Review Article
Dust events, pulmonary diseases and immune system

Nafiseh Esmaeil[1,2], Marjan Gharagozloo[1,3], Abbas Rezaei[1], Gabriele Grunig[2,4]

[1]Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; [2]Department of Environmental Medicine, New York University School of Medicine, Tuxedo, New York, USA; [3]School of Pharmacy, University of Waterloo, Ontario, Canada; [4]Division of Pulmonary Medicine, Department of Medicine, New York University School of Medicine, New York, USA

Abstract: Incidences of sand storms have increased in recent years and there is evidence that these dusts can move across long distances. Sand dusts have different adverse effects on health, but one of the most important of them is pulmonary disease. After inhalation of dust, many dust particles are moved to the airways. Dust particles can be sensed by airways epithelial cells, activate macrophages, dendritic cells and innate immune cells and then initiate responses in various populations of specific immune cells such as T helper cells subsets (Th1, Th2, Th17), T cytotoxic cells and B cells. Initiation of inflammatory immune responses, activation of immune cells and releases of many cytokines, chemokines and other inflammatory molecules, have variable pathologic affects on lung in different respiratory diseases. Unfortunately control of desert dusts is more difficult than control of air pollution. For prevention and treatment of respiratory diseases that are caused by desert dusts, researchers need well-designed epidemiological studies, combined with analysis of the precise composition of sand dusts, and the precise mechanisms of the immune responses. Recognizing the exact cellular and molecular immune mechanisms would be very useful to find new approaches for treatment of desert dust associated pulmonary diseases.

Keywords: Sand dusts, T helper cells, cytokines and chemokines, pulmonary disease

Introduction

Dust storms have an important influence on air quality management because they can have effects on a local, regional and even global scale in the short- and long-term [1-3]. Transport of dust across the Atlantic and Pacific oceans has significantly increased in past years and geological evidence shows that the dust clouds originate predominantly from Africa and Asia [4-6].

The increase in African dust transport to the Americas has adversely affected the health of Caribbean coral reefs and in south Florida almost half of airborne particles in the summer season have originated from Africa [7-9]. Transportation of dusts from North Africa to Southern and Central Europe has also been described [10, 11].

Studies have shown that occurrence of dust storm in the Middle East (called the Middle Eastern Dust (MED) storms), is characterized by high concentrations of particles with 2 to 20 μm diameter size, with more than 85% of particles measuring less than 10 μm in diameter [12, 13]. According to the study of Leon and Legrand, the major sources of MED storms are Arabian Peninsula, Kuwait, Iraq and parts of Iran [109]. In arid areas of Iraq and Kuwait there are high content of fine particles that are associated or suspected to be associated with respiratory disease, such as desert lung syndrome and severe acute pneumonitis [14-18].

