



OPEN ACCESS

EDITED BY

Daniel P Potaczek,
Philipps-University of Marburg, Germany

REVIEWED BY

Javad Nazari,
Arak University of Medical Sciences, Iran
Marcin Kurowski,
Medical University of Lodz, Poland

*CORRESPONDENCE

Dongdong Zhu
✉ zhudd@jlu.edu.cn
Nan Wu
✉ nanwu20@mails.jlu.edu.cn

RECEIVED 30 January 2026

REVISED 10 March 2026

ACCEPTED 13 March 2026

PUBLISHED 26 March 2026

CITATION

Liu Y, Sun Q, Meng C, Sha J, Zhu D and
Wu N (2026) Immune sentinel function
of nasal mucosal epithelial cells in
allergic rhinitis: a review on barrier
damage and inflammatory amplification
loops regulated by calcium signalling.
Front. Immunol. 17:1761813.
doi: 10.3389/fimmu.2026.1761813

COPYRIGHT

© 2026 Liu, Sun, Meng, Sha, Zhu and Wu.
This is an open-access article distributed
under the terms of the [Creative
Commons Attribution License \(CC BY\)](#).
The use, distribution or reproduction in
other forums is permitted, provided the
original author(s) and the copyright
owner(s) are credited and that the
original publication in this journal is
cited, in accordance with accepted
academic practice. No use, distribution
or reproduction is permitted which does
not comply with these terms.

Immune sentinel function of nasal mucosal epithelial cells in allergic rhinitis: a review on barrier damage and inflammatory amplification loops regulated by calcium signalling

Yiting Liu^{1,2,3}, Qingjia Sun^{1,2,3}, Cuida Meng^{1,2,3}, Jichao Sha^{1,2,3},
Dongdong Zhu^{1,2,3*} and Nan Wu^{4*}

¹Department of Otolaryngology Head and Neck Surgery, China-Japan Union Hospital of Jilin University, Changchun, China, ²Jilin Provincial Key Laboratory of Precise Diagnosis and Treatment of Upper Airway Allergic Diseases, Changchun, China, ³Otolaryngology Head and Neck Surgery Research Center, Changchun, China, ⁴Phase I Clinical Trial Research Laboratory, China-Japan Union Hospital of Jilin University, Changchun, China

Allergic rhinitis (AR) is a prevalent chronic inflammatory disorder characterized by complex pathophysiological mechanisms. Nasal mucosal epithelial cells serve as crucial “immune sentinels” that detect allergens and initiate immune responses, thereby playing a pivotal role in disease progression. Intracellular calcium signaling, as a vital second messenger, regulates epithelial barrier integrity and modulates immune functions within these cells. This review summarizes current understanding of the immune surveillance role of nasal mucosal epithelial cells in AR, emphasizing the regulatory mechanisms of calcium signaling pathways in barrier disruption and the amplification of inflammatory cycles. Recent studies reveal that aberrant calcium signaling contributes to nasal epithelial barrier dysfunction and excessive activation of inflammatory cells, which perpetuate chronic inflammation and exacerbate symptom severity. By integrating emerging evidence on calcium-mediated cellular processes, this article highlights the critical involvement of calcium signaling in maintaining epithelial homeostasis and controlling inflammatory responses in AR. Understanding these mechanisms provides novel insights into the pathogenesis of AR and identifies potential therapeutic targets aimed at restoring epithelial barrier function and modulating inflammatory cascades, thereby offering new directions for clinical intervention.

KEYWORDS

allergic rhinitis, barrier damage, calcium signaling, immune sentinel, inflammatory amplification loop, nasal mucosal epithelial cells

1 Introduction

Allergic rhinitis (AR), characterized by nasal congestion, sneezing, itching, and rhinorrhea, imposes substantial socioeconomic burdens worldwide (1, 2). The nasal epithelium functions as the first line of defense, sensing and responding to external stimuli, including allergens, pollutants, and pathogens, thereby orchestrating local immune responses to maintain mucosal homeostasis (3). Recent advances have expanded the conceptualization of the nasal epithelium beyond a mere physical barrier to that of an “immune sentinel” or “immune watchman.” (4) Nasal mucosal epithelial cells detect noxious stimuli through pattern recognition receptors (PRRs) and other sensor molecules, subsequently releasing cytokines, chemokines, and alarmins that modulate the activity of innate and adaptive immune cells such as group 2 innate lymphoid cells (ILC2s), eosinophils, and T lymphocytes (5). However, in AR, this finely tuned balance is disrupted, leading to epithelial barrier impairment and exaggerated inflammatory responses (6, 7). Central to the regulation of epithelial cell function and immune responses is intracellular calcium (Ca^{2+}) signaling, which serves as a ubiquitous second messenger controlling diverse cellular processes including barrier maintenance, cytokine secretion, and cell-cell communication (8, 9). Aberrant Ca^{2+} signaling has been increasingly recognized as a key contributor to epithelial barrier dysfunction and the amplification of inflammatory cascades in allergic diseases (10). This review aims to systematically synthesize current knowledge on the immune surveillance functions of nasal epithelial cells in AR, with a particular focus on the regulatory role of Ca^{2+} signaling in barrier disruption and inflammatory amplification. By elucidating these pathways, we hope to contribute to a deeper mechanistic insight into AR pathophysiology and foster the development of targeted therapeutic strategies that restore epithelial barrier function and modulate aberrant immune responses, ultimately improving clinical outcomes for patients suffering from this pervasive allergic condition (6, 11, 12). Building on these well-characterized research gaps, the present review is the first to put forward a novel conceptual model—the Ca^{2+} -mediated epithelial gatekeeper axis—for AR. At its core, this model holds that nasal mucosal epithelial cells, the key mucosal immune sentinels in the upper airway, initiate Ca^{2+} signaling cascades upon allergen recognition via PRRs, and in turn drive AR pathogenesis through a dual regulatory mechanism: direct modulation of epithelial tight junction integrity and activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B)/NLR family pyrin domain containing 3 (NLRP3) inflammatory signaling pathways. This signaling cascade ultimately gives rise to a self-sustaining vicious cycle in AR pathogenesis: aberrant Ca^{2+} signaling \rightarrow epithelial barrier impairment \rightarrow inflammatory amplification \rightarrow exacerbated Ca^{2+} signaling dysregulation. This integrated mechanistic framework thus serves as a central tenet for elucidating the chronic pathological process of AR.

2 Physiological functions of nasal mucosal epithelial cells as “immune sentinels”

The nasal mucosal epithelium constitutes a complex, multilayered cellular architecture that serves as the primary

physical barrier against inhaled environmental insults, including allergens, pathogens, and particulate matter (13). These tight junctions (TJs) form a dynamic seal that is responsive to environmental and immunological stimuli, ensuring selective permeability while preserving mucosal homeostasis (14). Disruption of this barrier function is increasingly recognized as a pivotal event in the pathogenesis of AR and other sinonasal inflammatory diseases (15).

Nasal mucosal epithelial cells serve as critical immune sentinels by detecting allergens and pathogens through an array of PRRs, which are essential for initiating immune responses in AR (16). These PRRs, including Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors, recognize conserved molecular patterns on pathogens (PAMPs) or damage signals (DAMPs), thereby triggering intracellular signaling cascades that activate innate immunity (17). These alarmins are pivotal in initiating type 2 inflammation characteristic of allergic diseases by activating ILC2s and promoting Th2 responses (18, 19). This epithelial-driven mechanism of type 2 inflammatory initiation is evolutionarily conserved across upper airway allergic inflammatory disorders, as supported by recent human upper airway immune endotyping data in patients with chronic rhinosinusitis with nasal polyps (CRSwNP)—a condition that shares overlapping type 2 inflammatory pathways and nasal epithelial dysfunction with AR (20). Nazari et al. demonstrated that in patients with the aspirin-exacerbated respiratory disease (AERD) subtype of CRSwNP, GATA3, IL-4 and IL-5 gene expression is markedly upregulated in nasal polyp tissues, with a pronounced Th2-skewed immune activation pattern linked to nasal epithelial dysfunction (20). This finding not only directly confirms that nasal epithelial cells act as central immune sentinels in driving the transcription and secretion of core Th2 cytokines, but also further underscores the universality of epithelial-immune crosstalk in mediating type 2 inflammation across upper airway allergic disorders. The sensing mechanism often involves the nuclear release of IL-33, which depends on apoptotic signaling pathways, highlighting a sophisticated regulatory system within epithelial cells to modulate immune activation based on the nature of the stimulus (21). Furthermore, epithelial PRRs can discriminate between different allergens and pathogens, enabling stimulus-specific immune responses that are tailored to the particular threat, rather than a generalized activation (22).

Upon recognition of allergens or pathogens, nasal epithelial cells secrete a complex milieu of cytokines, chemokines, and antimicrobial peptides that shape the local immune environment (23). The secretion of these molecules is tightly regulated by intracellular signaling networks downstream of PRR activation, including NF- κ B and mitogen-activated protein kinase (MAPK) pathways, ensuring a balanced response that promotes pathogen clearance while limiting tissue damage (24, 25). Moreover, epithelial cells interact with resident immune sentinels such as macrophages and dendritic cells, which further amplify and tailor the immune response through antigen presentation and cytokine production (26). This crosstalk is crucial for bridging innate and adaptive immunity and for maintaining mucosal homeostasis. In AR, dysregulation of these processes leads to barrier dysfunction and

chronic inflammation, underscoring the importance of epithelial immune sentinel functions in disease pathogenesis and potential therapeutic targeting (27–29).

