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Review

Environmental pollution and allergies

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Abstract: Environmental changes are thought to be the main factor in the rapid increase and worsening of allergic diseases. While there have been significant changes in many environmental factors, including in environments such as residential, health and sanitation, food, and water/soil/atmospheric environments, the root of each of these changes is likely an increase in chemical substances. In fact, various environmental pollutants, such as air pollutants and chemical substances, have been shown to worsen various allergies in experimental studies. For example, diesel exhaust particles (DEPs), which are an agglomeration of particles and a wide array of chemical substances, aggravate asthma, primarily due to the principle organic chemical components of DEPs. In addition, environmental chemicals such as phthalate esters, which are commonly used as plasticizers in plastic products, also aggravate atopic dermatitis. It has also become evident that extremely small nanomaterials and Asian sand dust particles can enhance allergic inflammation. While the underlying mechanisms that cause such aggravation are becoming clearer at the cellular and molecular levels, methods to easily and quickly evaluate (screen) the ever-increasing amount of environmental pollutants for exacerbating effects on allergies are also under development. To eliminate and control allergic diseases, medical measures are necessary, but it is also essential to tackle this issue by ameliorating environmental changes. (DOI: 10.1293/tox.2017-0028; J Toxicol Pathol 2017; 30: 193–199)

Key words: environmental pollution, air pollution, allergy, disrupting effect

Introduction

Allergies develop based on disruptions in the immune system. In recent years, there has been a rapid increase in allergic conditions/disorders such as bronchial asthma, hay fever, atopic dermatitis, and food allergies, and the most significant cause of the increase and worsening of such cases is thought to be changes in environmental factors. While the changes in so many environmental factors are clearly significant, including in environments such as residential, health and sanitation, food, and water/soil/atmospheric envirnments, underlying each of these changes is possibly the spread of environmental pollution caused by an increase in chemical substances.

In this review article, we introduce what we have come to understand regarding the relation between environmental pollution and the immune system, in particular, in relation to the increase and worsening of allergic diseases caused by aberrant activation of the immune system. In the process, the underlying mechanism is also discussed.

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Environmental Factors and Allergic Diseases

The cause of the rapid increase in allergies and other common diseases in recent years is generally changes in environmental factors rather than genetic factors. The following is a list of environmental factors that are considered potential contributors to the rapid rise in allergic diseases.

Changes in the residential environment

Due to the introduction of airtight construction methods, residential (indoor) environments have become tightly sealed. Furthermore, the increased use of air conditioning stabilizes indoor temperature and humidity, which creates conditions more suitable for mite breeding. For this reason, some think that allergens related to mites have therefore increased and that bronchial asthma and other allergic diseases have increased. There is also a potential problem regarding allergens themselves in the cases of mold, which tends to proliferate under warm and humid conditions, and pets, which are increasingly kept indoors. Additionally, pollen-related allergens have also been found indoors. Thus, these factors point to an increase in various types of allergens within the residential environment.

On the other hand, in recent years, chemical substances

have been used in treated wood and other construction materials for pest control and preservative purposes, and there has also been a significant increase in chemical substances used in wallpaper, paint, adhesives, particle board, and other interior products and in general home appliances, various kinds of office equipment, and machinery as plasticizers and flame retardants. Also, printer toners, cosmetic products, and other household goods may use extremely small particles called nanoparticles (particulate matters [PM] with a diameter of less than 100 nm). As a result, there are concerns about the increased chance of exposure to environmental pollutants within the residential environment.

Changes in the food environment

In general, new ingredients in food may become new allergens. However, many of the rapidly increasing allergic diseases show reactions specific to the types of allergens that have been long-term problems, such as mites, cedar pollen, eggs, and wheat, and thus, it is difficult to imagine that contact with new allergens is the source of the rapid rise in allergic diseases. On the other hand, some think that the westernization of the human diet is a factor in the increase in allergic diseases. A good representative case is the increase in meat intake and the decline in fish intake.

