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The Role of Oxidative Stress in the Pathogenesis of Asthma

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Oxidative stress plays a critical role in the pathogenesis of asthma. To effectively control oxidative stress in asthmatics, it is important to investigate the precise intracellular mechanism by which the development of immunity, rather than immune tolerance and progression of airway inflammation, is induced. In this article, we suggest that protein tyrosine phosphatases, as intracellular negative regulators, and intracellular antioxidant enzymes such as peroxiredoxins can be regulated by oxidative stress during intracellular signaling.

Key Words: Oxidative stress; asthma; protein tyrosine phosphatases; antioxidants; immune tolerance; airway inflammation; allergy

INTRODUCTION

Oxidative stress is believed to play a role in the development of human diseases such as cancer, cardiovascular disorders, and immunologic diseases. Asthma is a chronic inflammatory airway disease, and oxidative stress may be involved in its pathogenesis.[1,2] Despite an inconclusive debate about whether the enhanced oxidative stress observed in asthma subjects is caused by inflammation or is a causative factor in the pathogenesis of the disease, many recent reports have supported the critical role of oxidative stress in the development of various chronic immunologic diseases. Reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) transfer stimulating signals as a critical intracellular second messenger, resulting in the modulation of immune responses.[3]

In bronchial asthma, oxidative stress aggravates airway inflammation by inducing diverse proinflammatory mediators, enhancing bronchial hyperresponsiveness, stimulating bronchospasm, and increasing mucin secretion.[4-8] Although many studies have discussed the pivotal role of enhanced oxidative stress in the development and maintenance of airway inflammation, the therapeutic effects of many antioxidant agents on allergic airway inflammation are moderate at best.[4,5] These observations, however, do not necessarily imply a negligible role of oxidative stress in the pathogenesis of asthma. Rather, they reflect the need to investigate the proper antioxidants for each type of immunologic disease and the ideal situations for their use. Therefore, it is necessary to clarify the precise role of oxidative stress in the development of asthma.

ROLE OF OXIDATIVE STRESS IN INTRACELLULAR SIGNALING

Oxidative stress has traditionally been considered to be a toxic byproduct of aerobic metabolism and a factor involved in tissue damage. The results of many recent studies, however, have shown that compounds involved in oxidative stress, such as H_2O_2, act as key molecules in signal transduction.[3] In fact, many types of cellular stimuli, including antigens, infections, various chemical mediators, and growth factors, induce a transient increase in intracellular ROS—in particular H_2O_2—mainly through activation of NADPH oxidase immediately after the exposure of the stimuli to cells.[6] Furthermore, a broad field of antioxidant activity must be present within the cytosol to confine oxidative effects to the proximity of their origin and to maintain intracellular ROS levels within a narrow range.[3] The physiologic intracellular concentration of H_2O_2 is 0.002–0.2 μM at steady state, reaching up to 0.5–0.7 μM when intracellular signaling is generated. What is interesting is that this physiologic concentration range appears to be consistent throughout forms of life as diverse as plants and mammals, which is unlikely to be a coincidence.[3] Many functions of intracellular negative regulators, such as various types of phosphatases and the molecules in-

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volved in the ubiquitylation process, are inhibited after exposure to ROS.[7]

Taken together, these observations indicate that ROS are closely involved in the initiation and activation of intracellular signaling. In other words, intracellular ROS provide not only intracellular activating signals, which may have a detrimental effect on cells, but also essential surviving signals, which are critically involved in the appropriate functioning of the cells. Dynamic changes in intracellular levels of H_2O_2 from diverse microenvironments may lead to various intracellular signaling events. A recent concept involving cellular response to ROS involves a hierarchical oxidative stress response.[2,8] In brief, under lower levels of oxidative stress, appropriate antioxidant defense systems begin to operate through the activation of Nrf2, which is a critical transcription factor that induces more than 200 intracellular antioxidant molecules. If a higher level of oxidative stress occurs, inflammatory cellular responses caused by the activation of AP-1 and NF-kB can be expected. This results in the secretion of various types of proinflammatory cytokines and chemokines. The highest level of oxidative stress causes serious cytotoxic effects, including apoptosis and necrosis. Thus, the maintenance of intracellular ROS in a proper range should be considered an important factor in the management of various inflammatory diseases.

In summary, it is speculated that levels of ROS must be maintained within appropriate ranges and times as opposed to simply removing oxidative stress to manage certain pathologic conditions.

