

Relevance of arginase in atopic diseases and potential mechanisms of association

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Abstract. Atopic diseases have a high incidence all over the world, It affects about 25% of the global population, especially in developed countries and regions. At present, its incidence is still increasing year by year, which brings great pressure to the lives of patients and social economy. Arginase is an enzyme that catalyzes the hydrolysis of Larginine to ornithine and urea in human body and participates in a variety of physiological and pathological processes. Arginine metabolism is a key regulator of innate and adaptive immune responses. Study in atopic dermatitis (AD), (AS), atopic asthma rhinitis (AR) and allergic disease, the levels of arginase is closely related to the atopic diseases, this paper provides an overview of arginase biological function and role, analyses its in the blood, the airway and the role of mucous membrane of the skin, through a comprehensive review arginase applied in current clinical atopic disease research, to explore the relationship between arginase and the pathogenesis of atopic diseases, and to explore the potential role of arginase in the pathogenesis of atopic diseases, so as to provide a new plan for the treatment of allergic diseases.

1. Introduction

The incidence of allergic diseases has risen significantly over the past few decades and has become a public health issue of global concern. The World Health Organization (WHO) has listed allergic diseases as one of the three major diseases that need to be focused on research and prevention in the 21st century. With the increased research and attention to allergic diseases, people have gained an in-depth understanding of the etiology, pathogenesis, and developmental process of allergic diseases, and are constantly seeking effective methods for the prevention and treatment of allergic diseases. There are few studies on the role of arginase in allergic diseases, and the research focus is on cardiovascular diseases and tumor treatment. The innovation of this paper is to summarize the association and application of arginase and a variety of allergic diseases. On the basis of previous research on arginase and a single allergic disease, we further extended to a series of allergic diseases, focusing on four allergic diseases: allergic dermatitis, asthma, allergic rhinitis, and food allergy. To explore the relationship between arginase and four allergic diseases. This article elaborates on the role of arginase in the occurrence and development of allergic diseases, and analyze the scintification and feasibility of arginase as a prediction and treatment of allergic diseases, in order to provide clinical reference for the early prevention and early diagnosis of allergic diseases.

2. Arginase

Arginase (ARG) is a dinuclear manganese-containing metalloenzyme, which exists in the human body in the form of two isoenzymes, divided into arginase I (ARG-1) and arginase II (ARG-2). ARG-1, as a cytoplasmic enzyme, is most abundant in the liver, followed by cardiomyocytes, vascular smooth muscle cells, endothelial cells, and erythrocytes. ARG-2 was widely distributed in kidney, gastrointestinal tract, blood vessels and other tissues. Both isoforms are expressed in other peripheral tissues and in the central nervous system.

ARG is involved in several metabolic pathways under physiological and pathological conditions. It has a mutually antagonistic relationship with endothelial nitric oxide synthase (eNOS) in vivo. They have a common substrate, L-arginine, which is catabolized by ARG to urea and ornithine, and catalytically produced by eNOS to citrulline and NO. Although the affinity of NOS for arginine is about 1000 times higher than that of ARG, the maximal reaction rate (V_{max}) of ARG is about 1000 times higher than that of NOS, which indicates that they share the same metabolic pathway. This indicates that they have the same substrate utilization [1]. They maintain the concentration of NO in the body in dynamic equilibrium [2]. When the body is in a pathological state, ARG can be over-activated, resulting in the inhibition of eNOS activity. A large number of pro-inflammatory factors (IFN- γ , IL-4, IL-10), eosinophils and lymphocytes in the trachea and blood vessels can

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increase the expression level of ARG, thereby reducing the production of NO. ARG can competitively inhibit the production of NO. In addition, overexpression of ARG promotes the synthesis of excessive amines, which can stimulate the contraction of tracheal smooth muscle, increase capillary relaxation and permeability, and further enhance Arg-mediated inhibition of NO [3]. Therefore, the decrease of NO production caused by the increase of ARG activity leads to the dysfunction of tracheal and vascular endothelial cells, which is involved in the occurrence and development of allergic diseases and plays an important role in allergic diseases.