Another change within the food system is the use of additives (chemical substances) in food and containers in which food is packaged. Our food supply includes preservatives to prevent spoiling or food poisoning, antioxidant agents to prevent oxidation, coloring agents to vivify the food, and other chemical substances. Nanoparticles are also used in some cases. In addition, in order to more efficiently grow plants and raise livestock as food ingredients, herbicides and pesticides are used in the cultivation of plants, and antibiotics and hormone drugs are used in animal bleeding. It has also become common to use disposable utensils and containers, and there are many chemical substances used as plasticizers in the making of these plastics and polyvinyl chloride products, and we are exposed to these chemicals as they leach out. In particular, plasticizers that are highly soluble in lipids seep out into the fats within our food, making it highly likely that we will be orally exposed to these substances. Additionally, the large fish at the top of the food chain in the natural world may contain a concentration of water or sediment contaminants such as organic tin compounds, mercury, or dioxin; as we consume such food, we may be ingesting these environmental pollutants.

Changes in the health and sanitation environment

Some researchers point to the reduction in parasitic diseases and bacterial infections as a cause of the increase in allergic diseases. Within the lymphocytes that comprise a part of the immune system are the T helper (Th) cells, which are categorized as Th1, Th2, and other cell components. Th1 cells attack and destroy foreign bodies such as bacteria and viruses to prevent infection. On the other hand, Th2 cells instruct the B cells to produce/release immunoglobulin E-type antibodies (IgE), and in the presence of allergens, they stimulate mast cells and release histamine and leukotriene, which provoke allergic symptoms. Thus, it has been suggested that since people are experiencing fewer infections, Th1 cells and their biological responses have weakened, and correspondingly Th2 cells and their biological responses have become stronger, which has caused allergic reactions/diseases to more easily develop and/or worsen. Another important change in the health and sanitation environment has to do with the use of chemical substances such as pesticides, insect repellents, antibiotics, and products with antimicrobial agents. Thus, we may be exposed to chemical substances designed to kill or repel pests and bacteria in our day-to-day lives.

Changes in water/soil/atmospheric environments

There is plenty of evidence to support the theory that changes in environmental factors in the narrow definition of its sense, such as in the water/soil/atmospheric environments (or in other words, environmental pollution), have led to the increase and aggravation of allergic diseases. For example, we have elucidated that diesel exhaust particles (DEPs), which are a major component of fine particulate matter ($PM_{2.5}$), exacerbated allergic asthma[1]. The diameter of a DEPs average less than 1 micron, and DEPs are found not only outdoors but also indoors, as they easily enter indoor environments. DEPs were the first material to indicate to us that an environmental pollutant does, in fact, exacerbate allergic diseases.

Exacerbation of Allergic Asthma Due to Environmental Pollution

Bronchial asthma is a chronic airway inflammation in which eosinophils plays an important role, and it is a condition that is characterized by an increase in viscous sputum and increased airway reactivity. Through our own studies, we have found that DEPs aggravate various allergic asthmatic conditions in the presence of allergens such as eosinophilic airway inflammation, increased mucus production, airway hyperreactivity, and allergen-specific antibody hyperproduction. Furthermore, in the presence of allergens, DEPs increase the local (lung) expression of cytokines, and, in particular, it is thought that bronchial asthma is exacerbated by the enhanced expression of interleukin (IL)-5, which is produced by Th2 lymphocytes, as it has the effect of activating eosinophils.

Most often DEP consist of an elemental carbon as the nuclei, and generally the periphery or the nucleus contain many substances, including large molecular weight hydrocarbons and their derivatives, polycyclic aromatic hydrocarbons, ketones, alcohols, saturated fatty acids, cycloalkanes, aromatic acids, quinones, nitrates, sulfates, and lots of metals. In other words, DEPs are agglomerations of particles and a vast number of chemical substances. As we continued to study the allergic disease-exacerbating compounds contained in DEPs, it became clear that the main components in DEPs that aggravate bronchial asthma were organic

chemical substances. Moreover, it became evident that the allergic inflammation caused by DEPs was far worse than that caused by residual particles, i.e., the residual particles after extraction of organic chemicals (washed DEPs), or organic chemicals on their own[2]. Regarding the mechanisms of bronchial asthma aggravation, IL-5, which activates eosinophils and enhances lung expression of eotaxin, which causes eosinophils to migrate, plays a strong role. Furthermore, enhanced expression of IL-13, which increases mucus-producing cells; enhanced expression of monocyte chemotactic protein-1 (MCP-1), which promotes the infiltration of leukocytes such as mononuclear cells and neutrophils; and enhanced expression and promotion of a protein called macrophage inflammatory proteins (MIP)-1α, are all thought to play a significant role.