Notably, the immune surveillance capacity of nasal mucosal epithelial cells is tightly coupled to intracellular Ca^{2+} signaling—this critical molecular link bridges allergen sensing and downstream pathological responses. When epithelial PRRs detect allergens or DAMPs, they trigger intracellular signaling cascades that converge on Ca^{2+} -permeable ion channels. For example, TLR activation induces downstream G-protein-coupled receptor (GPCR) signaling, which in turn elevates intracellular Ca^{2+} concentrations via transient receptor potential vanilloid 1 (TRPV1) channel opening (30); at the same time, protease-containing allergens activate protease-activated receptors (PARs) on the nasal epithelial cell membrane, directly driving Ca^{2+} influx through store-operated Ca^{2+} entry (SOCE) channels (31, 32). This PRR-mediated Ca^{2+} signaling activation is not only a downstream outcome of immune surveillance by nasal epithelial sentinels, but also the primary trigger for subsequent epithelial barrier remodeling and inflammatory mediator secretion—this thus forms the initiating step of the Ca^{2+} -mediated epithelial gatekeeper axis we propose in this review.

3 Conceptual advances beyond existing reviews

Here, we synthesize seminal work in the field, with a focused analysis of two influential reviews (7, 29) that have advanced the current understanding of nasal epithelial biology in the context of AR. These foundational reviews have collectively propelled the field forward by comprehensively characterizing the link between AR pathogenesis and nasal epithelial barrier dysfunction, including a detailed account of TJ molecule downregulation in both AR patients and preclinical models. They have also rigorously dissected multifaceted regulatory factors governing this dysfunction, encompassing Th2 cytokines, epithelial-derived alarmins, epigenetic modifications, neuroimmune crosstalk, and environmental triggers. Notably, one review identified novel epithelial cell subsets and emphasized the “epithelial endotype” as a conserved feature across allergic airway diseases, while the other highlighted the genetic and epigenetic regulation of epithelial barrier integrity. Together, these two works have established a robust foundation for elucidating the contribution of nasal epithelial dysfunction to AR pathogenesis. Despite these advances, critical knowledge gaps persist: neither review identifies Ca^{2+} signaling as the central regulatory hub bridging epithelial “immune sentinel” function to TJ remodeling and inflammatory amplification. While transient receptor potential (TRP) channels were noted as potential mediators in this process, their specific role in driving Ca^{2+} influx and subsequent downstream signaling cascades was not defined. Furthermore, these works either conceptualized epithelial barrier impairment as a passive byproduct of inflammation or adopted a broad focus encompassing both upper and lower airways. This has resulted in an incomplete characterization of nasal epithelium-

specific regulatory mechanisms and a lack of clarity regarding the molecular switch that initiates the “barrier damage–inflammation” vicious cycle, leaving key pathological processes fragmented rather than integrated into a cohesive mechanistic network. Building on these foundational contributions, the present review addresses these critical gaps by proposing the “ Ca^{2+} -mediated epithelial gatekeeper axis in AR”—a unifying framework that integrates allergen sensing, Ca^{2+} signaling activation, TJ remodeling, and inflammatory amplification into a continuous mechanistic cascade. We further define the dual regulatory role of Ca^{2+} signaling in preserving epithelial barrier integrity and driving inflammatory activation via the NF- κ B/NLRP3 pathways, and link these molecular targets to clinical AR phenotypes through the integration of clinical and preclinical evidence, thereby strengthening the translational relevance of this mechanistic model.

4 Regulatory mechanisms of Ca^{2+} signaling pathway in nasal mucosal epithelial cells

As a key downstream signal of the nasal epithelial “immune sentinel” sensing pathway, Ca^{2+} signaling transduces allergen recognition into cellular functional responses, namely barrier regulation and inflammatory activation, through its unique spatiotemporal dynamics and the subsequent activation of downstream effector molecules. Activation of Ca^{2+} signaling downstream of PRRs, PAR-2 and PAR-4 depends on the coordinated activity of multiple Ca^{2+} -permeable ion channels and regulatory molecules, whose basic biological properties and functional mechanisms we systematically elaborate in the subsequent sections.

4.1 Basic biological characteristics of Ca^{2+} signaling

Ca^{2+} channels (including voltage-gated Ca^{2+} channels, transient receptor potential (TRP) channels, stretch-activated channels (SAC), and SOCE channels), calcium pumps, and calcium-binding proteins are key components of Ca^{2+} signaling (33, 34). The versatility of Ca^{2+} signaling as a second messenger arises from its ability to generate spatially and temporally diverse Ca^{2+} signals or “calcium signatures” that can be localized within subcellular compartments or propagate as waves across cells (35, 36). Ca^{2+} signaling is further modulated by complex feedback mechanisms. For example, TRPM4 and TRPM5 channels convert intracellular Ca^{2+} increases into membrane depolarization, which in turn affects Ca^{2+} entry, illustrating a bidirectional interplay between electrical and chemical signals (37). Additionally, Ca^{2+} signaling is integrated with other signaling pathways such as cyclic nucleotides and AMPK, contributing to cellular metabolism and viral infection processes (38, 39). The compartmentalization of Ca^{2+} signals within organelles, such as mitochondria and peroxisomes, adds another layer of regulation influencing both organelle-specific and global cellular functions (40). These signals orchestrate a multitude

of cellular processes through complex decoding mechanisms, underscoring calcium's central role in cellular physiology and pathophysiology (41).

4.2 Relationship between Ca²⁺ signaling and epithelial barrier function

Ca²⁺ serves as critical second messengers, modulating TJs assembly, disassembly, and remodeling through various signaling pathways (42). For instance, activation of G-protein coupled receptors (GPCRs) such as GPR120 can elevate intracellular Ca²⁺ levels, which subsequently triggers downstream effectors like myosin light chain kinase (43) (MLCK). MLCK phosphorylates myosin light chains, promoting actomyosin contraction that transiently increases paracellular permeability by modulating TJ protein distribution and function (44, 45). This mechanism was demonstrated in intestinal epithelial IPEC-J2 cells, where the c9, t11-conjugated linoleic acid (CLA) isomer activated GPR120, increased Ca²⁺, and stimulated MLCK signaling, resulting in decreased expression of TJ proteins and impaired barrier function both *in vitro* and *in vivo* (46). Ca²⁺ signaling is integral to the regulation of tight junction protein expression and function, thereby maintaining epithelial barrier integrity (47). Dysregulation of Ca²⁺ homeostasis, whether through environmental insults, inflammatory mediators, or pharmacological agents, can lead to TJ protein degradation, altered localization, and increased paracellular permeability (48, 49).

4.3 Ca²⁺ signal-mediated activation of inflammatory responses

Ca²⁺ signaling plays a pivotal role in the activation of key inflammatory pathways, including the NF-κB pathway and the NLRP3 inflammasome, thereby amplifying inflammation in allergic and other immune-mediated diseases (50, 51). However, this regulatory effect is not a simple linear causal relationship, but rather is governed by context-dependent cues, concentration/co-signaling thresholds, and intrinsic opposing regulatory circuits—key factors that collectively determine the activation status of the NF-κB/NLRP3 axis. First, context dependence is evident in microenvironmental and cell-type specificity: pro-inflammatory cytokines in the allergic nasal mucosal microenvironment can “sensitize” the pathway by potentiating the responsiveness of the NF-κB/NLRP3 axis to Ca²⁺ influx, while anti-inflammatory mediators such as IL-10 attenuate this responsiveness by downregulating STIM1 expression (52, 53). Cell-type specificity further shapes this regulatory process: in nasal mucosal epithelial cells, Ca²⁺ influx primarily drives NF-κB activation via the stromal interaction molecule 1 (STIM1)/calcium release-activated calcium modulator 1 (ORAI1) axis (30), whereas in immune cells such as macrophages, Ca²⁺-dependent NLRP3 activation requires synergistic TLR4 signaling to initiate this cascade (54, 55). Second, threshold effects are an essential requirement for pathway activation: intracellular Ca²⁺ concentrations in nasal epithelial cells must reach 100–300 nM to induce NF-κB nuclear translocation, and subthreshold Ca²⁺ fluctuations only sustain cellular homeostasis without eliciting inflammatory responses (30, 32); notably, house dust mites (HDM)-induced Ca²⁺ influx must reach a minimum of 150 nM to activate NF-

κB (32). For NLRP3 inflammasome activation, Ca²⁺ influx alone is insufficient—ROS-mediated oxidative stress acts as a “second signal” to synergistically overcome this activation threshold, and the NLRP3 inflammasome remains inactive even at sufficient Ca²⁺ concentrations in the absence of ROS (50, 56). Third, multiple endogenous opposing regulatory pathways prevent excessive pathway activation: SARAF (Store-operated Ca²⁺ Entry-associated Regulatory Factor) interacts with STIM1 to limit SOCE-mediated Ca²⁺ influx, thus attenuating NF-κB activation (57); the Ca²⁺-dependent phosphatase PP2A dephosphorylates the p65 subunit of NF-κB, inhibiting its transcriptional activity and blocking pro-inflammatory cytokine secretion (58); in addition, IL-10 secreted following NLRP3 activation downregulates ORAI1 expression, reducing Ca²⁺ influx and forming a negative feedback loop (53). The intracellular Ca²⁺ increase acts as a second messenger that triggers a cascade of molecular events leading to pro-inflammatory gene expression and cytokine production (59). In immune cells, SOCE mediated stromal interaction molecule 1 (STIM1) and ORAI1 channels is essential for NF-κB signaling and inflammatory cytokine production (60). For example, lipopolysaccharide (LPS) stimulation upregulates STIM1/ORAI1 expression in bovine mammary epithelial cells, increasing Ca²⁺ influx and activating NF-κB, which promotes the release of pro-inflammatory mediators (54, 61). Inhibition of these Ca²⁺ channels attenuates NF-κB activation and reduces inflammation, highlighting the centrality of Ca²⁺ signaling in inflammatory amplification (52, 58).