3. Arginase and allergic diseases

3.1. Arginase and allergic dermatitis

Atopic dermatitis (AD), also known as "allergic eczema", is one of the most common chronic, inflammatory, systemic skin diseases. It is characterized by an abnormal inflammatory response mediated by helper T cell type 2 (Th2) cells and elevated serum immunoglobulin E (IgE) and eosinophils. It is clinically characterized by dry skin, intractable itching and chronic eczema-like lesions.[4]. In recent years, the prevalence of AD has been on the rise worldwide. In China, the prevalence of AD has increased from 0.69% in 1998 to 3.07% in 2002 to 12.94% in 2016, and the prevalence in urban areas is higher than that in rural areas, and the prevalence in children is as high as 25%[5-6]. Studies have shown that AD patients are more likely to induce other allergic diseases, and many of them suffer from AD in childhood and have increased sensitivity to allergens in adulthood, with 30-60% of them accompanied by allergic rhinitis and asthma [7]. AD has complex etiology, diverse pathogenic pathways, and different clinical phenotypes. There are great differences in severity, age of onset, response to treatment, acute and chronic, Filaggrin (FLG), IgE levels, and types of inflammatory reactions [8], and the cure rate is low, which seriously affects the quality of life of patients.

Current studies suggest that the disease is related to genetics, environment and immunity. Existing studies suggest that AD may be associated with peripheral blood arginase activity in affected children [9], the results of this study showed that peripheral blood arginase activity was reduced in children with AD compared to normal children. In general TH2 cytokines dominate in allergic diseases, while TH1 cytokines found in chronic allergic dermatitis, especially interferon gamma (IFN γ) active protein, can be tilted toward the NOS pathway, leading to increased NO production. Whereas, large amounts of NO have been shown to have deleterious effects on wounds in wound repair mechanisms [10]. Meanwhile a study by Broccardo C J [11] et al. showed that in AD patients with a history of herpetic eczema, the expression level of arginase-1 was significantly lower at lesion sites compared to non-lesion sites. This was attributed to reduced expression of skin barrier-related protein (polyfilament protein-2) and enzymatic moisturizing

factor (ARG-1), which further exacerbated barrier defects and skin water loss [12-13].

The pathogenesis of AD is diverse and the disease is complex, and it is difficult to treat clinically. To explore the relationship between AD and ARG and to seek effective methods for the prevention and treatment of AD. Studies have shown that in AD, the ARG pathway is inhibited, metabolism is skewed toward the NOS pathway, and the amount of product NO is increased, and large amounts of NO are detrimental to wound repair. According to the results of this study, the following research can be carried out in the direction of monitoring and preventing AD by regulating the blood concentration of ARG.

3.2. Arginase and asthma

Asthma (AS) is a common and frequent disease of chronic respiratory system. Clinical manifestations include recurrent episodes of wheezing, shortness of breath, with or without cough. The continuous increase in the incidence of asthma has caused a huge economic and medical burden worldwide, seriously affecting people's quality of life. According to an epidemiologic survey, the prevalence of asthma in people aged 20 years and older in China is 4.2%, with a total number of patients of about 45.7 million, but only 28.8% of the patients have been clearly diagnosed [14].