In addition, quinones, which are environmental chemicals contained in DEPs, also showed a mildly aggravating effect in relation to allergic inflammation, but their effect was not as strong as compared with that of the organic chemical(s) contained in DEPs[3,4]. In addition to quinone, we have also established that exposure of the airway to benzpyrene promotes various pathologies of bronchial asthma and local expression of various cytokines associated with Th2 cells. Thus, it became evident that DEPs and the polycyclic aromatic hydrocarbons contained in them can exacerbate allergic diseases.

Exacerbation of Various Allergic Diseases Due to Environmental Pollution

Environmental pollution is not limited to air pollutants. Besides exposure to pollutants through inhalation, many environmental pollutants can enter the body orally or percutaneously. On the other hand, in terms of allergic diseases, besides bronchial asthma, which is inflammation of the airway, there are allergies such as food allergies and atopic dermatitis. Therefore, we focused on how environmental pollutants that are taken in by the whole body (oral exposure) would affect atopic dermatitis. For example, we selected di-(2-ethylhexyl)phthalate (DEHP), which is ubiquitously used as a plasticizer for plastics, and has been found in human umbilical cords. We used atopic-prone mice to develop a dermatitis model. We prompted completion of dermatitis by intradermal injection of mite allergens to the ears of these mice. Then we exposed the mice to DEHP at doses of 4.8, 24, 120, and 600 μg//kg/day, and we found that the severity of dermatitis and the lesions on the ears were worse with a low dosage of exposure to DEHP when the inflammation was primarily due to eosinophils and the degranulation of mast cells[5]. However, with a high degree of exposure, the exacerbating effect became less prominent. Since this type of dose-reaction relationship is a phenomenon often seen in the case of so-called "environmental hormones," this indicated that the aggravation of allergic responses to DEHP must be using a similar mechanism to that of the reaction to environmental hormones. Additionally, regarding the molecular biological mechanism of the aggravation of allergic diseases relating to phthalate ester, we determined that the expression of IL-5 and eotaxin on the skin is important. It is noteworthy that the amount of DEHP exposure that aggravated the atopic dermatitis was considerably less than the amount that causes pathological changes in the liver in a classical manner. We also discovered that exposure of mothers to DEHP exacerbates the atopic dermatitis of their male offspring, which were exposed to environmental chemicals during their neonatal period[6]. Additionally, plasticizers such as diisononyl phthalates also aggravate atopic dermatitis[7], yet it has became clear that there are many chemical substances that do not contribute to the aggravation of allergic responses. Also, diisononyl phthalate enhances the local expression of receptors for proteins involved in the infiltration of antigen-presenting cells, which are cells that first recognize allergens. These findings also suggested that the mechanisms by which allergic diseases are exacerbated are different depending on the chemical substance.

Toxic Effects of the Disrupting Effect

In recent years, at least in developed countries, the possibility of highly toxic materials or large amounts of pollutants being discharged into the environment has been reduced. However, many materials with low-toxicity are more present in all facets of our living environments, albeit in relatively small quantities. The products we use in our daily lives contain numerous chemical substances such as plasticizers, flame retardants, resins, paints, adhesives, surfactants, antibacterial agents, insect repellents, pesticides, preservatives, antioxidants, colorants, perfumes, and so on. In fact, a variety of chemical substances are detected in blood, including that from human umbilical cords; breast milk; fingernails; and hair. To date, few studies have been done on the health effects of small doses at "real world" levels or combined exposure to multiple environmental pollutants.

So, how do we understand the mechanism in which environmental pollutants with low toxicity aggravate allergic diseases? This is where a new concept we call "disruption of life and biological systems" enters the picture (Fig. 1). Currently, in order to evaluate or determine the influence of environmental pollutants, the "toxicity" against an organism, a system, organs, or cells is considered to be the main indicator of influence. That is to say, what has been investigated to date is whether or not a certain material will kill or injure an individual or a cell. However, can the influence on our health be measured only from the perspective of death or injury? Of course, the answer is "no." For example, allergic diseases are caused by inappropriate activation of the immune system, which is supposed to protect the body. Environmental hormones, which were previously a hot topic, are known endocrine disrupting substances. Many of these substances are more likely to inappropriately activate the endocrine system and cells rather than actually kill or injure them. It is also known that many environmental pollutants that mimic female hormones in fact act on the female hormone receptors to trigger female hormonal actions. In this