5 Abnormal activation mechanism of Ca²⁺ Signaling in nasal mucosal epithelial cells in AR

5.1 Clinical evidence of abnormal Ca²⁺ signaling in nasal mucosal epithelial cells of AR patients

Clinical investigations have increasingly demonstrated that nasal mucosal epithelial cells from patients with AR exhibit significant abnormalities in Ca²⁺ signaling pathways, which are crucial in modulating epithelial barrier function and immune responses (30). Transcriptomic analyses of nasal epithelial cells from AR patients have revealed significantly elevated mRNA levels of these Ca²⁺ channel components compared to healthy controls, a finding further corroborated by protein expression studies, indicating a robust upregulation at both transcriptional and translational levels (62). This aberrant expression likely contributes to enhanced Ca²⁺ influx responses upon allergen exposure. Functional Ca²⁺ imaging studies provide direct evidence of altered Ca²⁺ signal dynamics in AR epithelial cells (55). This heightened Ca²⁺ sensitivity and altered kinetic profile suggest a hyperresponsive state of the epithelial Ca²⁺ signaling machinery in AR, which may potentiate downstream inflammatory cascades (63). The involvement of TRPV1 channels, which are upregulated in AR nasal mucosa and mediate Ca²⁺ influx leading to

proinflammatory cytokine release such as IL-33, further supports the critical role of Ca^{2+} channels in epithelial immune activation (30). The dysregulated Ca^{2+} signaling not only disrupts epithelial barrier integrity but also amplifies the release of inflammatory mediators, creating a vicious cycle that exacerbates mucosal inflammation (64).

5.2 Allergen-induced aberrant activation of Ca^{2+} signaling

Allergen exposure, particularly to common triggers such as HDM and pollen, initiates aberrant Ca^{2+} signaling in nasal mucosal epithelial cells through receptor-mediated pathways, which plays a pivotal role in the pathogenesis of AR (63). Protease allergens from HDM, exhibit trypsin-like serine protease activity that activates protease-activated receptor-2 (PAR-2) on airway epithelial cells (31). This activation leads to an abnormal increase in intracellular Ca^{2+} levels, disrupting Ca^{2+} homeostasis and triggering downstream inflammatory cascades (65). Similarly, HDM allergens induce Ca^{2+} mobilization via PAR-2 and PAR-4, as well as TRPV1 channels, leading to increased intracellular cation levels and promoting alarmin release [IL-33 and Thymic Stromal Lymphopoietin (TSLP)] from epithelial cells in asthma patients (31). This aberrant Ca^{2+} signaling is closely associated with airway epithelial barrier dysfunction and inflammatory amplification (32). Beyond allergen-specific triggers, ambient air pollutants and irritants—including fine particulate matter ($\text{PM}_{2.5}$), volatile organic compounds (VOCs), and diesel exhaust particles (DEP)—also act as potent inducers of aberrant Ca^{2+} signaling in nasal epithelial cells (66). These chemical pollutants directly perturb Ca^{2+} -permeable ion channels or modulate SOCE pathways in nasal epithelial cells, triggering unregulated Ca^{2+} influx that disrupts intracellular Ca^{2+} homeostasis (67, 68). This dysregulation subsequently activates pro-inflammatory signaling cascades and impairs tight junction integrity, creating a pro-inflammatory microenvironment that favors the initiation and progression of allergic responses (69). Notably, these environmental stimuli often act synergistically with allergens: they can “prime” nasal epithelial cells to enhance their responsiveness to subsequent allergen exposure, leading to exaggerated Ca^{2+} influx and alarmin release, thereby exacerbating AR severity (70, 71).

In addition to chemical pollutants, physical environmental factors such as ambient temperature and humidity also modulate Ca^{2+} signaling dynamics (72). Extreme temperature changes directly activate temperature-sensitive Ca^{2+} channels in nasal epithelial cells, inducing Ca^{2+} influx that promotes the release of pro-inflammatory mediators and neuropeptides, which in turn disrupt epithelial barrier function and enhance inflammatory cell recruitment (73). Conversely, abnormal ambient humidity alters epithelial hydration status, leading to intracellular Ca^{2+} overload that triggers cellular stress responses or apoptotic pathways in nasal epithelial cells (74). These findings highlight that environmental factors are not merely passive co-factors but active modulators of the Ca^{2+} -mediated epithelial gatekeeper axis, capable of both initiating and amplifying the pathological cascade in AR.

6 The effect of Ca^{2+} signal regulation imbalance on the progression of AR disease

6.1 Aberrant Ca^{2+} signaling directly impairs nasal mucosal epithelial barrier integrity

The integrity of the nasal mucosal epithelial barrier is critically dependent on the precise regulation of Ca^{2+} signaling, which orchestrates tight junction assembly and epithelial cell survival (75). Disruption of Ca^{2+} homeostasis, particularly abnormal Ca^{2+} influx, initiates a cascade of molecular events that compromise barrier function (76, 77). One key mechanism involves the activation of the Ca^{2+} -dependent phosphatase calcineurin (CaN), which aberrantly modifies tight junction proteins such as occludin and zonula occludens-1 (ZO-1) (78). Elevated intracellular Ca^{2+} levels lead to hyperphosphorylation of these proteins, causing their dissociation from the cell membrane and subsequent degradation (79). This process results in the widening of intercellular spaces and loss of epithelial barrier continuity (80, 81). Concurrently, sustained high intracellular Ca^{2+} triggers mitochondrial apoptotic pathways, promoting caspase-3 activation and accelerating epithelial cell apoptosis (82, 83). The increased epithelial cell shedding further exacerbates barrier disruption, facilitating allergen penetration and inflammatory cell infiltration (84, 85). These findings underscore the direct deleterious impact of Ca^{2+} signaling abnormalities on nasal epithelial barrier function, highlighting a pivotal role of Ca^{2+} dysregulation in the pathogenesis of barrier impairment in AR (86).

6.2 Inflammatory cytokines feedback to exacerbate Ca^{2+} signal abnormalities: formation and amplification of a vicious cycle

Ca^{2+} signaling not only mediates epithelial barrier integrity but also profoundly influences the expression and release of key Th2-type cytokines, such as IL-4, IL-5, and IL-13, which are central to allergic inflammation (87, 88). Elevated intracellular Ca^{2+} levels activate transcriptional pathways that upregulate these cytokines, thereby promoting the type 2 inflammatory milieu characteristic of AR. Moreover, Ca^{2+} -dependent mechanisms regulate the secretion of chemokines like CCL11 (eotaxin-1) and CCL26 (eotaxin-3), which are potent chemoattractants for eosinophils and other inflammatory cells, facilitating their recruitment to the nasal mucosa (89). Importantly, the sustained Ca^{2+} signal abnormalities maintain continuous release of inflammatory mediators, establishing a self-amplifying loop that reinforces barrier dysfunction and inflammation (90). This vicious cycle is further supported by evidence that targeting Ca^{2+} signaling pathways can attenuate inflammatory cytokine production and cellular activation, suggesting potential therapeutic avenues (56, 91). In chronic inflammatory states, dysregulated Ca^{2+} signaling emerges as a critical node that sustains and amplifies the inflammatory microenvironment, making Ca^{2+} channels, pumps, and their

