1 comprises two DNA-binding functional domains (A-box and B-box) and a C-terminal region that is negatively charged and rich in acidic amino acids [50]. The B-box region is the primary active region of HMGB1, and its release into the extracellular system promotes the release of cytokines and contributes to a pro-inflammatory response. In contrast, the A-box region lacks the pro-inflammatory properties of the B-box, but it competes with the B-box for binding sites, resulting in a dampening of the inflammatory cascade [51, 52]. HMGB1 is a crucial chromatin protein primarily located in the nucleus and widely distributed in various tissues, such as the heart, brain, liver, lymphatic system, lungs, kidneys, nasal mucosa, and others. It plays a significant role in regulating DNA stability, replication, transcription, and translation. Recent studies have shown a strong correlation between HMGB1 and various pathophysiological processes. HMGB1 primarily exerts its effects through four pathways: the receptor for advanced glycation end products (RAGE), Toll-like receptor 4 (TLR4), Toll-like receptor 2 (TLR2), and chemokine receptor 4 [53]. The pivotal role of HMGB1 in the production and regulation of inflammation has been well-established. In colorectal cancer, LPS promotes tumor formation by releasing inflammatory factors through pathways associated with HMGB1 [54]. Furthermore, researchers have discovered that HMGB1 exhibits proinflammatory effects in the treatment of infectious diseases and sepsis. They found that the prognosis of sepsis improves after administering monoclonal antibodies targeting HMGB1 without causing immunosuppression [20, 55]. HMGB1 also contributes to the regulation of inflammation in aseptic inflammation, chronic inflammation, rheumatoid arthritis, and other autoimmune diseases [20, 56]. During the inflammatory response, HMGB1 stimulates the migration of innate immune cells, promotes the innate recognition of bacterial products, activates various innate

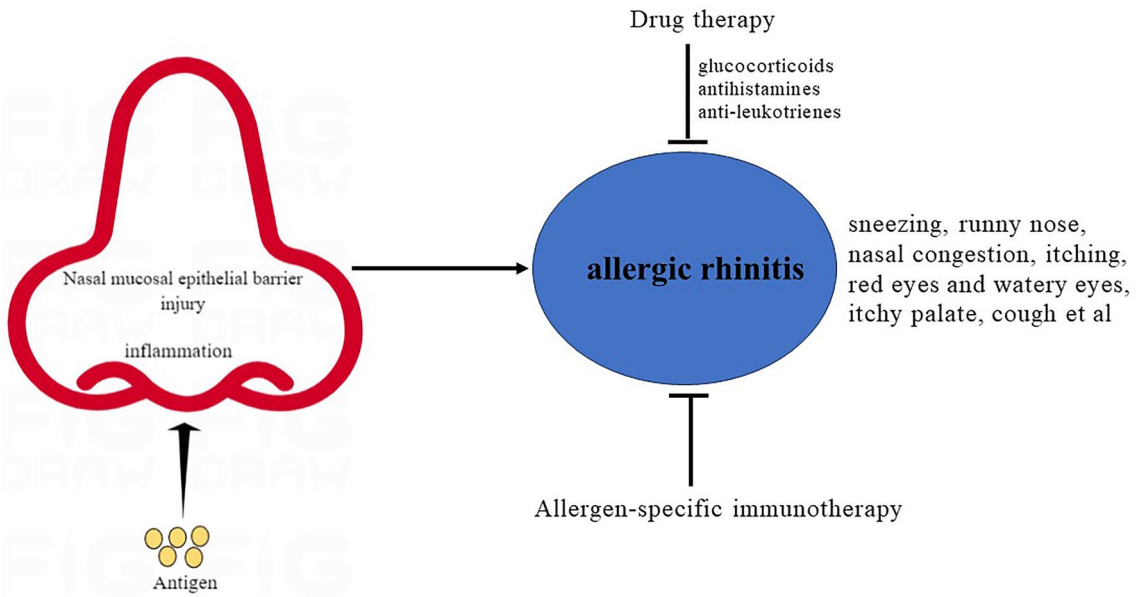

Fig. 1 Pathogenesis, symptoms and treatment of AR. Nasal mucosal epithelial barrier injury, antigen presentation and sensitization, inflammation collectively contribute to AR, accompanied by repeated sneezing, runny nose, nasal congestion and itching, red eyes and watery eyes, itchy palate and cough et al. Drug therapy and allergen-specific immunotherapy are the most commonly employed approaches. Conventional treatment drugs for AR include glucocorticoids, antihistamines, and anti-leukotrienes

immune cells, inhibits the phagocytosis of apoptotic cells to sustain the inflammatory response, and acts as an alarm signal to further activate innate immune cells, thereby maintaining the potential for harmful inflammation [57].