ROLE OF OXIDATIVE STRESS IN BRONCHIAL ASTHMA

Losing control of intracellular oxidants through inappropriate responses to environmental cellular stress may lead to degenerative diseases by inducing unscheduled death and cell cycle arrests, neoplasia (triggered by insensitivity to stress), and allergic or autoimmune disorders (caused by immune cell overstimulation and a break in immune tolerance).[9-11] In the airway, losing control of oxidants may bring about initiation of Th2-dominant immunity instead of inducing immune tolerance in the initial phase of development of airway allergic inflammation. Some researchers have reported that increased ROS in antigen-presenting cells can derive immunity instead of a Th2 response.[12-14] Furthermore, enhanced oxidative stress may contribute to the progression or perpetuation of existing airway inflammation through enhanced airway hyperresponsiveness, stimulation of mucin secretion, and induction of various proinflammatory chemical mediators,[15-19] all of which are believed to be related to severe asthma.[20-22]

A large amount of epidemiological and clinical evidence exists to support the relationship between increased ROS and the pathogenesis of bronchial asthma. Higher levels of the molecules involved in enhanced oxidative stress were found in biological samples taken from asthmatic patients compared with normal control subjects.[23-28] Higher incidences of bronchial asthma have been reported in areas with air pollution, which is a representative stimulus among exogenous oxidants.[20,29,30] Reduced intake of foods containing antioxidants is also related to the increased incidence of asthma.[4,5,31] Moreover, air pollution was suggested to cause more severe asthma and more frequent asthma attacks.[30] Increased oxidative stress in asthmatic patients is also related to suppressed pulmonary function.

Despite these findings, it is still unclear whether increased oxidative stress in the asthmatic airway is simply a consequence of chronic airway inflammation or a principal contributor to the development of allergic inflammation. Recently, an elegant study concluded that increased oxidative stress plays a critical role in mounting an immune response in a murine model of asthma using a ragweed pollen extract.[32] In the study, removal of ROS generated by intrinsic pollen NADPH oxidase prevented an immune response and airway inflammation, demonstrating that ROS provide an essential signal in the initiation and augmentation of antigen-induced allergic airway inflammation. We used the mouse model of asthma to analyze the kinetics of various aspects of allergic asthma.[33] The results showed that increased oxidative stress in the airway precedes the development of allergic inflammation, airway hyperresponsiveness, and other pivotal features of asthma such as enhanced mucus secretion. Therefore, it is strongly suggested that an increased level of ROS acts as a critical contributor to the induction of allergic airway inflammation. Controlling intracellular oxidative stress with appropriate timing, as opposed to simply focusing on the reduction of oxidative stress, is important for effectively managing bronchial asthma.

ENHANCED OXIDATIVE STRESS IN THE AIRWAY

Epidemiological studies have shown that the incidence of allergic asthma has surged in recent decades. Changes in the external environmental can reasonably explain this change. An increase in air pollution, an increased use of oxidant medication, and a decreased intake of antioxidants account for increased airway oxidative stress, which can cause immunity and airway inflammation.

Another explanation for the recent increase in the development of asthma may be associated with individual variations in the cellular machineries that handle intracellular antioxidants. A partial deficiency in the intracellular antioxidant defense system may critically affect oxidants when the level of increased oxidative stress goes beyond the capability of the system.[34-37] Increased oxidative stress in the environment may contribute to allergic airway inflammation by inducing a break in immune tolerance in genetically predisposed individuals whose antioxidant systems are unable to handle the oxidative stress burden imposed on immune cells. The association between oxidative

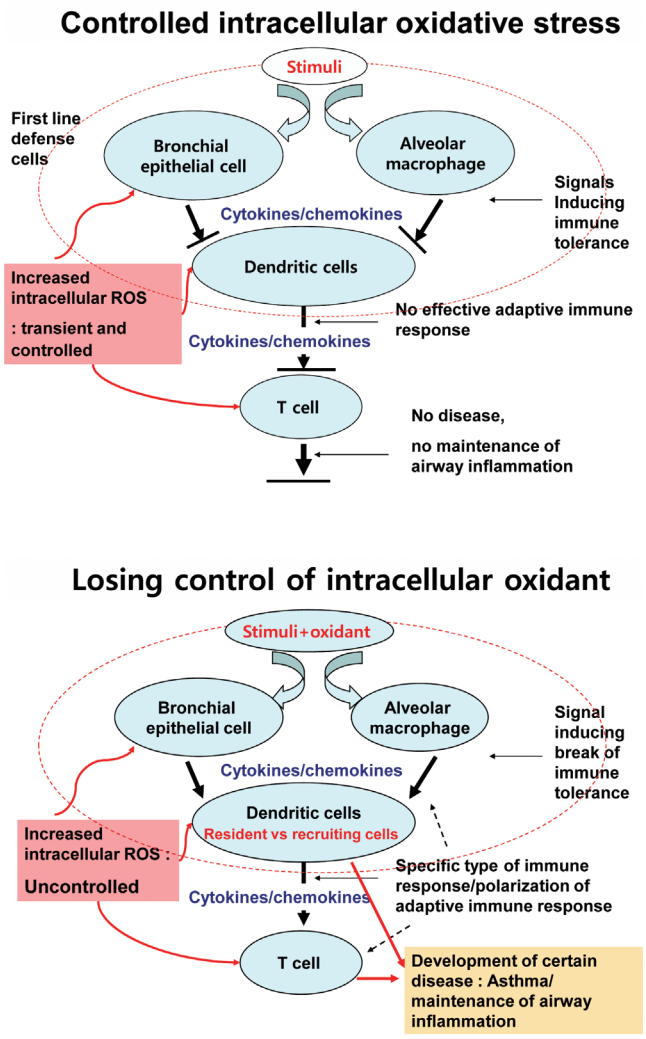

Fig. 1. Results of properly controlled oxidative stress and consequences of inadequately controlled intracellular oxidative stress in the pathogenesis of asthma.