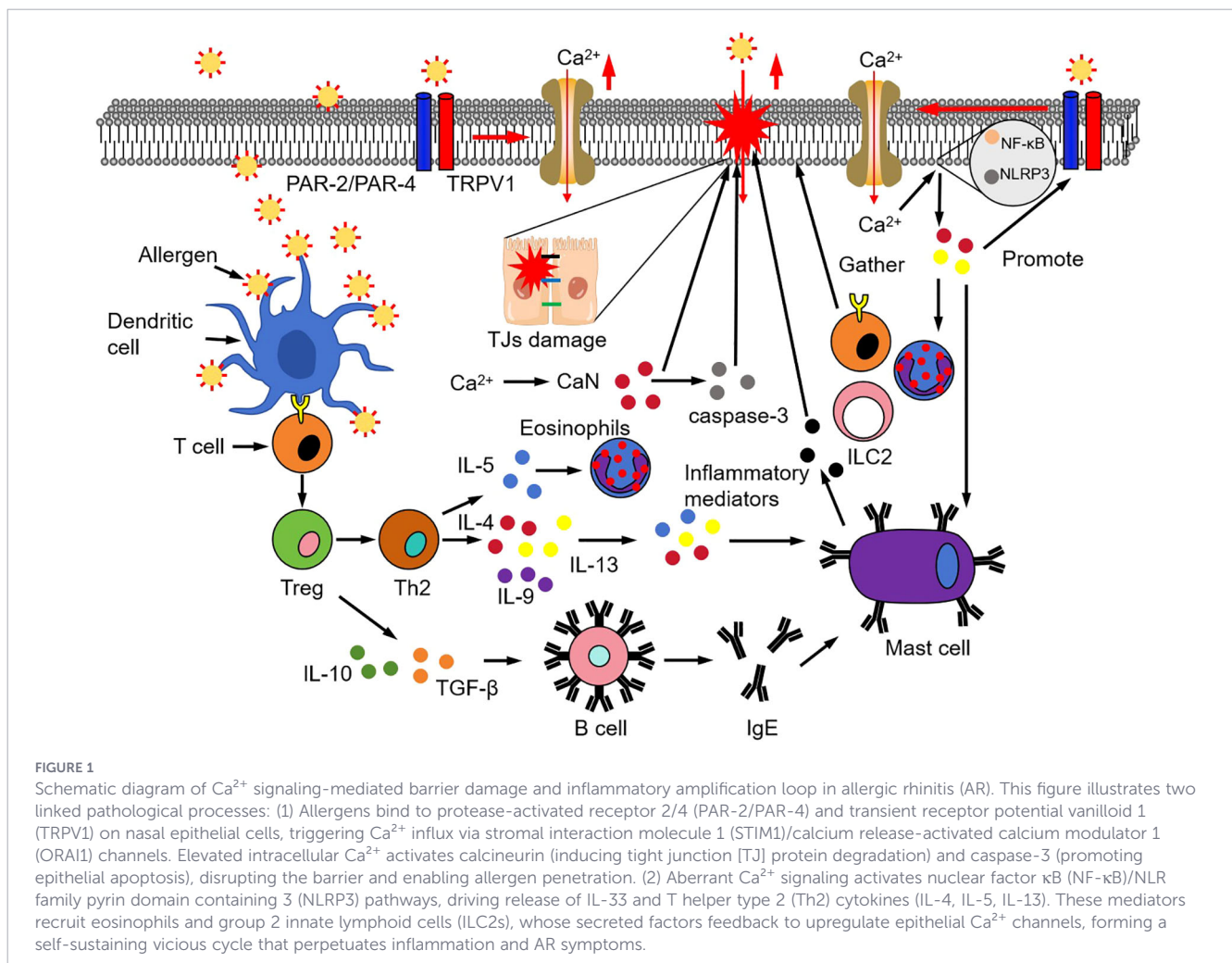
regulators promising targets for intervention to disrupt this deleterious feedback loop (92) (Figure 1).

7 Therapeutic potential of AR targeting Ca^{2+} signaling regulation in nasal mucosal epithelial function

7.1 Intervention effects and mechanisms of Ca^{2+} channel blockers

Calcium Release-Activated Calcium (CRAC) channel inhibitors: Selective inhibitors such as GSK-7975A and YM-58483 target the STIM1/Orai1 interaction, and have shown promising preclinical efficacy in AR mouse models by reducing epithelial permeability and suppressing IL-33 secretion (93). However, their clinical translation potential remains limited to date: first, no Phase II/III clinical trials have been performed in AR patients to assess these agents, and most efficacy data come from animal models and *in vitro* nasal epithelial cell assays (93, 94); second, significant safety

concerns remain—non-selective CRAC channel inhibition may disrupt physiological Ca^{2+} signaling in non-target tissues, with the potential to induce adverse events like cardiac arrhythmias and neurotoxicity (95). While STIM1/Orai1-selective inhibitors are developed to reduce these off-target effects (95), their long-term safety profiles are largely undefined. Specificity is thus a key consideration in the design of CRAC channel inhibitors, as different Orai isoforms have distinct regulatory properties: Orai1 and Orai2 are sensitive to intracellular pH fluctuations and dependent on STIM1, while Orai3 is not subject to this STIM1-mediated regulation. This means selective targeting of the STIM1/Orai1 interaction can yield therapeutic effects without globally disrupting physiological Ca^{2+} signaling (95). In addition, agents like YM-58483 have been shown to boost cell viability and increase junctional protein expression in nasal epithelial cells under inflammatory conditions, a finding that further supports their preclinical potential to preserve epithelial barrier integrity (94). Apart from direct small-molecule inhibition of CRAC channels, SPLUNC1-derived peptides can induce Orai1 internalization and subsequent lysosomal degradation, thus effectively reducing SOCE and suppressing inflammatory



responses *in vitro* (96). This points to a promising alternative strategy for targeting STIM1/Orai1 function, though the *in vivo* stability and bioavailability of these peptide agents need further optimization (57).

Transient Receptor Potential Canonical (TRPC) channel inhibitor SKF-96365 corrects aberrant Ca²⁺ signaling in nasal mucosal epithelial cells from AR patients by inhibiting TRPC6 channel activity, and exhibits symptom-relieving effects in murine AR models (97, 98). However, its clinical translatability is limited by key drawbacks: first, SKF-96365 is a non-selective TRPC inhibitor that also targets TRPC3/4/5 channels alongside TRPC6 (99), and this lack of selectivity can disrupt physiological Ca²⁺-dependent processes in nasal epithelial cells, potentially causing adverse effects such as nasal dryness and impaired pathogen clearance at the nasal mucosa (100); second, clinical evidence for AR is very limited, with all current data restricted to *in vitro* cell assays and small animal models, and no large-scale human trials have been performed to confirm its efficacy and safety in AR patients (98, 101). Dysregulation of TRPC6-mediated Ca²⁺ signaling is a major contributor to pathological processes linked to abnormal cell proliferation, excessive inflammation, and epithelial barrier dysfunction (100, 102). While SKF-96365 acts as a potent pharmacological tool that modulates TRPC6 channel activity and restores Ca²⁺ signaling homeostasis in preclinical models, its lack of selectivity and corresponding clinical translational potential for AR are yet to be validated (99, 101).

7.2 Targeted blocking strategies of the inflammatory factor - Ca²⁺ signaling axis

Neutralizing IL-33 using specific monoclonal antibodies reverses excessive Ca²⁺ influx and subsequent signaling dysregulation in nasal epithelial cells, thereby restoring the expression and function of tight junction proteins in preclinical models (30, 103). Occludin is critical for maintaining epithelial tight junction integrity, and its reduced expression correlates closely with increased epithelial permeability and greater allergen penetration across the mucosal barrier. Restoring occludin expression after IL-33 blockade reinforces the nasal epithelial barrier, reducing allergen-induced immune activation and breaking the vicious cycle of inflammatory amplification (104, 105). However, IL-33 targeting with monoclonal antibodies has key clinical limitations for AR treatment: first, IL-33 inhibition is highly effective only in Th2-predominant AR subtypes, and has little to no efficacy in non-Th2 AR phenotypes (103); second, safety risks include a higher risk of upper respiratory tract infections due to impaired mucosal innate immunity (103), and the long-term risks of immune dysregulation in AR patients remain unassessed; third, tozorakimab has demonstrated encouraging efficacy in Phase II trials for CRSwNP (103), but no dedicated Phase III trials have been done to confirm its efficacy in AR patients, and extrapolating efficacy across these diseases is not a reliable approach. These findings confirm that excessive IL-33-driven Ca²⁺ signaling activation contributes to nasal epithelial barrier dysfunction in Th2-skewed AR (103).

Furthermore, bispecific anti-IL-4/IL-13 antibodies exert their therapeutic effects in part by reducing Ca²⁺ channel expression on nasal epithelial cells; this process is critical for regulating intracellular Ca²⁺ signaling that controls nasal epithelial barrier integrity and the secretion of inflammatory mediators (106). By lowering Ca²⁺ channel expression, these antibodies reduce Ca²⁺-dependent activation of nasal epithelial cells, which in turn decreases the secretion of proinflammatory mediators such as thymus and activation-regulated chemokine (TARC) and other Th2-associated cytokines. That said, their clinical use in AR is limited by several key issues: high treatment costs that could limit clinical access; suboptimal response rates in patients with mild-to-moderate AR (106); and potential adverse events like injection-site reactions and eosinophilia, which call for long-term clinical monitoring (106).

7.3 Therapeutic challenges and future perspectives

Despite compelling preclinical evidence supporting Ca²⁺ signaling as a novel therapeutic target for AR, several key barriers hinder its clinical translation. First, a lack of AR-specific targeted agents: most available Ca²⁺ channel inhibitors and antibodies targeting inflammatory factors are not selective for nasal epithelial cells or distinct AR endotypes, leading to off-target effects and limited efficacy in the heterogeneous AR patient population. Second, insufficient clinical evidence: most efficacy data comes from *in vitro* experiments and small-animal models, and there have been few large-scale, long-term clinical trials in AR patients to confirm safety, optimal dosing, and durability of response. Third, achieving a favorable safety-efficacy balance remains a challenge: although targeting Ca²⁺ signaling or related inflammatory mediators can alleviate AR-related inflammation, this can disrupt physiological Ca²⁺-dependent processes in the nasal mucosa, which increases the risk of mucosal infections or epithelial dysfunction. Fourth, a lack of biomarker-guided precision therapy: currently, there are no validated predictive biomarkers to identify and stratify AR patients who are most likely to benefit from Ca²⁺-targeted therapies, leading to the potential for overtreatment in non-responsive patients.