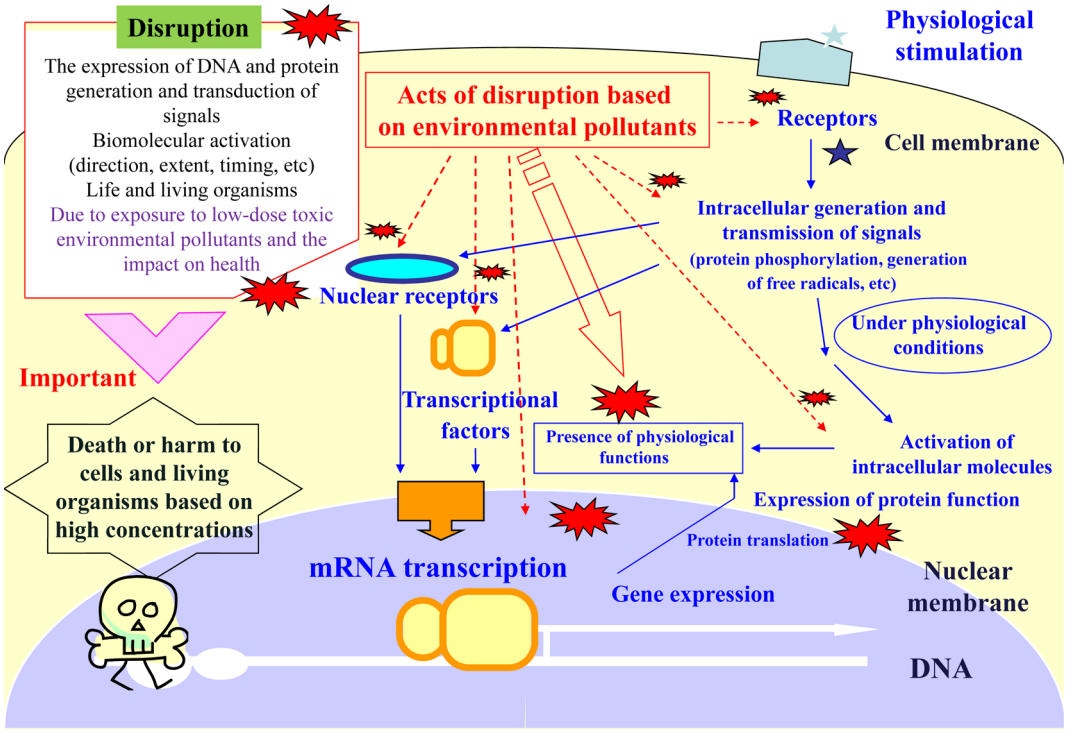

Fig. 1. The disruption of life and living organisms due to environmental pollutants.

way, it has become clear that there are environmental pollutants that will inappropriately activate various molecules, including biological receptors and transcription factors. Of course, biological molecules are not limited to the endocrine system. There are various molecules related to the nervous system as well as the immune system. Is it not possible then to consider that many of these biomolecules such as receptors and transcription factors are inappropriately activated or deactivated to provoke "disruption of life and biological systems"? That is to say, can evidence of influence other than toxicity not be found when we look at such disruptions? We think that the disruptions to the immune system due to environmental pollutants are causing the high morbidity of allergic diseases. Additionally, there are many researchers besides us who are wondering if such disruptions in the nervous system could be causing the abnormal behavior in children in recent years.

If we were to focus on the quality of life for all individuals, the future of humanity, and its sustainable development, we think a perspective that considers the expression, exacerbation, and increase in disrupting effects of exposure to small amounts of multiple substances with low toxicity would, over time, become increasingly important.

Elucidation of the Mechanisms in Which Environmental Pollution Aggravates Allergic Diseases and the Development of a Screening Method