stress and the development of airway inflammation is depicted in Fig. 1. It is assumed that a higher severity of asthma is also closely related to a lower ability to control oxidative stress in genetically predisposed patients.[34]

Therefore, intrinsic defects in certain intracellular molecules involved in the processes of intracellular oxidative stress signaling may be a plausible molecular mechanism explaining the crucial and direct role of oxidative stress in the pathogenesis of bronchial asthma, especially the chronic, severe asthma phenotype.

ROLE OF PROTEIN TYROSINE PHOSPHATASES IN THE PATHOGENESIS OF ASTHMA UNDER INCREASED OXIDATIVE STRESS

A variety of intracellular molecules are directly or indirectly involved in signal transduction in oxidative stress. These molecules, which include protein tyrosine phosphatases (PTPs), have cysteine residues, which are highly reactive to oxidative stress, at their active catalytic sites. In general, PTP enzymes behave as important negative regulators by inhibiting the function of protein tyrosine kinases. Oxidative stress leads to conformational changes in the PTPs, which then lose functionality. It is speculated that overactivation of protein tyrosine kinases would occur if the activities of PTPs were not properly controlled by inappropriately enhanced intracellular oxidative stress.[3,7]

SHP-1, a critical negative regulator in intracellular signaling, is expressed predominantly in hematopoietic and epithelial cells.[38] SHP-1 had an inhibitory role in the development of allergic airway inflammation in a mouse model of asthma using heterozygous SHP-1-deficient mutant mice (mev/+).[39] SHP-1-deficient homozygous mice (mev/mev) also developed spontaneous allergic lung inflammation without an identified allergen.[40] We have also demonstrated that oxidative stress contributes to the development of lung inflammation in SHP-1-deficient mice through a break in immune tolerance to aeroallergens.[39] In summary, because SHP-1 plays a role in regulating oxidative stress, increased intracellular oxidative stress with a lack of SHP-1 may lead to the development of allergic airway inflammation in the presence of Th2-prone cellular activation.

SHIP-1, another type of PTP, may also play a role in the development of Th2-dominant inflammation, as demonstrated in an experiment using genetically engineered mice.[41] The precise role of SHIP-1 in increased oxidative stress, however, has not been clearly determined.[42] It is assumed that other types of phosphatases may play roles in regulating intracellular oxidative stress and may also be involved in signaling processes. Therefore, further studies of other phosphatases are needed to clarify the precise role of PTPs in the pathogenesis of allergic airway inflammation in an environment of increased oxidative stress.

INTRACELLULAR ANTIOXIDANT ACTIVITIES IN THE DEVELOPMENT OF ASTHMA

Myriad intracellular molecules play roles as antioxidants in increased oxidative stress. The intracellular concentration of glutathione is critically important in keeping the intracellular oxidant level within the proper range.[43] Genetic polymorphisms of glutathione-S-transferase, which helps to maintain intracellular glutathione levels, are associated with the development of asthma.[44-46] Nrf2 is an essential transcription factor that is able to induce many antioxidant enzymes and molecules when oxidative stress occurs in cells.[8,47] Nrf2 knockout mice developed exaggerated allergic airway inflammation in a mouse model of asthma.[47] A defect in peroxiredoxin 2 was also recently reported to be involved in the pathogenesis of asthma in the murine model of asthma using peroxiredoxin knockout mice.[48]

All of these results strongly support the idea that defects in the intracellular antioxidant defense system may be critical contributors to the development of asthma under increased oxidative stress. There is an urgent need to investigate the exact role of intracellular antioxidant molecules and to discover a way to regulate the molecules to achieve effective management of asthma.

CONCLUSIONS

Oxidative stress is increased in the asthmatic airway, and this increased oxidative stress may play a role in the pathogenesis of asthma. We have summarized studies supporting the viewpoint that oxidative stress can be a critical contributor to asthma development and can initiate various intracellular signaling pathways that lead to a break in immune tolerance and exaggerated allergic inflammation. Recent increases in the incidence of asthma may be attributed not only to increased oxidative stress in the environment but also to intrinsic functional variability in intracellular antioxidant molecules such as protein phosphatases, Nrf2, glutathione and peroxidase system. Controlling oxidative stress at the appropriate times and with the proper methods is critical for effectively managing asthma.

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