Importantly, the impact of environmental factors on Ca²⁺ signaling also has critical implications for therapeutic development. The modulatory effects of ambient pollutants and physical factors on Ca²⁺ signaling dynamics can significantly alter the responsiveness of nasal epithelial cells to Ca²⁺-targeted interventions, thereby influencing both therapeutic efficacy and safety profiles. This context-dependent variability necessitates a more personalized approach to treatment, where therapeutic strategies are tailored to account for individual environmental exposure histories. Future studies should therefore incorporate environmental exposure data into clinical trial design, to better stratify patients and optimize therapeutic outcomes. Future research should thus prioritize the following key areas: (1) developing nasal mucosa-targeted Ca²⁺ channel modulators to minimize systemic adverse effects; (2)

designing and conducting endotype-specific clinical trials to confirm the efficacy of these targeted agents; (3) identifying and validating predictive biomarkers to enable rational patient stratification for Ca²⁺-targeted therapy; (4) exploring rational combination therapies to achieve synergistic therapeutic effects, while lowering individual drug doses and their corresponding adverse effects. Overcoming these key barriers will allow Ca²⁺ signaling-targeted strategies to reach their full therapeutic potential as novel treatment options for AR.

8 Discussion

The role of nasal mucosal epithelial cells as “immune sentinels” in AR represents a critical nexus in understanding the disease’s pathogenesis and progression (107, 108). From an expert perspective, this review underscores the central importance of Ca²⁺ signaling pathways in regulating both the epithelial barrier function and local immune responses. The intricate balance maintained by Ca²⁺ signals ensures mucosal integrity and appropriate immune activation; however, disruptions in this signaling cascade precipitate epithelial barrier dysfunction and amplify inflammatory circuits, thereby perpetuating a chronic inflammatory milieu that exacerbates disease severity. Nasal mucosal epithelial cells act as critical “immune sentinels” in AR, with their function representing a key nexus for understanding the disease’s pathogenesis and progression. In summary, this review highlights the central role of Ca²⁺ signaling pathways in coordinating both nasal epithelial barrier function and local nasal mucosal immune responses. The delicate spatiotemporal balance of Ca²⁺ signaling maintains nasal mucosal integrity and coordinates appropriate immune activation; in contrast, dysregulation of this signaling cascade leads to epithelial barrier dysfunction and amplifies inflammatory pathways, in turn maintaining a chronic inflammatory microenvironment that exacerbates AR severity.

The development of research in this area has significantly advanced our comprehension of AR beyond a simplistic view of immune hypersensitivity. It highlights a nuanced interplay between epithelial cells and immune effectors mediated through Ca²⁺-dependent mechanisms. This evolving paradigm bridges molecular insights with clinical manifestations, offering a more integrated understanding of disease dynamics. Nevertheless, the complexity of Ca²⁺ signaling—encompassing diverse channels, pumps, and downstream effectors—poses challenges in reconciling disparate findings across studies. Notably, Ca²⁺ influx does not regulate the NF-κB/NLRP3 axis through a unidirectional causal relationship; instead, this regulation depends on the inflammatory microenvironment and cell-type specificity, requires sufficient intracellular Ca²⁺ levels and synergistic signals to hit activation thresholds, and is further modulated by intrinsic negative feedback mechanisms such as SARAF, PP2A, and IL-10. Some research emphasizes specific Ca²⁺ channels’ roles, while others focus on broader signaling networks or cross-talk with other intracellular pathways. Balancing these perspectives requires

a holistic approach that appreciates both the specificity of molecular targets and the systemic context in which they operate.

Critically, aberrant Ca²⁺ signaling not only compromises the epithelial barrier but also fuels a self-perpetuating inflammatory loop, underscoring its dual role in both initiating and sustaining allergic inflammation (53, 55). This duality presents both challenges and opportunities for therapeutic intervention. Targeting Ca²⁺ signaling pathways offers a promising avenue for novel treatments aimed at restoring barrier integrity and modulating immune responses simultaneously. Such strategies could potentially interrupt the vicious cycle of inflammation characteristic of AR, thereby improving patient outcomes.

Future research must prioritize the precise modulation of Ca²⁺-related molecular targets to translate these mechanistic insights into effective clinical therapies. This entails rigorous characterization of Ca²⁺ signaling components in nasal epithelial cells under both physiological and pathological conditions, as well as the development of selective modulators with minimal off-target effects. Additionally, integrating emerging technologies such as single-cell transcriptomics and advanced imaging can deepen our understanding of the spatiotemporal dynamics of Ca²⁺ signaling in the nasal mucosa.

Ultimately, advancing targeted Ca²⁺ signaling interventions holds the promise of not only mitigating AR symptoms but also enhancing patients’ quality of life by addressing the disease’s underlying pathophysiology. As the field progresses, a multidisciplinary approach combining molecular biology, immunology, pharmacology, and clinical research will be essential to fully harness the therapeutic potential of Ca²⁺ signaling modulation. This balanced and comprehensive perspective will drive the evolution of personalized medicine strategies tailored to the complex immunological landscape of AR.

Author contributions

YL: Funding acquisition, Writing – original draft, Writing – review & editing. QS: Methodology, Writing – original draft. CM: Methodology, Writing – original draft. JS: Methodology, Writing – original draft. DZ: Methodology, Writing – review & editing. NW: Writing – review & editing, Writing – original draft.

Funding

The author(s) declared that financial support was received for this work and/or its publication. Scientific and Technology Development Program of Jilin Province (YDZJ202501ZYTS816).

Acknowledgments

Thank you to all authors for their contributions to this article.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial

intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Rosenfield L, Keith PK, Quirt J, Small P, Ellis AK. Allergic rhinitis. *Allergy Asthma Clin Immunol.* (2024) 20:74. doi: 10.1186/s13223-024-00923-6
- Rosenwasser LJ. Treatment of allergic rhinitis. *Am J Med.* (2002) 113:17s–24s. doi: 10.1016/s0002-9343(02)01433-x
- Cho HJ, Ha JG, Lee SN, Kim CH, Wang DY, Yoon JH. Differences and similarities between the upper and lower airway: focusing on innate immunity. *Rhinology.* (2021) 59:441–50. doi: 10.4193/rhin21.046
- Himi T, Takano K, Ogasawara N, Go M, Kurose M, Koizumi J, et al. Mucosal immune barrier and antigen-presenting system in human nasal epithelial cells. *Adv Otorhinolaryngol.* (2011) 72:28–30. doi: 10.1159/000324590
- Vanderhaegen T, Gengler I, Dendooven A, Chenivresse C, Lefèvre G, Mortuaire G. Eosinophils in the field of nasal polyposis: towards a better understanding of biologic therapies. *Clin Rev Allergy Immunol.* (2022) 62:90–102. doi: 10.1007/s12016-021-08844-7
- Zhang S, Wu W, Gu M, Zhao Y, Wang L, Liu K, et al. House dust mite induced mucosal barrier dysfunction and type 2 inflammatory responses via the MAPK/AP-1/IL-24 signaling pathway in allergic rhinitis. *Int Immunopharmacol.* (2025) 148:113972. doi: 10.1016/j.intimp.2024.113972
- Nur Husna SM, Tan HT, Md Shukri N, Mohd Ashari NS, Wong KK. Nasal epithelial barrier integrity and tight junctions disruption in allergic rhinitis: overview and pathogenic insights. *Front Immunol.* (2021) 12:663626. doi: 10.3389/fimmu.2021.663626
- Samanta K, Parekh AB. Store-operated Ca²⁺ channels in airway epithelial cell function and implications for asthma. *Philos Trans R Soc Lond B Biol Sci.* (2016) 371:20150424. doi: 10.1098/rstb.2015.0424
- Jairaman A, Prakriya M. Calcium signaling in airway epithelial cells: current understanding and implications for inflammatory airway disease. *Arterioscler Thromb Vasc Biol.* (2024) 44:772–83. doi: 10.1161/atvbaha.123.318339
- Bai W, Liu M, Xiao Q. The diverse roles of TMEM16A Ca(2+)-activated Cl(-) channels in inflammation. *J Adv Res.* (2021) 33:53–68. doi: 10.1016/j.jare.2021.01.013
- Steelant B, Seys SF, Van Gerven L, Van Woensel M, Farré R, Wawrzyniak P, et al. Histamine and T helper cytokine-driven epithelial barrier dysfunction in allergic rhinitis. *J Allergy Clin Immunol.* (2018) 141:951–963.e8. doi: 10.1016/j.jaci.2017.08.039
- Chiang S, Lee SE. New concepts in barrier dysfunction in CRSwNP and emerging roles of tezepelumab and dupilumab. *Am J Rhinol Allergy.* (2023) 37:193–7. doi: 10.1177/19458924231154061
- Bardet G, Mignon V, Momas I, Achard S, Seta N. Human reconstituted nasal epithelium, a promising *in vitro* model to assess impacts of environmental complex mixtures. *Toxicol Vitro.* (2016) 32:55–62. doi: 10.1016/j.tiv.2015.11.019
- Cha HJ. Tight junction proteins at the crossroads of inflammation, barrier function, and disease modulation. *Int J Mol Sci.* (2025) 26:8115. doi: 10.3390/ijms26178115
- London NR, Ramanathan M. The role of the sinonasal epithelium in allergic rhinitis. *Otolaryngol Clin North Am.* (2017) 50:1043–50. doi: 10.1016/j.otc.2017.08.002
- Tengroth L, Millrud CR, Kvarnhammar AM, Kumlien Georén S, Latif L, Cardell LO. Functional effects of Toll-like receptor (TLR)3, 7, 9, RIG-I and MDA-5 stimulation in nasal epithelial cells. *PLoS One.* (2014) 9:e98239. doi: 10.1371/journal.pone.0098239
- Durán A, Alvarez-Mon M, Valero N. Role of toll-like receptors (TLRs) and nucleotide-binding oligomerization domain receptors (NLRs) in viral infections. *Invest Clin.* (2014) 55:61–81.
- Rao Z, Liu S, Li Z, Wang Q, Gao F, Peng H, et al. Alarmin-loaded extracellular lipid droplets induce airway neutrophil infiltration during type 2 inflammation. *Immunity.* (2024) 57:2514–2529.e7. doi: 10.1016/j.immuni.2024.09.001
- Mathä L, Romera-Hernández M, Steer CA, Yin YH, Orangi M, Shim H, et al. Migration of lung resident group 2 innate lymphoid cells link allergic lung inflammation and liver immunity. *Front Immunol.* (2021) 12:679509.
- Nazari J, Shahba F, Jafariaghdam N, Mohebbi S, Arshi S, Bemanian MH, et al. Immune endotyping and gene expression profile of patients with chronic rhinosinusitis with nasal polyps in the aspirin-exacerbated respiratory disease (AERD) and the non-AERD subgroups. *Allergy Asthma Clin Immunol.* (2024) 20:14. doi: 10.1186/s13223-024-00876-w
- Juncadella IJ, Kadl A, Sharma AK, Shim YM, Hochreiter-Hufford A, Borish L, et al. Apoptotic cell clearance by bronchial epithelial cells critically influences airway inflammation. *Nature.* (2013) 493:547–51. doi: 10.1038/nature11714
- Nabipur L, Mouawad M, Agrawal DK. Bioaerosols and airway diseases: mechanisms of epithelial dysfunction, immune activation, and strategies for exposure mitigation. *Arch Intern Med Res.* (2025) 8:178–91. doi: 10.26502/aimr.0210
- Jukosky J, Gosselin BJ, Foley L, Dechen T, Fiering S, Crane-Godreau MA. *In vivo* cigarette smoke exposure decreases CCL20, SLPI, and BD-1 secretion by human primary nasal epithelial cells. *Front Psychiatry.* (2015) 6:185.
- Son SU, Lee SJ, Shin KS. Immunostimulating and intracellular signaling pathways mechanism of rhamnogalacturonan-I type polysaccharide purified from radish leaves. *Int J Biol Macromol.* (2022) 217:506–14. doi: 10.1016/j.ijbiomac.2022.07.084
- Son SU, Lee HW, Park JH, Shin KS. Identification of intracellular activation mechanism of rhamnogalacturonan-I type polysaccharide purified from Panax ginseng leaves in macrophages and roles of component sugar chains on activity. *J Nat Med.* (2024) 78:328–41. doi: 10.1007/s11418-023-01768-w
- Fakhoury HMA, Kvietys PR, Alkattan W, Anouti FA, Elahi MA, Karras SN, et al. Vitamin D and intestinal homeostasis: barrier, microbiota, and immune modulation. *J Steroid Biochem Mol Biol.* (2020) 200:105663. doi: 10.1016/j.jsbmb.2020.105663
- Bulek K, Swaidani S, Aronica M, Li X. Epithelium: the interplay between innate and Th2 immunity. *Immunol Cell Biol.* (2010) 88:257–68. doi: 10.1038/icc.2009.113
- Ghezzi M, Pozzi E, Abbattista L, Lonoce L, Zuccotti GV, D'auria E. Barrier impairment and type 2 inflammation in allergic diseases: the pediatric perspective. *Children (Basel).* (2021) 8:1165. doi: 10.3390/children8121165
- Hellings PW, Steelant B. Epithelial barriers in allergy and asthma. *J Allergy Clin Immunol.* (2020) 145:1499–509. doi: 10.1016/j.jaci.2020.04.010
- Wang Y, Qi X, Li H, Zhang H, Zhu X, Wang L, et al. Inhibition of TRPV1 attenuates innate nasal epithelial responses via NF-κB signaling pathway in allergic rhinitis. *Int Immunopharmacol.* (2025) 158:114807. doi: 10.1016/j.intimp.2025.114807
- Ouyang X, Reihill JA, Douglas LEJ, Dunne OM, Sergeant GP, Martin SL. House dust mite allergens induce Ca(2+) signalling and alarmin responses in asthma airway epithelial cells. *Biochim Biophys Acta Mol Basis Dis.* (2024) 1870:167079. doi: 10.1016/j.bbdis.2024.167079
- Post S, Nawijn MC, Jonker MR, Kliphuis N, Van Den Berge M, Van Oosterhout AJ, et al. House dust mite-induced calcium signaling instigates epithelial barrier dysfunction and CCL20 production. *Allergy.* (2013) 68:1117–25. doi: 10.1111/all.12202
- Smyth JT, Hwang SY, Tomita T, Dehaven WI, Mercer JC, Putney JW. Activation and regulation of store-operated calcium entry. *J Cell Mol Med.* (2010) 14:2337–49. doi: 10.1111/j.1582-4934.2010.01168.x