The mineralogical and chemical compositions of dust particles depend on geographic locations. For example the sand in Middle East is mostly composed of silicate minerals, carbonates, oxides, sulfates, and salts in different proportions. In addition recent studies have shown organic nitrogen in rainwater is related to dust originating from Sahara desert dust [19-21]. These small and insoluble particles contain various soluble contaminants in their matrix and on their surface and may also be carriers of anthropogenic pollutants [22-24]. In addition, many microorganisms associated with these
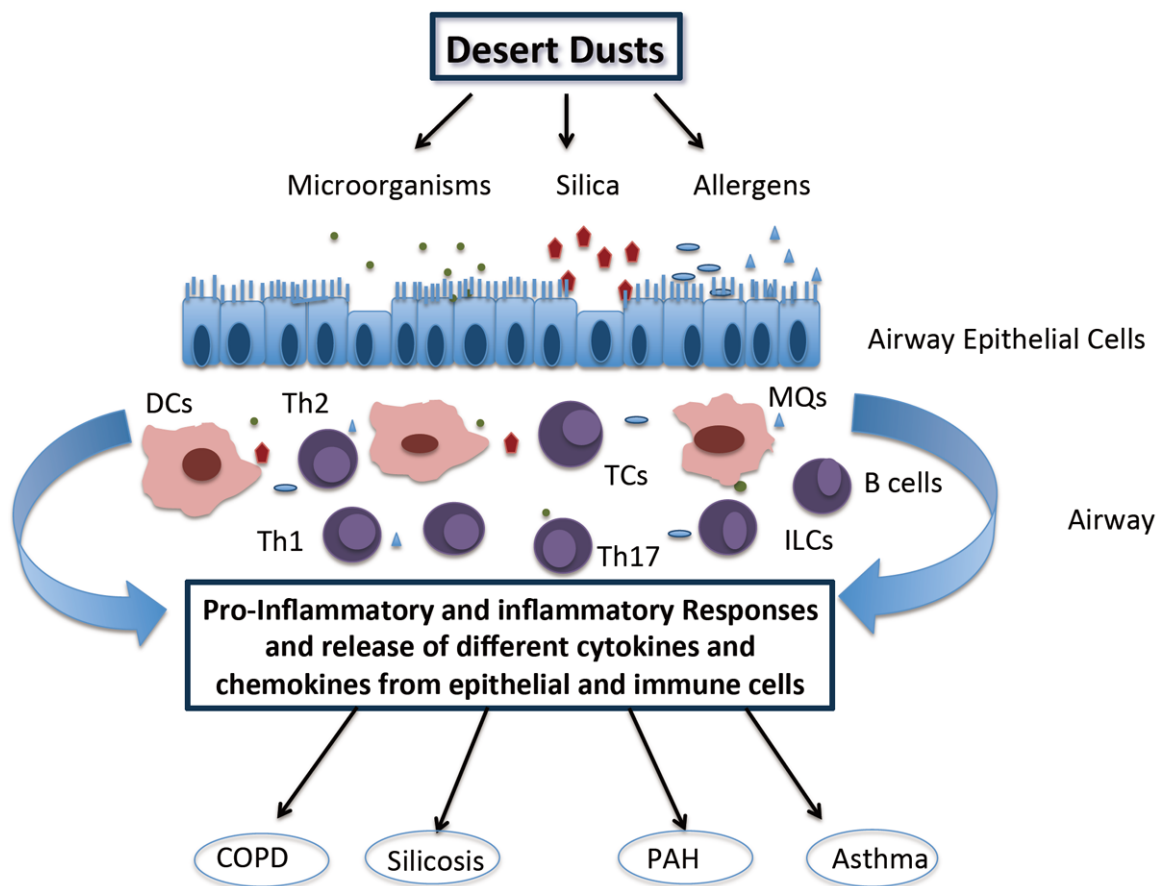
Figure 1. Immune responses to different particles in desert dust. Various components of dust that penetrate into the airways have effects on the epithelium. In addition to the physical barrier role of airway epithelial cells, these cells also play important roles for the immune response. Interacting with airway epithelial cells, macrophages, dendritic cells and innate lymphoid cells are activated and contribute to the inflammatory immune response. Furthermore, cross-talk between epithelial cells and dendritic cells (DCs) can mature the antigen presenting capabilities. DCs can present antigen to different subsets of T helper cells. As result of the cellular interactions, other immune cells such as B cells and T cytotoxic cells can also be activated in response to dust particles in the airways. Finally activation of immune responses and release of various cytokines and chemokines contributes to different pulmonary diseases including asthma, chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH) and silicosis. Abbreviations: Dcs = Dendritic cells, MQs = Macrophages, ILCs = Innate lymphoid cells, TCs = T cytotoxic cells, Th1 = T helper cell type 1, Th2 = T helper cell type 2, Th17 = T helper cell type 17.

dusts can withstand environmental stresses such as high temperatures, ultraviolet (UV) radiation, and atmospheric transport [25].

Various components of dust can access the respiratory system by inhalation and directly affect the epithelium of the human airways [26]. These responses can be exacerbated by biological agents and other trace elements (such as mercury, cadmium, arsenic) that are part of the dust cloud [27]. The exposure to these dust particles and associated contaminants can cause pulmonary diseases that have significant impact on health and quality of life. In many dust induced respiratory diseases, the immune system is playing a dual role. Although activation of the immune system is necessary for removal of dust particles, microorganisms and antigens from the airways; an inappropriate or unchecked immune response can result in severe lung disease and pathologic outcomes (**Figure 1**). Recently many studies have focused on the suppression of the immune responses for the treatment of asthma and other pulmonary diseases. Likewise, precise tracking of critical immune cells and mediators, such as cytokines, would constitute an important step forward for the management of dust-storm associated pulmonary diseases.

Asthma, chronic obstructive pulmonary disease (COPD) and desert dusts

The highest prevalence of asthma has been reported in areas with desert dust storm events, such as Middle East [28, 29]. Indeed in many parts of the world, sand storms have been linked to asthma exacerbation [30-32]. In the 1980s, Packe and colleagues observed an epidemic of asthma after a thunderstorm [33]. In Athens, Greece, Saharan dust events have been associated with pediatric asthma emergency admittances and in Italy, respiratory mortality has increased among elderly during Saharan dust days [34, 35].

