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SUPPLEMENT ARTICLE

Targeting Antiviral Pathways for Treatment of Allergic Diseases

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Atopic diseases, including atopic eczema, allergic asthma, and allergic rhinitis, are major causes of childhood morbidity. Epidemiologic evidence closely links virus infections to both development and exacerbation of allergic diseases. This is best appreciated in the context of allergic asthma where seasonal increases in exacerbation rates coincide with fall respiratory virus epidemics. Viruses, predominantly rhinoviruses (RVs), can be isolated from respiratory secretions in up to 80% of asthma exacerbations [1], and early infection in children with allergic sensitization increases the risk of asthma development in childhood by 20-fold [2]. These associations are not exclusive to asthma. Early respiratory virus infections are also implicated in the development of allergic rhinitis, with subsequent infections contributing to symptom severity [3]. In a subset of atopic dermatitis patients, infection with deoxyribonucleic acid (DNA) viruses such as herpes simplex virus, also results in increased morbidity [4]. The mechanisms underlying these connections are largely undefined, but a growing body of evidence indicates that the allergic milieu induces deficient antiviral responses in multiple cell types [5], likely contributing to disease pathogenesis.

ANTIVIRAL RESPONSES: INTERFERONS

Cellular antiviral responses encompass pathways dedicated to the recognition and inhibition of viruses. The innate antiviral capability across diverse cells and tissues highlights the evolutionary conservation and critical role these pathways play in immunity. Interferons (IFNs)—type I (α, β), type II (γ), and type III (λ)—are the main effectors of antiviral responses. Since the discovery of IFNs, there is now an appreciation for complex signaling pathways regulating cellular antiviral immunity. Pattern recognition receptors (PRRs), including endosomal Toll-like receptors ([TLR]-3, -7, -8, and -9) and the cytosolic receptors RIG-I, MDA-5, and c-GAS, recognize either foreign ribonucleic acid (RNA) or DNA (ie, viral genomes). Pattern recognition receptor activation and downstream signaling events upregulate numerous antiviral response genes, including type I and III IFNs. Interferon secretion induces a paracrine response to combat virus replication and dissemination [6]. Interferons are required for controlling virus infections; the functions are multifaceted including regulation of innate and adaptive immune responses. For example, type I IFN activates antigen-presenting cells promoting T-helper (Th)1 T-cell priming [7], whereas direct action on T cells inhibits Th2 differentiation and memory effector functions [8]. Thus, inadequate type I IFN responses in allergic disease may both enhance virus infection and replication and alter virus-induced T-cell development through increased allergic Th2 inflammation.

Deficient IFN responses in allergic disease have been well demonstrated in multiple cell types. In subjects with allergic rhinitis and asthma, the upper and lower respiratory epithelial cells have impaired IFN (type I and III) responses after virus infection in vivo and ex vivo [9, 10]. Cellular mechanistic studies showed altered signaling of the PRRs TLR-3, MDA-5, and RIG-I upstream of IFN release [9]. Ex vivo, exogenous type I IFN treatment restored some observed deficits, including control of virus replication [11]. The importance of PRR pathways in asthma was demonstrated in a recent clinical trial evaluating a TLR-3-blocking antibody to decrease virus-induced inflammation. Toll-like receptor-3 inhibition had an opposite intended effect, resulting in increased severity of virus-induced asthma exacerbations [12], suggesting that TLR-3-induced antiviral responses are required for adequate asthma control.

ANTIVIRAL RESPONSES: ANTIGEN-PRESENTING CELLS

Innate immune cells, including dendritic cells (DCs), monocytes, and macrophages, are also affected by the allergic environment. Peripheral blood mononuclear cells (PBMCs) and plasmacytoid DCs (pDCs) from allergic asthmatics exhibit impaired IFNα secretion after ex vivo exposure to influenza or RV. Furthermore, virus-induced IFNα secretion was significantly inhibited by

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activation of the high-affinity immunoglobulin (Ig)E receptor, FcεRI, via ex vivo receptor cross-linking [13, 14]. Reduced TLR-7 expression in alveolar macrophages was associated with deficient RV-induced IFN responses in severe asthmatics and mechanistically linked to expression of specific microRNAs that negatively regulate TLR-7 transcripts [15]. Our group has shown that multiple monocyte functions are impaired by IgE-mediated allergic stimulation, including bacterial phagocytosis [16], influenza-induced upregulation of antigen-presenting molecules and T-cell costimulatory molecules, and virus-induced monocyte-driven CD4 Th1 T-cell priming [17].

INTERFERONS AS THERAPY

It remains challenging to prevent virus-induced allergic exacerbations using standard therapies, potentially due to the deficiencies in cellular antiviral responses. Patients with severe disease on maximal therapy remain at high risk of hospitalization and morbidity secondary to virus-induced exacerbations [18]. There are no available interventions to prevent development of virus-induced allergic disease, indicating gaps in our clinical toolbox. Many biologic therapies are either approved or in clinical trials; however, most target late effectors of allergic inflammation [18] and do not address underlying viral components. Therapeutic augmentation of host antiviral pathways could improve treatment and potentially prevent allergic diseases. Recent clinical trials have begun to address this specific objective.