The role of HMGB1 in AR

There have been numerous studies on HMGB1 and bronchial asthma [58, 59]; however, despite the shared characteristics of AR and bronchial asthma, such as their highly reactive nature and similar pathogenesis and pathological changes, there is a dearth of research on the correlation between HMGB1 and AR. This review aims to explore the existing literature on HMGB1 and AR and elucidate the role and mechanism of HMGB1 in AR, focusing on the three aspects of AR pathogenesis mentioned earlier.

HMGB1 leads to epithelial cell injury

Previous research has demonstrated the involvement of HMGB1 in various forms of epithelial cell injury. Evidence suggests that HMGB1 can induce acute lung inflammation, epithelial-cell barrier leakage, and even mortality in vivo [60–62]. Alveolar epithelial cells were found to exhibit HMGB1–RAGE signaling in response to LPS-induced lung injury [63]. Interestingly, Wang et al. [64] demonstrated that propofol has the potential to safeguard rats and human alveolar epithelial cells from acute lung injury induced by lipopolysaccharide by suppressing HMGB1 expression. Furthermore, HMGB1 is also implicated in renal tubular epithelial cell injury. Liu et al. discovered that downregulation of H19 suppressed HMGB1 expression, leading to the inhibition of CaOx nephrocalcinosis-induced renal tubular epithelial cell injury, NADPH oxidase, and oxidative stress both in vivo and in vitro [65]. As for the expression and function of HMGB1 in nasal epithelial cells, Chen et al. acquired epithelial cells of nasal polyps from 10 patients. They conducted an experiment where they stimulated primary cultured human nasal epithelial (HNE) cells with LPS. The results showed that LPS affects the translocation and release of HMGB1, suggesting its potential involvement in chronic rhinosinusitis with nasal polyps mediated by inflammatory factors [66]. Actually, LPS has been identified as a vital factor to induce the HMGB1 expression in nasal epithelial cells [67]. Zheng et al. conducted a study in which they obtained nasal mucosal epithelial cells from patients with nasal septal deviation and cultured them to observe the release of HMGB1 under hypoxic conditions. They employed exogenous HMGB1 to stimulate nasal mucosal epithelial cells and evaluated its impact on the permeability of fluorescein isothiocyanate-dextran 4 (FD4). In addition, they assessed the expression of ZO-1, Occcudin, Claudin-1, and E-cadherin, which are epithelial tight junction proteins. The results demonstrated a significant increase in HMGB1 release by nasal mucosal epithelial cells under hypoxic conditions. HMGB1 caused a concentration-dependent and time-dependent increase in the permeability of epithelial cells to FD4. In addition, the expression of ZO-1, Occcudin, and Claudin-1, which are epithelial tight junction proteins, was decreased, indicating compromised epithelial barrier function. This impairment increases the susceptibility of nasal mucosa to the invasion of allergens and exogenous harmful substances. These findings suggest that targeting HMGB1 may be an effective approach to intervene in nasal mucosal inflammation [68]. In another study conducted by Min et al., primary normal human nasal epithelium (NHNE) cells were cultured under hypoxic conditions. Subsequently, western blotting, immunofluorescence, and ELISA techniques were employed to evaluate the expression of HMGB1. As part of the study, the researchers also measured the level of reactive oxygen species (ROS) to investigate the translocation mechanism of HMGB1. In addition, samples of nasal mucosa and nasal lavage fluid were collected from both hypoxic and normoxic patients. The expression of HMGB1 in human nasal mucosa samples was analyzed through immunohistochemistry, while the levels of HMGB1 in lavage fluids were assessed using an ELISA assay. The findings from the study revealed that both in vitro and in vivo conditions induce the secretion of HMGB1 by nasal epithelium under hypoxic conditions. Moreover, the secretion of HMGB1 led to an upregulation of interleukin (IL)-8 production. The researchers concluded that HMGB1 secreted by nasal epithelium plays a contributory role in the inflammatory response by mediating the upregulation of IL-8 under hypoxic conditions through ROS-dependent mechanisms [69].