The pathogenesis of asthma is very complex, with the deepening research on the pathogenesis of asthma, it is now generally accepted that the three main pathological changes of bronchial asthma are airway inflammation, smooth muscle dysfunction and airway remodeling [15-18]. Currently, the diagnosis of asthma is mainly in accordance with the Global Initiative for Asthma Control and the Guidelines for the Prevention and Control of Bronchial Asthma (2020 edition), with pulmonary function tests, bronchodilator tests, and bronchial provocation tests as the gold standard [19-20]. Studies have shown that Fractional exhaled nitric oxide (FeNO) has many applications in the diagnosis, monitoring and prediction of airway eosinophilic inflammation. FeNO measurement can be used as an effective method to identify asthma and other eosinophil-mediated, corticosteroid-responsive airway inflammatory diseases, and has been recommended as one of the objective assessment tools for asthma by many asthma guidelines [21-22]. However, because asthma has a stable period and an acute attack period, a single diagnostic test can be negative, and follow-up and repeated tests are necessary to make a definite diagnosis.

The potential role of the ARG pathway in arginine dysregulation and NO metabolism has attracted attention in recent years. It has been shown that the relative deficiency of NO due to increased ARG activity and altered L-arginine homeostasis is a major factor in asthma pathology,[23-24].Ale Sca[25] and others have shown that the ARG1 gene may be an asthma-causing gene as a potential novel bronchodilator-responsive gene, with only a few studies investigating a possible link between the two.The ARG1 gene is localized on

chromosome 6q23 and encodes an ARG that is an isoform metabolizing L-arginine. L-arginine regulates homeostasis involved in the regulation of airway function as this amino acid influences NOS and determines endogenous bronchodilator NO production [26-27]. Bratt [28-29] et al. used the guinea pig asthma model as the research object and found that after asthma caused by allergen challenge, the activity of ARG in the airway increased significantly, leading to NO deficiency and airway hyperresponsiveness after the early response of asthma, which proved that arginase regulated airway responsiveness through the production of bronchodilator NO [30]. Xu W [31] et al. demonstrated that increased arginine production and overexpression of ARG2 in bronchial epithelial cell lines accelerated oxidative bioenergetic pathways in an asthma model mouse, inhibited the hypoxia-inducible factors (HIFs) and phosphorylation of the allergic Th2 inflammatory signaling transducer STAT6 (pSTAT6), both of which have been implicated in the etiology of asthma. The results of Holguin [32] et al. showed that healthy controls had higher arginine bioavailability and higher levels of arginine catabolism, as indicated by higher FeNO levels and serum ARG activity, compared with asthmatic subjects. The bioavailability of ARG is associated with airflow obstruction in severe asthma. Our experimental model also confirmed that measurement of arginine bioavailability can predict airflow obstruction in severe asthma.

There are many studies focus on AS, but due to the complexity of its pathogenesis, so far no effective methods have been found for the prevention and treatment of AS. Experimental studies show that ARG1 gene, as a potential bronchodilator response gene, may be one of the pathogenic genes of asthma. ARG1 gene can encode ARG, which reduces the production of endogenous bronchodilator NO and is not conducive to bronchiectasis. Arginine catabolism is more active and serum ARG activity is higher in asthmatic subjects than in healthy control subjects, and the bioavailability of ARG correlates with airflow obstruction in severe asthma. Based on this, topical application of specific and selective arginase inhibitors may provide a new therapeutic strategy for the treatment of acute and chronic asthma, which is worthy of further study.

3.3. Arginase and allergic rhinitis

Allergic rhinitis (AR) is a type I allergic inflammation caused by IgE mediated, Th2 immune response after nasal mucosa exposure to allergens. It is a non-infectious chronic disease of the nasal mucosa, which is characterized by nasal itching, sneezing, nasal hypersecretion, and nasal mucosal swelling. It often occurs in childhood and is the most common chronic allergic disease in children. In children with AR, bronchial asthma can be complicated at the same time, accompanied by cough, wheezing, chest tightness and other pulmonary symptoms [33]. In recent years, the incidence of the disease has been on the rise, and the global prevalence of the disease is about 10% to 25%,

and about 30% to 40% of patients with allergic rhinitis have asthma. Allergic rhinitis is an important risk factor for asthma, and there is a close relationship between them [34]. The onset of AR usually leads to the aggravation of asthma. Therefore, the lower respiratory tract, especially asthma, should be examined and evaluated in the diagnosis of AR. Although AR has no fatal effect on individuals, it has seriously affected human health and quality of life, and has become a global social problem that needs to be solved urgently [35].