In Trinidad, Saharan dusts were linked to pediatric asthma exacerbations and in other parts of world such as East China, the Korean peninsula, Japan and Kuwait, studies have shown a clear association between Asian dust events and respiratory disease particularly asthma [1, 36-39].

The incidence of allergic asthma has increased steadily globally. Some of the asthma causing allergens, for example fungal spores, dust mites, plant and grass pollens, anthropogenic emissions, and organic detritus are also found in desert dusts [40-43].

Among these allergens, house dust mites have been a predominant cause of the increase in allergic asthma. Ichinose et al. have shown that Dermatophagoides Farinae transported in Asian sand dust, enhances the incidences of allergic asthma [42, 44].

Chronic Obstructive Pulmonary Disease (COPD) can be induced by long-term inhalation of harmful dust particles. In COPD, patients have different respiratory symptoms and systemic outcomes. In general, there is a non-infectious inflammation of the airways and lung parenchyma in COPD [45-48]. The content of chemical elements in rainwater is a useful indicator of airborne dust components and Tubek et al. have found a strong correlation between the concentration of several chemical elements in rainwater and COPD [49].

Mechanism of desert dust mediated exacerbations of inflammatory lung diseases

Airway epithelial cells act as physical barrier in the lung, and also play important roles in the immune response against dust (**Figure 1**). These cells express different receptors such as Toll-like receptors (TLRs), C-type lectin receptors (CTRs) and protease-activated receptors (PARs) that can be triggered by environmental allergens or microbial components [50]. Following receptor mediated signaling, epithelial cells produce pro-inflammatory cytokines such as IL-6 and IL-8 in response to environmental particles. In addition, these cells release inflammatory mediators such as IL-25, IL-33 and TSLP [51]. This mechanism stimulates lymphocytes, dendritic cells, and granulocytes, including recruitment of neutrophils, resulting in acute inflammation [52-54]. In addition, elaboration of these cytokines initiates and exacerbates Th2 type immune response in asthmatic patients [50, 55].

Th2 immune cells are most important cells in progress for allergic asthma and eosinophilic inflammation. After activation of Th2 cells the Th2 cytokine pathway will be triggered; IL-4 and IL-13 are two major cytokines of Th2 cells, assisting in the production of IgE. Among the other cytokines produced by Th2 cells, IL-5 has important roles in the terminal maturation of eosinophils. On the other hand, Interleukin 13 is being involved in mucus production, airway remodeling and fibrosis [56].

In addition to Th2 cells, Th17 cells have important roles in pathogenesis of asthma and allergic airway disease. Th17 cells are a T cell effector subset that produce high levels of IL-17 and IL-22 cytokines [57]. The family of IL-17 cytokines consist of six members (IL-17A, B, C, D, E, F). IL-17E is also known as IL-25 and is an initiator of Th2 responses. Il-17A and IL-17F have important roles in the recruitment, activation, and migration of neutrophils to inflamed sites. These two cytokines also induce production of down-stream cytokines, chemokines and metalloproteinases, all of which are important contributors to inflammation of the Th17 type [58, 59].

Innate lymphoid cells 2 (ILC2), another group of innate lymphocyte-like cells, are also involved in inflammation and remodeling in asthma. ILC2 cells resemble Th2 cells, produce IL-4, IL-5, and IL-13 after activation. ILC2 are activated via innate receptors. This represents a different activation pathway when compared to stimulation of Th2 cells. Th2 cells are classical T cells that are activated via the T cell receptor

recognizing cognate antigen preferentially presented by dendritic cells. ILC2 cells contribute to airway hyperreactivity and could be important in the initiation of the acute allergic responses [60, 61].

The pattern of immune response in COPD is different from asthma. In COPD the innate immune response is perhaps more important than the acquired immune response for the development of persistent and progressive inflammation and remodeling of the lungs. Several studies have shown that T cytotoxic cell mediated immune responses have a critical role in COPD [62-64]. Moreover, Th1 and Th17 cells are also frequently found in COPD [65-70].

Silicosis

Silica (SiO_2), which is mainly derived from feldspar and quartz, is the major mineralogical component of Asian sand dusts. Long-term exposure to crystalline silica causes silicosis. Silicosis is a chronic occupational pulmonary disease, which is characterized by inflammation and fibrosis of the lung [71, 72]. After inhalation, silica particles are quickly engulfed by alveolar macrophages and in response these cells release inflammatory mediators [73, 74]. Excessive exposure to silica also has been associated with tuberculosis, chronic bronchitis, COPD, and lung cancer [75]. McCormic et al. have found that silica can be a risk factor for developing Systemic Sclerosis (SSc) in men and in SSc, pulmonary fibrosis and pulmonary arterial hypertension (PAH) are causes of SSc-related deaths [76].