HMGB1 regulates immune

HMGB1 is a protein expressed in cells and plays a vital role in regulating the immune response [16, 70], It is involved in the function of eosinophils, macrophages, and dendritic cells, among others [71, 72]. It functions as a damage-associated molecular pattern molecule, meaning it is released by cells in response to tissue damage, infection, or inflammation. Upon release, HMGB1 acts as an alarmin, alerting the immune system to danger and initiating immune responses [73]. HMGB1 can activate the innate immunity, which interacts with pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and the RAGE, on immune cells, including macrophages, dendritic cells, and neutrophils [74]. The binding of HMGB1 to these receptors triggers intracellular signaling pathways, resulting in the activation of innate immune responses. These responses include the

production of pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) and the recruitment of other immune cells to the site of inflammation [75–78]. HMGB1 also can modulate the adaptive immunity, which influences adaptive immune responses by regulating antigen presentation and T cell activation [79]. It promotes the maturation and activation of dendritic cells, which are crucial for initiating adaptive immune responses [77]. HMGB1 stimulates the expression of co-stimulatory molecules on dendritic cells, enhancing their ability to activate T cells. Furthermore, HMGB1 directly promotes the proliferation and activation of T cells, contributing to the adaptive immune response [79]. Overall, HMGB1 plays a multifaceted role in regulating immune responses. Its release and interaction with immune cells orchestrate innate and adaptive immune processes, contributing to inflammation, tissue repair, and immune defense. However, dysregulated HMGB1 signaling can also be detrimental, leading to excessive inflammation and tissue damage in various pathological conditions [80].

The imbalance of Th1/Th2 immune responses is widely recognized to play a dominant role in the pathogenesis of AR. Ma et al. [71] demonstrated that recombinant high mobility group protein (rHMGB1) exacerbates airway inflammation and mucus production in asthmatic mice. It also induces Th2 and Th17 polarization by regulating the function of dendritic cells. Conversely, antiHMGB1 was shown to impede Th2 and Th17-mediated inflammatory reactions. Another study conducted by Cavone L et al. [72] demonstrated that stimulation of the nasal mucosa by pathogens leads to the release of a significant quantity of HMGB1 into the extracellular space. Consequently, it fosters the eosinophil aggregation, thereby enhancing the Th2-mediated immune inflammatory response. Subsequently, the expression of HMGB1 is stimulated in reverse following the Th2 reaction, resulting in the production of a large number of inflammatory cytokines that further exacerbate the aggregation of eosinophils. Indeed, HMGB1 plays a crucial role in immune regulation during the pathogenesis of AR. Therefore, gaining a comprehensive understanding of the precise mechanisms underlying HMGB1 regulation and its interactions with the immune system in AR is of great interest for developing therapeutic interventions that aim to modulate immune responses.

HMGB1 is also involved in diverse inflammatory immune responses pathways. Upon exogenous invasion, immune cells actively or passively secrete HMGB1 into the extracellular space, where it binds to airway epithelial cell surface PRRs. These receptors include RAGE, certain members of the TLR family (e.g., TLR2/TLR4), and thrombospondin (TM) et al. Consequently, HMGB1 can participate in crucial inflammatory signal transduction pathways and initiate the inflammatory response [81, 82]. RAGE can be expressed in vascular smooth muscle cells, nasal mucosal epithelial cells, and other cell surfaces. It is the first receptor known to bind to HMGB1 and is considered one of the most effective receptors for HMGB1 in participating in the body's inflammatory response [83, 84]. According to Lee et al. [85], the binding of HMGB1 to the cell membrane receptor RAGE is the primary signaling pathway that triggers related inflammatory diseases. NF-κB can be translocated directly through the NF-κB pathway or indirectly through MAPK and other pathways. Moreover, this binding promotes the release of inflammatory factors, such as TNF, IL-6, and IFN-γ [16, 86], which contribute to the pathological processes of various inflammatory and immune diseases. However, the application of RAGE antibody or RAGE gene knockout methods does not fully inhibit the inflammatory response caused by HMGB1. In addition, the exact inflammatory mechanism of RAGE-mediated HMGB1 remains incompletely understood. Zhu et al. [87] observed high expression levels of HMGB1, TLR2 and TLR4 in nasal secretion samples from AR patients. However, there were no significant differences in mRNA levels of TLR3 and RAGE. They proposed that the HMGB1/TLR4 signaling pathway could serve as a potential target for AR immunotherapy. In a recent study, Yuan et al. [88] found that the HMGB1–TLR4 axis plays a crucial role in the development of AR. They also identified down-regulation of HMGB1–TLR4 as a promising therapeutic strategy to attenuate AR.