As AR is very stubborn, current treatment options aim to reduce complications, alleviate patients' symptoms, promote functional recovery, and improve quality of life, and cannot be completely eradicated [36]. A study by SN et al. showed [37] that during the symptomatic phase, the arginase activity was higher in the AR group than in the control group, but the difference in serum arginase levels between the study group and the control group was not statistically significant, which may be related to the study methodology. A study by WSC et al. showed [38] that the expression of ARG was significantly higher in allergic rhinitis nasal mucosa than in normal nasal mucosa. In normal nasal mucosa, ARG was expressed on the mucosal epithelial surface, submucosal glands, vascular endothelial cells and fibroblasts. In the allergic nasal mucosa, ARG-1 and ARG-2 were localized to inflammatory cells in addition to similar sites, and their expression levels were significantly higher than those in the normal nasal mucosa. These results suggest a role for ARG in allergic rhinitis and suggest that the L-arginine metabolic pathway may play a role in the pathogenesis of allergic rhinitis by regulating arginine as a substrate for NOS and ARG. The results of a study by Yasar H [39] et al. showed that treatment of patients with allergic rhinitis with the leukotriene antagonist montelukast resulted in reduced serum levels of ARG, compared to controls, suggesting that in allergic rhinitis, ARG may be affected by the release of mast cell mediators, resulting in reduced bioavailability of ARG-1 for NOS.

Although AR is not a life-threatening serious disease, it underlies many complications and is a major risk factor for poorly controlled asthma. At present, some progress has been made in the research of ARG and AR. The results show that the serum ARG level in AD patients treated with leukotriene antagonists is lower than that in patients without leukotriene antagonists, suggesting that ARG is affected by mast cell release mediators, confirming that ARG plays an important role in allergic rhinitis. However, the application of ARGs to AR patients faces many problems, and the research of ARGs as biomarkers or targeted therapy for AR is still in the early stage and needs to be further developed. It is believed that with the more thorough exploration of the biological properties and mechanism of ARG, the research on all aspects of ARG can make greater progress, and finally make a breakthrough in the clinical application of AR.

3.4. Arginase and food allergy

Food allergy (FA) refers to the phenomenon of adverse specific immune response when the body is repeatedly exposed to specific foods, which is the result of immune disorders and loss of normal oral tolerance. The allergen is often food protein [40-41]. The incidence of FA in children ranges from 0.02% to 8% and varies by age, region, and allergen. A survey in the United States shows that 0.8% of people are allergic to food, and the prevalence of food allergy in infants and young children is higher than that in adults. [42-44]. The symptoms of FA were mainly skin, gastrointestinal and respiratory symptoms. For infants and young children, the most common skin symptoms are acute urticaria, allergic dermatitis and angioedema. Gastrointestinal symptoms include diarrhea, vomiting and constipation. Severe patients may have hematochezia or shock. Respiratory symptoms include allergic rhinitis and asthma [45-46]. The common tests used to diagnose food allergy are skin prick test and serum-specific IgE test, but double-blind placebo-controlled food provocation test is still the gold standard for the diagnosis of food allergy. However, due to its high risk of acute allergic reactions, it is not widely available in most hospitals. There is still a lack of safe, rapid and efficient methods to diagnose food allergy in clinical practice.