34. Dalrymple A, Slater DM, Beech D, Poston L, Tribe RM. Molecular identification and localization of Trp homologues, putative calcium channels, in pregnant human uterus. *Mol Hum Reprod.* (2002) 8:946–51. doi: 10.1093/molehr/8.10.946
35. Matthus E, Sun J, Wang L, Bhat MG, Mohammad-Sidik AB, Wilkins KA, et al. DORN1/P2K1 and purino-calcium signalling in plants: making waves with extracellular ATP. *Ann Bot.* (2020) 124:1227–42. doi: 10.1093/aob/mcz135
36. Matthus E, Wilkins KA, Mohammad-Sidik A, Ning Y, Davies JM. Spatial origin of the extracellular ATP-induced cytosolic calcium signature in Arabidopsis thaliana roots: wave formation and variation with phosphate nutrition. *Plant Biol (Stuttg).* (2022) 24:863–73. doi: 10.1111/plb.13427
37. Tian Y, Zheng J. The TRP channels serving as chemical-to-electrical signal converter. *Physiol Rev.* (2025) 105:1033–74. doi: 10.1152/physrev.00012.2024
38. Zhang JQ, Wu PF, Long LH, Chen Y, Hu ZL, Ni L, et al. Resveratrol promotes cellular glucose utilization in primary cultured cortical neurons via calcium-dependent signaling pathway. *J Nutr Biochem.* (2013) 24:629–37. doi: 10.1016/j.jnutbio.2012.02.015
39. Shen KZ, Yakhnitsa V, Munhall AC, Johnson SW. AMP kinase regulates K-ATP currents evoked by NMDA receptor stimulation in rat subthalamic nucleus neurons. *Neuroscience.* (2014) 274:138–52. doi: 10.1016/j.neuroscience.2014.05.031
40. Giulivi C. Mitochondria as generators and targets of nitric oxide. *Novartis Found Symp.* (2007) 287:92–100. doi: 10.1002/9780470725207.ch7
41. Saternos H, Ley S, Aboualwai W. Primary cilia and calcium signaling interactions. *Int J Mol Sci.* (2020) 21:7109. doi: 10.3390/ijms21197109
42. Amoozadeh Y, Anwer S, Dan Q, Venugopal S, Shi Y, Branchard E, et al. Cell confluence regulates claudin-2 expression: possible role for ZO-1 and Rac. *Am J Physiol Cell Physiol.* (2018) 314:C366–78. doi: 10.1152/ajpcell.00234.2017
43. Ancel D, Bernard A, Subramaniam S, Hirasawa A, Tsujimoto G, Hashimoto T, et al. The oral lipid sensor GPR120 is not indispensable for the osensory detection of dietary lipids in mice. *J Lipid Res.* (2015) 56:369–78. doi: 10.1194/jlr.m055202
44. Alcalá DB, Haldeman BD, Brizendine RK, Krenc AK, Baker JE, Rock RS, et al. Myosin light chain kinase steady-state kinetics: comparison of smooth muscle myosin II and nonmuscle myosin IIB as substrates. *Cell Biochem Funct.* (2016) 34:469–74. doi: 10.1002/cbf.3209
45. Cunningham KE, Turner JR. Myosin light chain kinase: pulling the strings of epithelial tight junction function. *Ann N Y Acad Sci.* (2012) 1258:34–42. doi: 10.1111/j.1749-6632.2012.06526.x
46. Su H, Zhao W, Zhang F, Song M, Liu F, Zheng J, et al. cis 9, trans 11, but not trans 10, cis 12 CLA isomer, impairs intestinal epithelial barrier function in IPEC-J2 cells and mice through activation of GPR120-[Ca(2+)](i) and the MLCK signaling pathway. *Food Funct.* (2020) 11:3657–67. doi: 10.1039/d0fo00376j
47. Yang D, Yuan L, Qi Y, Li H, Ren Q, Li Y. Transcriptomics and proteomics association analysis demystify the molecular mechanisms underlying epididymal sperm maturation disorders in yaks with cryptorchidism. *J Anim Sci.* (2025) 103:skaf397. doi: 10.1093/jas/skaf397
48. Lee W, An G, Kim J, Lee H, Song G, Lim W, et al. Evaluation of thiobencarb herbicide-induced cytotoxicity mediated via disruption of calcium homeostasis in bovine mammary glands: a comprehensive *in vitro* and *in silico* study. *Pestic Biochem Physiol.* (2025) 208:106267. doi: 10.1016/j.pestbp.2024.106267
49. Meduri GU, Psarra AG. The glucocorticoid system: a multifaceted regulator of mitochondrial function, endothelial homeostasis, and intestinal barrier integrity. *Semin Respir Crit Care Med.* (2025) 47:32–46. doi: 10.1055/a-2684-3689
50. Qian L, Mehrabi Nasab E, Athari SM, Athari SS. Mitochondria signaling pathways in allergic asthma. *J Invest Med.* (2022) 70:863–82. doi: 10.1136/jim-2021-002098
51. Che D, Hou Y, Zeng Y, Li C, Zhang Y, Wei D, et al. Dehydroandrographolide inhibits IgE-mediated anaphylactic reactions via calcium signaling pathway. *Toxicol Appl Pharmacol.* (2019) 366:46–53. doi: 10.1016/j.taap.2019.01.019
52. Xue C, Gao Y, Li X, Zhang M, Yang Y, Han Q, et al. Mesenchymal stem cells derived from adipose accelerate the progression of colon cancer by inducing a MT-CAFs phenotype via TRPC3/NF-KB axis. *Stem Cell Res Ther.* (2022) 13:335. doi: 10.21203/rs.3.rs-940209/v1
53. Kim HJ, Woo J, Nam YR, Nam JH, Kim WK. Flos magnoliae and its constituent linoleic acid suppress T lymphocyte activation via store-operated calcium entry. *Am J Chin Med.* (2019) 47:1627–41. doi: 10.1096/fasebj.2020.34.s1.03177
54. Meng M, Huo R, Ma N, Chang G, Shen X. β -carotene alleviates LPS-induced inflammation through regulating STIM1/ORAI1 expression in bovine mammary epithelial cells. *Int Immunopharmacol.* (2022) 113:109377. doi: 10.2139/ssrn.4225768
55. Balghi H, Robert R, Rappaz B, Zhang X, Wohlhuter-Haddad A, Evagelidis A, et al. Enhanced Ca²⁺ entry due to Orail plasma membrane insertion increases IL-8 secretion by cystic fibrosis airways. *FASEB J.* (2011) 25:4274–91. doi: 10.1096/fj.11-187682
56. Schieven GL, De Fex H, Stephenson L. Hypochlorous acid activates tyrosine phosphorylation pathways leading to calcium signaling and TNF α production. *Antioxid Redox Signal.* (2002) 4:501–7. doi: 10.1089/15230860260196308
57. Albarran L, Lopez JJ, Woodard GE, Salido GM, Rosado JA. Store-operated Ca²⁺ entry-associated regulatory factor (SARAF) plays an important role in the regulation of arachidonate-regulated Ca²⁺ (ARC) channels. *J Biol Chem.* (2016) 291:6982–8. doi: 10.1074/jbc.m115.704940
58. Wang W, Li Z, Meng Q, Zhang P, Yan P, Zhang Z, et al. Chronic calcium channel inhibitor verapamil antagonizes TNF- α -mediated inflammatory reaction and protects against inflammatory arthritis in mice. *Inflammation.* (2016) 39:1624–34. doi: 10.1007/s10753-016-0396-1
59. Marriotti I, Inscho EW, Bost KL. Extracellular uridine nucleotides initiate cytokine production by murine dendritic cells. *Cell Immunol.* (1999) 195:147–56. doi: 10.1006/cimm.1999.1531
60. Waldron RT, Chen Y, Pham H, Go A, Su HY, Hu C, et al. The Orail Ca(2+) channel inhibitor CM4620 targets both parenchymal and immune cells to reduce inflammation in experimental acute pancreatitis. *J Physiol.* (2019) 597:3085–105. doi: 10.1113/jp277856
61. Qiu X, Dong K, Sun R. STIM1 regulates endothelial calcium overload and cytokine upregulation during sepsis. *J Surg Res.* (2021) 263:236–44. doi: 10.1016/j.jss.2020.12.016
62. Sun LW, Liu ZY, Sha JC, Meng CD, Zhu DD. Bioinformatics analysis of nasal epithelial cell gene expression in seasonal and perennial allergic rhinitis. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* (2022) 57:425–32.
63. Kang M, Seo Y, Seo JH, Jeong Y, Jeon H, Jang SM, et al. Selective PAR2 inhibition attenuates HDM-induced Th1/Th2 responses in human epithelial and murine models of allergic rhinitis and asthma. *Int Forum Allergy Rhinol.* (2025) 15:e23623. doi: 10.1002/alr.23623
64. Rauchman SH, Zubair A, Jacob B, Rauchman D, Pinkhasov A, Placantonakis DG, et al. Traumatic brain injury: Mechanisms, manifestations, and visual sequelae. *Front Neurosci.* (2023) 17:1090672. doi: 10.3389/fnins.2023.1090672
65. Yang K, Liu S, Yan H, Lu W, Shan X, Chen H, et al. SARS-CoV-2 spike protein receptor-binding domain perturbs intracellular calcium homeostasis and impairs pulmonary vascular endothelial cells. *Signal Transduct Target Ther.* (2023) 8:276. doi: 10.1038/s41392-023-01556-8
66. Papińska-Goryca M, Misiukiewicz-Stepień P, Wróbel M, Mycroft-Rzeszotarska K, Adamska D, Rachowka J, et al. The impaired response of nasal epithelial cells to microplastic stimulation in asthma and COPD. *Sci Rep.* (2025) 15:4242. doi: 10.1038/s41598-025-87242-x
67. Csutora P, Su Z, Kim HY, Bugrim A, Cunningham KW, Nuccitelli R, et al. Calcium influx factor is synthesized by yeast and mammalian cells depleted of organelle calcium stores. *Proc Natl Acad Sci USA.* (1999) 96:121–6. doi: 10.1073/pnas.96.1.121
68. Brinckmann BC, Le Ferrec E, Pedechar N, Lagadic-Gossmann D, Shoji KF, Penna A, et al. Lipophilic chemicals from diesel exhaust particles trigger calcium response in human endothelial cells via aryl hydrocarbon receptor non-genomic signalling. *Int J Mol Sci.* (2018) 19:1429. doi: 10.3390/ijms19051429
69. Lei P, Ma X, Zhang Y, Xie S, Hu S, Wang Y, et al. Kukoamine A attenuates allergic rhinitis via H(1)R antagonism: Dual suppression of inflammatory signaling and epithelial barrier disruption. *Biochem Pharmacol.* (2026) 247:117792. doi: 10.1016/j.bcp.2026.117792
70. Srisomboon Y, Tojima I, Iijima K, Kita H, O'grady SM. Allergen-induced activation of epithelial P2Y(2) receptors promotes adenosine triphosphate exocytosis and type 2 immunity in airways. *J Allergy Clin Immunol.* (2025) 155:1607–22. doi: 10.1016/j.jaci.2025.01.019
71. Ogulur I, Mitamura Y, Yazici D, Pat Y, Ardicli S, Li M, et al. Type 2 immunity in allergic diseases. *Cell Mol Immunol.* (2025) 22:211–42. doi: 10.1038/s41423-025-01261-2
72. Aguayo-Orozco A, Bois FY, Brunak S, Taboureaux A. Analysis of time-series gene expression data to explore mechanisms of chemical-induced hepatic steatosis toxicity. *Front Genet.* (2018) 9:396. doi: 10.3389/fgene.2018.00396
73. Sun W, Wang Z, Cao J, Wang X, Han Y, Ma Z. Enhanced production of nitric oxide in A549 cells through activation of TRPA1 ion channel by cold stress. *Nitric Oxide.* (2014) 40:31–5. doi: 10.1016/j.chest.2016.02.178
74. Han D, Choi J, Park MK, Kim N, Han DH. Inflammatory responses and cilia reorganization induced by daily exposure to diesel exhaust particles in primary human nasal epithelium. *Environ Res.* (2026) 294:123849. doi: 10.1016/j.envres.2026.123849
75. Stuart RO, Sun A, Bush KT, Nigam SK. Dependence of epithelial intercellular junction biogenesis on thapsigargin-sensitive intracellular calcium stores. *J Biol Chem.* (1996) 271:13636–41. doi: 10.1074/jbc.271.23.13636
76. Farber JL. The role of calcium ions in toxic cell injury. *Environ Health Perspect.* (1990) 84:107–11. doi: 10.2307/3430711
77. Denda M, Fujiwara S, Hibino T. Expression of voltage-gated calcium channel subunit α 1C in epidermal keratinocytes and effects of agonist and antagonists of the channel on skin barrier homeostasis. *Exp Dermatol.* (2006) 15:455–60. doi: 10.1111/j.0906-6705.2006.00430.x
78. Wen L, Javed TA, Yimlamai D, Mukherjee A, Xiao X, Husain SZ. Transient high pressure in pancreatic ducts promotes inflammation and alters tight junctions via calcineurin signaling in mice. *Gastroenterology.* (2018) 155:1250–1263.e5. doi: 10.1053/j.gastro.2018.06.036
79. Yang X, Wang T, Lin X, Yue X, Wang Q, Wang G, et al. Genetic deletion of Rnd3/RhoE results in mouse heart calcium leakage through upregulation of protein kinase A signaling. *Circ Res.* (2015) 116:e1–10. doi: 10.1161/circresaha.116.304940

