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Retinoic Acid (RA): A Critical Immunoregulatory Molecule in Asthma and Allergies

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ABSTRACT

Introduction: Asthma and allergies are chronic inflammatory disorders that are triggered owing to aberrant responses of the immune system against typically innocent environmental substances. Retinoic acid (RA) represents a biologically active metabolite of vitamin A (VA) and high-affinity ligand for RA receptor (RAR) that is implicated in a wide variety of biological processes, including cell proliferation, differentiation, apoptosis, organogenesis, reproduction, and immune responses. In the immune system, RA contributes to the induction of regulatory T (Treg) cells, adhesion molecules required for homing of B and T cells in the gut, and tolerance. Noteworthy, RA has a pivotal role in maintaining the balance of Th17-Treg cells and is also indispensable for appropriate responses of T helper (Th) cells.

Aims: This mini-review article intends to expose the immune functions of RA, with an emphasis on the enzymatic pathways converting VA into RA and its receptor-dependent actions in asthma and allergies.

Conclusions: Recent findings have depicted that RA levels are reduced in asthma and allergies and that treatment with RA alleviates allergy symptoms and airway inflammation. RA also modulates allergic airway disorders by inhibiting Th2/Th17 response and increasing Treg cells. Therefore, RA could be considered a novel and promising therapeutic agent to be studied and used for treating these diseases.

1 | Introduction

The prevalence of asthma and allergic diseases (allergies) has rapidly increased over the recent decades in both developed and developing countries, now becoming a public health problem around the world [1, 2]. Asthma and allergies are chronic inflammatory disorders developed in genetically prone persons due to the inappropriate responses of the immune system against foreign, usually innocuous, substances [2, 3].

Genetic factors, immune system, as well as changing lifestyle and/or environment are the most identified risk factors in the development of these diseases. The alterations in dietary patterns may particularly exert a key role. For instance, decreased intake of the antioxidant vitamins A, C, and E may be related to the increased prevalence of asthma and allergic diseases [4–6]. In this regard, the intake of dietary vitamin A (VA) and serum levels of VA are strikingly decreased in asthmatic patients compared with healthy people or in patients having severe asthma relative to mild asthma. Epidemiological investigations have also found an inverse relationship between asthma and the intake of VA [7–10]. Other studies; however, have achieved no such relationships between VA and allergic rhinitis (AR) [11, 12]. In a murine model of allergic airway inflammation with high levels of immunoglobulin E (IgE) and IgG1 antibodies, it was found that high dietary intake of VA

effects of ATRA on AHR, allergic airway inflammation, and the count of Treg cells in the lungs were entirely inverted [70]. In a mouse airway allergy model, therapy with ATRA diminished inflammation and Th17 cell-associated cytokines whereas Treg cell count in the lung was increased [10, 70, 71]. Nonetheless, this enhancement of Treg cells was time-dependent, and the useful effects of ATRA in asthma may be fading due to the increased eosinophilia that also happened upon ATRA treatment [13, 71]. In aggregation, these findings show that RA has anti-allergic effects and can be applied as a therapeutic agent for treating asthma and allergies in the coming years. The therapeutic effects of RA on asthma and allergies are summarized in Table 1.

6 | RA Receptors and Signaling

RA exerts its bioactions primarily through interaction with the nuclear receptors of the RAR family, which belongs to the nuclear hormone receptors (NHR) superfamily of transcription factors. The RAR family has three major isoforms, including RARα, RARβ, and RARγ. These form heterodimers with the members of the retinoid X receptor (RXR) subfamily, namely, RXRα, RXRβ, and RXRγ, thereby acting as ligand-dependent transcriptional regulators by interacting with RA response elements (RAREs) located in the promoters of RA-responsive genes [19, 72, 73]. Besides, RA can bind to the PPARβ/δ nuclear receptor when it heterodimerizes with RXR, which this signaling pathway is probably important for lipid metabolism and glucose homeostasis [49]. The ratio of CRABPs to FABP5 determines whether RA signaling occurs via RAR or PPARβ/δ, which translates as distinct functional consequences [49]. RA also has low-affinity receptors; including chicken ovalbumin upstream promoter transcription factor II (COUP-TFII) and hepatocyte nuclear factor 4 (HNF-4) receptors when they form a heterodimer with RXR. Signaling from these receptors is important for lipid metabolism and glucose homeostasis, similar to PPARβ/δ [74, 75].

7 | Conclusions and Future Perspectives

In summary, RA plays a critical function in regulating immune responses, and evidence has indicated that it possesses a dual role. Numerous factors, including the signaling of TLR, the existence of other cytokines, local concentrations of RA, and the cellular and molecular composition of the microenvironment, ascertain the effector actions of RA. In addition to promoting the transcription of multiple genes, RA can also affect translation or stimulate epigenetic effects by connecting to its nuclear receptors, including RARs, RXRs, and PPAR-β/δ. As mentioned in this review, several studies have shown the beneficial therapeutic effects of RA in asthma and allergies, introducing RA as a novel and promising therapeutic agent for the treatment of these diseases. Nonetheless, an essential point to keep in mind is that since the effector functions of RA are dependent on the local microenvironment as well as the clinical and immunological condition of the patient, the therapeutic consequence of RA therapy is also anticipated to be varied. Therefore, more investigations would be imperative for further deciphering the interaction of RA with the local microenvironment and how these interactions are adjusted to be able to design efficacious remedies.

Author Contributions

Ramin Lotfi: conceptualization; methodology; validation; writing–original draft; writing–review & editing.

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Conflicts of Interest

There are no conflicts of interest with respect to this manuscript.

Data Availability Statement

Data sharing does not apply to this article as no datasets were generated or analyzed during the present study.

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