As there are now vast amounts of environmental pollutants, which are increasing daily, it is important to evaluate materials for their aggravating impact on allergic diseases in a simple and quick manner, along with elucidation of their toxic mechanisms. The previously mentioned *in vivo* evaluation on atopic dermatitis does have a great advantage in that it indexes the exacerbation of actual conditions (atopic dermatitis), but it takes three to four weeks to complete, and as it uses animals for the tests, the number of chemical substances we could target is limited. Therefore, we have examined whether it is possible to develop a far simpler and quicker screening method. In doing so, we turned to dendritic cells—cells that are deeply involved with immunoreactions, allergic reactions, and diseases—and individual splenocytes, or even composite culture systems, to see if we could develop an *in vivo* screening method to accurately reflect the act of allergic disease aggravation. Specifically, we collected and examined dendritic cells derived from bone marrow, spleen cells, and T-cells derived from the spleen in NC/Nga mice, a representative model for allergic diseases. We examined the expression of cell surface molecules including MHC class II, CD80, CD86, CD11c, DEC-205, and others that are associated with antigen-presenting cells, expression of cell surface molecules such as T-cell receptors (TCR) and others, and the production and proliferation of various types of cytokines and chemokines by comparing these cells in the presence or absence of chemical environmental pollutants. As a result, we found that increased expression of CD86 in dendritic cells, expression of TCR in spleen cells, and production of IL-4 and enhancement of cell production due to antigen stimulation reflected the effects seen in the aggravation of allergic diseases, *in vivo*, and thus

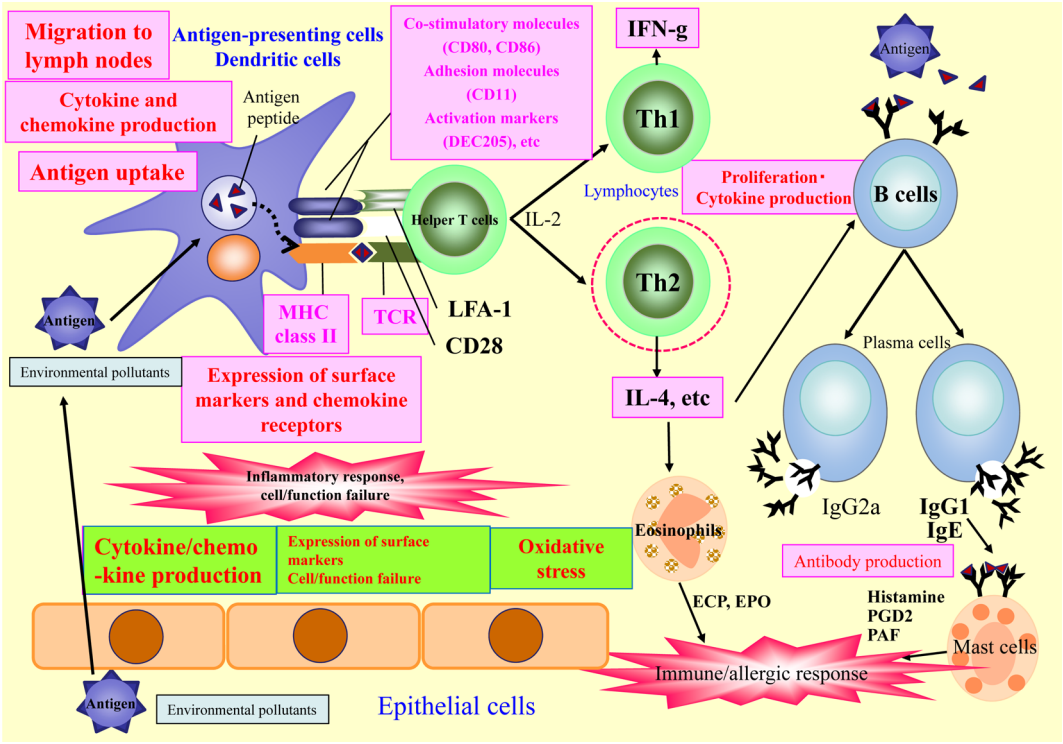

Fig. 2. *In vitro* evaluation and analysis items and their physiological significance.

demonstrated that this is very useful as an *in vitro* screening system and as an index[7,8]. Also, it is gradually becoming known that not only is the impact on the immune cells important but also that cells that are sources of biological responses, such as epithelial cells, are as important in the exacerbation and aggravation of allergic diseases, and thus we are in the process of creating a screening system that uses these cells (Fig. 2). Ultimately, we aim to construct an allergic diseases aggravation impact assessment system targeting the immunoresponse and allergic reaction systems that would be used after *in vitro* screening of certain compounds suspected of aggravating allergic diseases and then applied to disease models to evaluate whether such substances do indeed aggravate allergic diseases *in vivo* as well.

Aggravation of Allergic Diseases by Nanoparticles—Are These "Dream Materials" the Beginning of a Nightmare?