80. Paris S, Zhang X, Davis D, Nguyen AD, Ustaoglu A, Genta RM, et al. In obesity, esophagogastric junction fat impairs esophageal barrier function and dilates intercellular spaces via hypoxia-inducible factor 2 α . *Gastroenterology*. (2025) 168:914–930.e19. doi: 10.1053/j.gastro.2024.12.012
81. Meyers RL, Shabo AL, Maxwell DS. Effect of prostaglandin on the blood aqueous barrier in the rabbit ciliary process. *Prostaglandins*. (1975) 9:167–73. doi: 10.1016/0090-6980(75)90021-0
82. Zhao QL, Kondo T, Noda A, Fujiwara Y. Mitochondrial and intracellular free-calcium regulation of radiation-induced apoptosis in human leukemic cells. *Int J Radiat Biol*. (1999) 75:493–504. doi: 10.1080/0955530099140429
83. Wang H, Liu Z, Li X, Zhao R, Pu Y, Wu H, et al. Shikonin causes apoptosis by disrupting intracellular calcium homeostasis and mitochondrial function in human hepatoma cells. *Exp Ther Med*. (2018) 15:1484–92. doi: 10.3892/etm.2017.5591
84. Pai VP, Horseman ND. Multiple cellular responses to serotonin contribute to epithelial homeostasis. *PLoS One*. (2011) 6:e17028. doi: 10.1371/journal.pone.0017028
85. Wang LC, Yu Q, Edwards V, Lin B, Qiu J, Turner JR, et al. Neisseria gonorrhoeae infects the human endocervix by activating non-muscle myosin II-mediated epithelial exfoliation. *PLoS Pathog*. (2017) 13:e1006269. doi: 10.1371/journal.ppat.1006269
86. Lee RJ, Chen B, Doghramji L, Adappa ND, Palmer JN, Kennedy DW, et al. Vasoactive intestinal peptide regulates sinonasal mucociliary clearance and synergizes with histamine in stimulating sinonasal fluid secretion. *FASEB J*. (2013) 27:5094–103. doi: 10.1096/fj.13-234476
87. Rafiq K, Bullens DM, Kasran A, Lorré K, Ceuppens JL, Van Gool SW. Differences in regulatory pathways identify subgroups of T cell-derived Th2 cytokines. *Clin Exp Immunol*. (2000) 121:86–93. doi: 10.1046/j.1365-2249.2000.01273.x
88. Madison JM, Ethier MF. Interleukin-4 rapidly inhibits calcium transients in response to carbachol in bovine airway smooth muscle cells. *Am J Respir Cell Mol Biol*. (2001) 25:239–44. doi: 10.1165/ajrcmb.25.2.4286
89. Garcia-Zepeda EA, Combadiere C, Rothenberg ME, Sarafi MN, Lavigne F, Hamid Q, et al. Human monocyte chemoattractant protein (MCP)-4 is a novel CC chemokine with activities on monocytes, eosinophils, and basophils induced in allergic and nonallergic inflammation that signals through the CC chemokine receptors (CCR)-2 and -3. *J Immunol*. (1996) 157:5613–26. doi: 10.4049/jimmunol.157.12.5613
90. Nakamura Y, Oscherwitz J, Cease KB, Chan SM, Muñoz-Planillo R, Hasegawa M, et al. Staphylococcus δ -toxin induces allergic skin disease by activating mast cells. *Nature*. (2013) 503:397–401. doi: 10.1038/nature12655
91. Son GY, Bak EJ, Kim JH, Lee DE, Kang SM, Lee SY, et al. Endothelin regulates Porphyromonas gingivalis-induced production of inflammatory cytokines. *PLoS One*. (2016) 11:e0167713. doi: 10.1371/journal.pone.0167713
92. Li X, Kong D, Chen H, Liu S, Hu H, Wu T, et al. miR-155 acts as an anti-inflammatory factor in atherosclerosis-associated foam cell formation by repressing calcium-regulated heat stable protein 1. *Sci Rep*. (2016) 6:21789. doi: 10.1038/srep21789
93. Ben Dhaou C, Terrié E, Déliot N, Harnois T, Cousin L, Arnault P, et al. Neural stem cell self-renewal stimulation by store-operated calcium entries in adult mouse area postrema: Influence of leptin. *Front Cell Neurosci*. (2023) 17:1200360. doi: 10.3389/fncel.2023.1200360
94. He J, Fu J, Wang R, Liu X, Yao J, Xing W, et al. Tissue repair mechanisms of dental pulp stem cells: A comprehensive review from cutaneous regeneration to mucosal healing. *Curr Issues Mol Biol*. (2025) 47:509. doi: 10.3390/cimb47070509
95. Rychkov GY, Zhou FH, Adams MK, Brierley SM, Ma L, Barritt GJ. Orai1- and Orai2-, but not Orai3-mediated I(CRAC) is regulated by intracellular pH. *J Physiol*. (2022) 600:623–43. doi: 10.1101/2020.11.01.364299
96. Goriounova AS, Flori Sassano M, Wrennall JA, Tarran R. ELD607 specifically traffics Orai1 to the lysosome leading to inhibition of store operated calcium entry. *Cell Calcium*. (2024) 123:102945. doi: 10.1016/j.ceca.2024.102945
97. Tai K, Vandenberg G, Hamaide MC, Wibo M, Morel N. Effect of organ culture on noradrenaline-evoked contraction, calcium signalling and TRPC expression in rat mesenteric artery. *J Vasc Res*. (2009) 46:353–64. doi: 10.1159/000189796
98. Chen S, He FF, Wang H, Fang Z, Shao N, Tian XJ, et al. Calcium entry via TRPC6 mediates albumin overload-induced endoplasmic reticulum stress and apoptosis in podocytes. *Cell Calcium*. (2011) 50:523–9. doi: 10.1016/j.ceca.2011.08.008
99. Ilatovskaya DV, Polygin O, Chubinskiy-Nadezhdin V, Negulyaev YA, Ma R, Birnbaumer L, et al. Angiotensin II has acute effects on TRPC6 channels in podocytes of freshly isolated glomeruli. *Kidney Int*. (2014) 86:506–14. doi: 10.1038/ki.2014.71
100. Tauseef M, Knezevic N, Chava KR, Smith M, Sukriti S, Gianaris N, et al. TLR4 activation of TRPC6-dependent calcium signaling mediates endotoxin-induced lung vascular permeability and inflammation. *J Exp Med*. (2012) 209:1953–68. doi: 10.1085/jgp.14050ia9
101. Zhang L, Guo F, Kim JY, Saffen D. Muscarinic acetylcholine receptors activate TRPC6 channels in PC12D cells via Ca²⁺ store-independent mechanisms. *J Biochem*. (2006) 139:459–70. doi: 10.1093/jb/mvj065
102. Patel CA, Patel S, Patel S, Parmar D, Beladiya J, Sundar SR, et al. Targeting TRPC6 in podocytopathies: Why clinical translation remains a challenge? *Pharmacol Rep*. (2025) 78:102–22. doi: 10.1007/s43440-025-00766-x
103. England E, Rees DG, Scott IC, Carmen S, Chan DTY, Chaillan Huntington CE, et al. Tozorakimab (MEDI3506): an anti-IL-33 antibody that inhibits IL-33 signalling via ST2 and RAGE/EGFR to reduce inflammation and epithelial dysfunction. *Sci Rep*. (2023) 13:9825. doi: 10.1038/s41598-023-36642-y
104. Miao Q, Yu R, Shi F, Li K, Du X, Gao Y, et al. Respiratory syncytial virus infection disrupts airway epithelial barriers via IL-33/ST2/MyD88 signaling axis. *J Med Virol*. (2025) 97:e70432. doi: 10.1002/jmv.70432
105. Subramanian VS, Marchant JS, Ye D, Ma TY, Said HM. Tight junction targeting and intracellular trafficking of occludin in polarized epithelial cells. *Am J Physiol Cell Physiol*. (2007) 293:C1717–26. doi: 10.1152/ajpcell.00309.2007
106. Wang JM, Yang J, Xia WY, Wang YM, Zhu YB, Huang Q, et al. Comprehensive analysis of PANoptosis-related gene signature of ulcerative colitis. *Int J Mol Sci*. (2023) 25:348. doi: 10.3390/ijms25010348
107. Sha J, Yang M, Lei Y, Sun L, Meng C, Zhu D. Interaction between nasal epithelial cells and Tregs in allergic rhinitis responses to allergen via CCL1/CCR8. *Front Immunol*. (2025) 16:1526081. doi: 10.3389/fimmu.2025.1526081
108. Klimov V, Cherevko N, Klimov A, Novikov P. Neuronal-immune cell units in allergic inflammation in the nose. *Int J Mol Sci*. (2022) 23:6938. doi: 10.3390/ijms23136938