The immune response polarization in silicosis is not fully understood. In experimental silicosis both Th1 and Th2 cells are associated with the development of silicosis in experimental animals (**Figure 1**) [77-82]. Moreover, Holian et al. has shown that innate immune responses have a marked and predominant role in the pathogenesis of silicosis in mice [83].

Microorganisms in desert dust and respiratory disease

Different species of pathogenic and non-pathogenic bacteria are constituents of desert dust. However, currently the virulence characteristics of these microorganisms are not well understood and need to be further investigated [84]. However it is clear that the presence of potentially pathogenic microorganisms in respirable particles (≤ 2.5 μm) could contribute to various health effects, especially in the respiratory system. Gwang Pyo. et al. have suggested that different microorganisms are transported in East Asia during Yellow Sand events which is known to be linked to increased incidence of infection which leads to significant adverse health effects [85, 86].

It is believed that dust storms can serve as carriers for the pathogens, promoting infections upon inhalation. For example Neisseria meningitides residing in the mucosa can gain access to underlying tissue and blood following exposure to particles from dust storms [87]. Other pathogens have also been detected in dust storm particles. According to a current outline of the current state of affairs in the Middle East, many of the opportunistic dust-borne pathogens can play an important role in human health [25, 88-93].

Microbial products including lipopolysaccharide (LPS) that is a glycolipid of gram-negative bacteria cell wall, and β-glucan that is the major constituent of fungi wall are also found in sand dust particles. These microbial components can cause neutrophilic pulmonary inflammation [94, 95]. Pathogen-associated molecules of bacteria, viruses, and other pathogens, such as LPS and β-glucan are recognized by pattern recognition receptors (PRRs), for example Toll Like Receptors (TLRs), on epithelial cells, macrophage and dendritic cells in the lungs (**Figure 1**). Signaling via the PRRs results in the release of different pro-inflammatory cytokines and chemokines, and combined with the induced maturation of the antigen-presenting capacity of dendritic cells can precipitate activation of innate lymphoid cells, T helper cells (Th1, Th2, Th17), T cytotoxic cells and B cells. Hence, in a microbial infection related to variety of antigens, different immune cells would be activated. In the case of dust-storm associated microbial exposures the immune activation could be the cause of pathogenic outcomes in the lungs [96, 97].

Pulmonary arterial hypertension and Deseret events

Pulmonary arterial hypertension (PAH) describes a group of pulmonary diseases that are distinguished by remodeling of the small pulmonary arteries and increases in the pressure of the pulmonary circulation and the right ventricle. Furthermore, PAH is a prevalent co-morbidity of COPD, and silicosis [98-100]. Tubek et

al. have shown a positive correlation between some chemical elements in rainwater (as an indicator of airborne dust) such as Zinc and Cadmium and arterial hypertension [49].

Different pathogenic mechanisms contribute PAH and recent studies have shown a role for inflammation (**Figure 1**) [101-106]. Although the exact mechanism of immune response in PAH has not yet determined, specific type 1 and type 2 immune response, and also pathologic roles of Th17 cells have demonstrated [104, 107, 108].

Conclusion

In conclusion, future research should focus on the pulmonary effects of chronic exposure with desert dust in different parts of the world by well-designed epidemiological studies. This could be made possible by collaborative research programs. In these studies the chemical and biological characterization of ambient particulate matter in urban areas before and after of dust events will be crucial. These data are expected to provide critical information for improving public health.

Although the knowledge of adverse health effects of desert dusts exposure would be useful to prevent deleterious outcomes, for example by establishing an alarm system that would warn the public to avoid outdoor exposures during dust events, the development of therapeutic options for the management of dust storm related respiratory disease is also very important. Today immunotherapy and immunosuppressive therapy methods are used as a treatment approach for many diseases such as allergic asthma. Induction of allergen-specific tolerance by allergen-injection-therapy is a common therapeutic modality, and anti-cytokine therapy is in advanced development with many of preclinical, phase I and II trials planned or currently ongoing for asthma and other respiratory disease. More knowledge about the exact immune mechanisms that elaborated cytokines and other mediators, could lead to an effective treatment for respiratory diseases that are caused by desert dust exposure.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Nafiseh Esmaeil, Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98-311-7922428; Fax: +98-311-7922431; E-mail: nafesm5@gmail.com; Gabriele Grunig, Department of Environmental Medicine, Division of Pulmonary Medicine, Department of Medicine, New York University School of Medicine, Tuxedo, New York, USA. E-mail: Gabriele.Grunig@nyumc.org

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