There is growing concern over increased exposure to extremely small particles that are used in our everyday environment, such as those used in cosmetics, sunscreens, toners, and inks. For example, as we studied and considered the impacts of airway exposure to nanoparticles that are comprised of elemental carbon particles with diameters of less than 100 nm, we found that extremely small nanoparticles had a tendency to aggravate inflammation. However, the impact and influence of nanoparticles alone were not as noticeable[9]. In addition, an atopic dermatitis model induced with a mite allergen, for which we assumed that a failure occurred in skin barrier function, was significantly deteriorated by composite exposure to titanium oxide nanoparticles[10,11]. In this case, too, the impact of nanoparticles alone was not particularly noticeable.

We believe sufficient care should be taken with new substances that are lauded as "dream substances" for their properties and functionalities so that they do not become nightmares for human health. We should not forget past lessons, such as those learned from asbestos, polychlorinated biphenyls, and chlorofluorocarbons.

Aggravation of Allergic Diseases by Asian Sand Dust Particles

Although Asian sand dust particles in transported from the Asian continent as micrometer-sized particles do indeed induce injury to the respiratory system, we have previously reported that when the particles coexist with an allergen, allergies such as bronchial asthma and allergic rhinitis become far worse. It has also been elucidated that organisms that are inactivated by heat and chemical components are considered an important factor in this hazardous effect[12]. Based on these facts, and even when only considering the rise and aggravation of allergic diseases, perhaps we have entered an age in which we can no longer protect our health with only a narrow or local view; instead, we must consider the protection of the environment on a global scale.

Worsening of Lifestyle-based Diseases Due to Environmental Pollution—Obesogen Theory

In epidemiological studies regarding $PM_{2.5}$, it has been pointed out that certain types of environmental pollutants negatively impact "lifestyle-based diseases" relating to the cardiovascular system. More recently, there have been epidemiological reports that positively link the concentration of $PM_{2.5}$ and deaths in association with diabetes.

Recently, we have begun to suspect that environmental pollution not only causes an increase and worsening of "life environment diseases" such as allergies but also may be linked to the increase and exacerbation of "lifestyle-based diseases." It has already been shown that exposure to DEPs through the airway worsens the fatty liver of type II diabetic models[13] and that oral intake of brominated flame retardant material, which is a persistent organic pollutant (POP), exacerbates obesity caused by a high-fat diet, adipose tissue inflammation, insulin resistance, and fatty liver[14].

Certain types of environmental pollutants (benzopyrenes, etc.) are known carcinogens. However, is it not possible to consider that certain "environmental pollutants act as 'obesogens' that act as initiators, inducers, promoters, or enhancers of obesity, diabetes, and other lifestyle-based diseases"? In particular, we think it is necessary to pay sufficient attention to environmental pollutants that persist in the environment and in organisms for a long time and that have high lipid solubility. Perhaps in a few decades, people will be saying that the main causes of lifestyle-based diseases include only actually lifestyle but also environmental pollution.

Conclusion

There is sufficient probability that environmental pollutants (air pollutants, chemical substances, nanoparticles, Asian sand dust particles, etc.) that are ubiquitous are able to cause a rise in and exacerbate the common living environment-based diseases such as allergies and other lifestyle-based diseases. In particular, we should pay attention to the environmental pollutants that are considered to have low toxicity on their own and see how small but combined exposure can impact those that are highly sensitive to such diseases (that is to say, we should study how highly sensitive groups are impacted by exposure to a combination of low-toxicity substances at low levels). Such a risk is ever present.

Finally, this fiscal year, the Ministry of Education, Culture, Sports, Science, and Technology of Japan selected our research project titled "A comprehensive, systematic environmental and medical study aimed at controlling and eradicating allergies" for a Grant-in-Aid for Scientific Research (S). Through this research, we aim to be the first to clarify the mechanism of allergic diseases and the essence and root cause of how they are aggravated by environmental pollutants at the source of biological and immunological responses; at the same time we will determine the target molecules for therapy under realistic and ordinary combined exposure (to environmental pollutants and allergens), in order to find useful ways to control and take medical countermeasures against allergic diseases. On the other hand, by evaluating the impact of environmental pollution that is ubiquitous, we would like to determine the cause and factors that have contributed to the increase and exacerbation of allergies in our environment and thus hope to contribute to environmental science in order to help control and take countermeasures against such factors.

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