Many effects on antiviral pathways involve IgE-mediated inhibitory mechanisms downstream of the IgE receptor, FcεRI. Studies demonstrate that decreasing serum IgE levels (and thus receptor expression) with the therapeutic anti-IgE antibody, omalizumab, reduces exacerbation of multiple atopic diseases, including allergic asthma, allergic rhinitis, and atopic dermatitis [5, 18]. In the recent National Institute of Allergy and Infectious Diseases-funded Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) study conducted in children with allergic asthma, omalizumab therapy reduced seasonal virus-induced asthma exacerbations [19]. Treatment also restored antiviral responses as shown by increased ex vivo RV-induced PBMC and pDC IFNα responses and normalized virus-induced IFNβ and RIG-I transcripts [20]. Furthermore, the group with greater changes in ex vivo IFNα responses after omalizumab had a lower proportion of asthma exacerbations during the outcome period [19]. Children treated with omalizumab also had less RV-induced upper respiratory symptoms, shorter duration of virus shedding, and decreased peak virus titers in respiratory secretions [21], suggesting that IgE-mediated processes modulate in vivo RV infection.

The PROSE study provides evidence that restoring deficient type I IFN responses has a potential clinical role in treating atopic asthma. Type I IFN complementation or activation of antiviral signaling pathways with small molecule agonists could potentially restore the deficient antiviral responses observed in allergic diseases. A recent clinical trial of inhaled IFNβ was conducted in adults to prevent asthma exacerbations. The primary outcome of overall asthma symptom improvement was not significant in the IFNβ-treated group, but subanalyses indicated that IFNβ treatment promoted faster recovery of morning peak expiratory flow and decreased exacerbations in those with severe disease [22].

NOVEL TREATMENT STRATEGIES: TARGETING INTRACELLULAR ANTIVIRAL SIGNALING PATHWAYS

Targeting intracellular antiviral signaling pathways is an alternative to IFN therapy, and therapeutic agonists of TLR-9 and TLR-7 are in early clinical trials. An injectable nanoparticle composed of a bacteriophage virus-like particle complexed with the TLR-9 ligand CpG (CYT003-QgB10) has been developed. In allergic rhinitis subjects, treatment with CYT003-QgB10 decreased daily rhinoconjunctivitis symptoms, improved quality of life, and improved allergen tolerance upon nasal challenge with house dust mite compared with placebo [23]. A Phase IIa study conducted in allergic asthmatic patients similarly revealed decreased asthma symptoms upon withdrawal of daily inhaled steroid controller medication in the group treated with the TLR-9 agonist [24]. Unfortunately, no effect on asthma symptoms was observed in the subsequent Phase IIb study, likely due to continuation of inhaled corticosteroids in both treatment and placebo groups [25], suggesting that TLR-9 agonists may not improve asthma control beyond standard of care therapies. Toll-like receptor-7 agonists have similarly shown promising early results in individuals with allergic rhinitis [26, 27]. Pretreatment with the intranasal TLR-7 agonist, AZD8848, decreased allergic rhinitis symptoms for up to 8 days after nasal allergen challenge and resulted in upregulation of antiviral response genes and Th1-inducing factors [26]. Nonhuman primate studies are being conducted as the next step towards using AZD8848 in human asthma studies [28]. Evidence that the TLR-7 agonist imiquimod induces bronchorelaxation of human airway smooth muscle cells also suggests a potential role for TLR-7-based therapies for asthma [29] and is supported by results from TLR-7 agonist treatment of allergic asthma in animal models [30].

It is currently unclear whether these therapies will affect virus-induced allergic exacerbations. Immunoglobulin E-mediated allergic signals downregulate both TLR-7 and TLR-9 in innate immune cells [14, 31], which could limit the effectiveness of these drugs. Additional negative regulatory mechanisms have been implicated in airway epithelial cells, such as upregulation of suppressor of cytokine signaling 3 (SOCS-3) and dysregulated activation of the IFN receptor signaling molecule, STAT1 [reviewed in 5]. In innate immune cells, IgE-mediated stimulation also induces interleukin-10 [16], a cytokine shown to impair virus-induced IFN in vitro [32].

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Therefore, a single "magic bullet" monotherapy is unlikely to be effective, and instead combination therapies targeting multiple pathways may be needed for maximal impact. For example, the TLR-2/6/9 agonist, PUL-042, is effective in decreasing mortality in a mouse model of influenza [33], and is in early human clinical trials (clinicaltrials.gov, NCT02124278), suggesting that combination therapies could be safe and effective. Agonists of the cytosolic receptors, RIG-I, MDA-5, c-GAS, and STING, are in early development as antivirals [34], vaccine adjuvants, and anticancer therapies [35], demonstrating broad therapeutic potential as stimulators of antiviral responses, and could also be considered in treatment of allergic disease.

CONCLUSIONS

Virus-induced allergic disease exacerbations represent complex interactions between the virus, host genetics, and environment, and the effects of allergic sensitization on antiviral responses are multifactorial. Although the future clinical role of targeting antiviral pathways in allergic disease is unknown, early studies suggest that this strategy has potential to identify additional therapeutic options. Although antiviral signaling pathways are well characterized, a greater understanding of how allergic and antiviral signals intersect at the molecular level is needed to identify additional candidate viral and cellular targets for improved treatment and prevention strategies for virus-induced allergic diseases.

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