Related inhibitors of HMGB1 in AR

Currently, there is limited availability of animal experiments and clinical trials focused on HMGB1-targeted therapy. Overall, research concerning HMGB1 in AR is nascent; however, extant studies indicate that inhibiting HMGB1 could serve as a promising and novel therapeutic approach for AR patients. HMGB1 inhibitors can be categorized into endogenous and exogenous inhibitors. Endogenous inhibitors encompass neutralizing antibodies, anticoagulants, acute phase proteins, and endogenous hormones. Exogenous inhibitors consist of herbal extracts (e.g., angelica sinensis, mung bean, and prunella sinensis) as well as herbal ingredients, such as glycyrrhizin and nicotine [89]. Ethyl pyruvate, glycyrrhizic acid, and glycyrrhetinic acid have received more attention in the context of AR studies. In the following section, we provide a brief introduction to ethyl pyruvate, glycyrrhizic acid, and glycyrrhetinic acid.

Ethyl pyruvate is a straightforward aliphatic ester derived from pyruvate and is classified as an endogenous inhibitor. Numerous studies have confirmed the efficacy

of ethyl pyruvate as an HMGB1 inhibitor in various conditions, such as human malignant mesothelioma, acute kidney injury, endotoxemia, and liver injury [89–92]. Shin et al. demonstrated that ethyl pyruvate can impede the phosphorylation of HMGB1 through calcium ion chelation, preventing the nucleoplasmic translocation of HMGB1 and subsequently reducing its release [93]. Moreover, Chen et al. [94] administered ethyl pyruvate to AR mouse models, observing a substantial inhibition of Th2 cytokine expression, total IgE levels, and goblet cell proliferation in AR mice. Furthermore, ethyl pyruvate demonstrated a dose-dependent reduction in the expression and release of HMGB1.

In addition, Bhat et al. [95] discovered that ethyl pyruvate inhibits the nucleoplasmic translocation of HMGB1 induced by organic dust extract. Moreover, it decreases the expression of HMGB1 and RAGE in the cytoplasm, resulting in the alleviation of airway inflammation triggered by organic dust.

Glycyrrhizic acid and glycyrrhetinic acid are two specific compounds that are isolated from the licorice plant and belong to the group of exogenous inhibitors. Glycyrrhizic acid is utilized as an antiviral and immunomodulatory agent to prevent or treat viral infections, inflammation, and allergic reactions. It achieves this by directly binding to two BOX sites of HMGB1, which inhibits the chemotactic and mitogenic activities of HMGB1.

Glycyrrhizin, among HMGB1 inhibitors, has demonstrated the ability to reduce HMGB1 levels in the nasal fluid of patients with AR. It is effective in both adults and children and is well-tolerated compared to corticosteroids or antihistamines, without causing any adverse effects in humans [96].

Glycyrrhetinic acid exhibits anti-inflammatory and anti-allergic activities. It selectively binds to the extracellular release of HMGB1 protein and inhibits its cytokine activity by clearing the HMGB1 protein [97]. Glycyrrhetinic acid can inhibit the release of HMGB1 by up-regulating Sirt6 in cases of rhinitis [98].

Conclusion

The identification of HMGB1 as a potential therapeutic target for AR presents exciting prospects for the future. While the field is still in its early stages, further research and development in this area hold promise for improving the management of AR and enhancing patient outcomes. Future studies should aim to deepen the understanding of the intricate mechanisms by which HMGB1 contributes to the pathogenesis of AR. This includes elucidating the specific receptors and signaling pathways involved in the HMGB1-mediated inflammatory response. By gaining a more comprehensive understanding of these mechanisms, researchers can identify new targets for intervention and develop more precise therapeutic strategies. Moreover, exploring the potential of HMGB1-targeted therapies in combination with existing treatments for AR could lead to synergistic effects and improved symptom control. Investigating the optimal timing, dosage, and administration routes for HMGB1 inhibitors in conjunction with standard anti-allergic medications may result in enhanced therapeutic efficacy. Another important aspect to consider is the development of selective and potent HMGB1 inhibitors. Currently, most HMGB1 inhibitors used in preclinical and clinical studies have shown promising results, but their specificity and potential off-target effects need to be thoroughly evaluated. Developing more specific and selective inhibitors would help minimize adverse effects and enhance the safety profile of HMGB1-targeted therapies [89]. Overall, targeting HMGB1 as a therapeutic strategy for AR is promising. Continued research, collaboration, and innovative approaches will pave the way for the development of effective and safe HMGB1-targeted therapies that can significantly improve the lives of individuals affected by AR.

Abbreviations

AR	Allergic rhinitis
HMGB1	High mobility group box-1
HDAC	Histone deacetylase
Th	T lymphocytes
RAGE	The receptor for advanced glycation end products
TLR4	Toll-like receptor 4
FD4	Fluorescein isothiocyanate-dextran 4
NHNE	Normal human nasal epithelium
ROS	Reactive oxygen species
PRRs	Pattern recognition receptors

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Competing interests

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