There are fewer studies on the application of ARG in food allergy, and the regulatory mechanism of food allergic reactions is still unclear. Numerous studies have shown that the functions of cells such as dendritic cells, mast cells and basophils, which play a key role in antigen presentation and immune response in food allergic reactions, are regulated by arginine [47]. Arginine is involved in the maturation and activation of various allergic effector cells. Arginine regulates dendritic cell maturation through its metabolites and reduces the production of the inflammatory factors IL-12, IL-6, and tumor necrosis factor- α (TNF- α) [48]. Mondanelli G [49] et al. demonstrated that ARG-catalyzed degradation of arginine caused local amino acid deficiency, and that dendritic cell polyamine production is dependent on ARG-1 expression. It is well known that dendritic cell-generated polyamines regulate the immunosuppressive phenotypic differentiation of dendritic cells, and this study shows that the physiological functions of dendritic cells are strictly regulated by arginine. Arginine inhibits the expression of the mast cell chemokine monocyte chemokine ligand 2 (C-C Motif chemokine ligand 2, CCL2), and also inhibits the release of the newly synthesized intracellular mediator of leukotriene C4 (LTC4) from activated mast cells, as well as inhibits the gene expression of pro-inflammatory factors through the MAPK signaling pathway [50]. In reports of malaria-related studies, arginine deficiency in the organism was found to be associated with increased intestinal mast cell proliferation and elevated histamine levels, suggesting that arginine may also be involved in intestinal mast cell recruitment and cellular activation processes [51].

In conclusion, FA is a global problem. Although great progress has been made in the research of food

allergy in recent years, there are few studies on the application of ARGs in FA. ARG regulates DCS through its metabolites to reduce the production of polyamines, suppress the immunophenotypic differentiation of DCS, inhibit CCL2 expression, LTC4 release, and suppress the gene expression of inflammatory factors through the MAPK signaling pathway. With the deepening of the research on FA, while exploring the immune tolerance and immune sensitization mechanism of FA, many studies have also paid attention to the exploration of its prevention, diagnosis and treatment methods. These studies will help to formulate diagnosis and treatment plans according to different mechanisms of FA, in order to achieve the goal of cure, and provide a basis for individualized and precise treatment of food allergy.

4. Summary and prospects

ARG is involved in the reaction in the human body, which can decompose arginine into ornithine and urea, and reduce the toxic ammonia content in the body. At the same time, it mediates various cellular functions and processes such as proliferation, senescence, apoptosis, autophagy and inflammatory response of various types of cells. At present, the research on ARG and allergic diseases is endless, not only because ARG is widely distributed and easy to monitor, but also because ARG is involved in the occurrence and development of allergic diseases through regulating L-arginine metabolism, affecting immune response and other mechanisms to regulate immune factors and cell function, and has obvious correlation. This is unmatched by other clinically relevant biological measures. However, due to its involvement in a variety of reactions and low targeting, it is not well used in clinical practice.

Recent basic and clinical studies have shown that the role of ARGs in allergic diseases is real, but the specific mechanism is not clear. The reason may be that the two isoenzymes of ARG have different effects on inflammation and immunity in allergic diseases, and the specific role of Arg-1 and Arg-2 in the changes of allergic diseases is not clear, which restricts their clinical application.

Therefore, it is necessary to further explore the biological characteristics of ARG and clarify the specific mechanism of action of the two isoenzymes *in vivo*. Since there is no ideal serological marker for the diagnosis and prediction of allergic diseases, a single index value can provide limited reference. Therefore, attempts were made to combine two or more indicators (NO, ARG-1, ARG-2) for the diagnosis and prognosis evaluation of allergic diseases, and to verify the accuracy of the best combined indicators in the diagnosis of allergic diseases by setting up the control group, evaluating the confidence and selecting the best threshold through the receiver operating characteristic curve and ROC curve. To clarify the role of ARG-1 and ARG-2 in the screening and prediction of allergic diseases, in order to identify and screen candidates more accurately, and to provide an important basis for formulating a more scientific diagnosis, individualized

precise treatment and follow-up plan for patients with allergic diseases. At the same time, in order to further realize the precision of the role of ARG, it is necessary to master the threshold of arginase concentration to make it a specific indicator for monitoring the early stage of allergic diseases and evaluating the severity and therapeutic effect of allergic diseases, which will be the focus of future research.

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