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Review

Research advances in pathogenic mechanisms underlying air pollution-induced ocular surface diseases

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ABSTRACT

Background: The harmful effect of aerial fine particulate matter ($PM_{2.5}$) has been a serious public health issue and has attracted worldwide attention, especially in developing countries.
Main Text: Numerous previous clinical and experimental studies have demonstrated that $PM_{2.5}$ has a clear pathogenic effect on diseases related to the respiratory and cardiovascular systems. Recent researches have pointed out that $PM_{2.5}$ plays a pivotal role in the occurrence and progression of ocular surface diseases. The current studies have shown that $PM_{2.5}$ may promote the appearance of conjunctivitis, keratitis, blepharitis, dry eye, meibomian gland dysfunction (MGD) and other ocular surface diseases through regulating a series of mechanisms such as inflammation, immune reaction, oxidative stress, autophagy, cell migration, and epigenetics.
Conclusions: This review aims to summarize the current research progress on the pathogenic mechanism of $PM_{2.5}$-related ocular surface diseases.

A WHO's air-quality guidelines in 2006 pointed out that aerial fine particulate matter ($PM_{2.5}$) plays a vital role in health issues caused by air pollution (especially in respiratory and cardiovascular diseases).[1,2] $PM_{2.5}$ is fine particulate matter with an aerodynamic diameter of less than 2.5 μm, which can adsorb toxic polycyclic aromatic hydrocarbons (PAHs), heavy metals, organic carbon and so on in the air and has a biological effect that damages a series of systems of our body. For instance, $PM_{2.5}$ is involved in the occurrence and development of various respiratory, cardiovascular, and ocular surface diseases through mechanical destruction, immune reaction, inflammation, oxidative stress reaction, and epigenetic changes.[3–10] Previous worldwide studies have confirmed that short-term or long-term exposure to air pollution is closely related to the increased mortality and morbidity in population (the United States,[11] Europe,[12] China[13]) .

The ocular surface is the structure that protects our eyeball. Normally, the ocular surface includes the eyelashes, eyelids, cornea, conjunctiva, lacrimal glands and accessory lacrimal glands, meibomian glands, the Moll and Zeis glands, nasolacrimal ducts and etc.[14,15] Because the ocular surface directly contacts with the outside world, external stimuli, especially $PM_{2.5}$ in the air pollution, can easily damage the protective barrier of the tear film, causing discomfort such as redness, itching, edema, foreign body sensation, and irritation. The impact of air pollution on ocular surface diseases is often overlooked by ophthalmologists during consultations, and relative research is still rare.[16] Though the direct contact of the ocular surface structure with the outside environment improves its susceptibility to external stimuli, it also facilitates ocular surface diseases monitoring. For instance, intuitive ocular surface examinations such as tear secretion test (Schirmer test), tear film break up time (BUT), corneal staining experiment, slit lamp inspection, vision assessment and etc, can be used as indicators to reflect the impact of $PM_{2.5}$ on ocular surface health.[14,17,18] In recent years, various studies have explored the pathogenic effect and mechanism of $PM_{2.5}$ on single ocular surface disease. This review aims to summarize the current research progress of $PM_{2.5}$ on the pathogenic mechanisms of different ocular surface diseases.

1. The pathogenic effect of $PM_{2.5}$ on different ocular surface diseases

1.1. Dry eye and meibomian gland dysfunction (MGD) induced by $PM_{2.5}$

Dry eye is a disease that decreases the stability of the tear film and damages the ocular surface function by multiple factors, which causes ocular discomfort, foreign body sensation, visual dysfunction and other symptoms, accompanied by increased tear osmotic pressure and ocular surface inflammation. Dry eye symptom questionnaire, tear river width, Schirmer test, BUT, fluorescein staining, lissamine green staining, tear

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osmotic pressure test are frequently used in clinic for screening and diagnosing dry eye.[19,20] MGD is a chronic, non-specific inflammation of the meibomian glands with blocked ducts of the meibomian glands and abnormal secretion of the meibomian glands, which causes hyper-evaporative dry eye.[21,22] In an *in vitro* study performed on mice, the researchers found that compared to the control group, the tear secretion and BUT of the mice eye treated with PM drops were significantly reduced, together with corneal epithelial damage, conjunctival epithelial cell apoptosis and conjunctival goblet cell reduction. Meanwhile, increased inflammatory factors such as IL-18, IL-22, Il-23 and MCP-1 were detected in the conjunctiva and cornea of mice in PM-treated group. Moreover, apoptosis and reactive oxygen species (ROS) production were increased in PM-exposed HCEC.[23] Another cross-sectional study conducted in Argentina assessed the ocular surface alterations after subjects exposed in different PM levels. The result indicated that under different PM exposure levels, the ocular surface parameters of subjects such as eye redness, eyelid swelling, fluorescein staining, and lissamine green staining, BUT were statistically altered. Subjects under higher PM levels showed lower scores of BUT, and higher grade of meibomian gland dysfunction.[24] In addition, tear hyperosmolarity also plays an vital role in the pathogenesis of dry eye, and high tear film osmolarity (>=316 mOsm/L) indicates the occurrence of dry eye. A panel study conducted in Brazil, recruited 71 traffic controllers and taxi drivers indicated that $PM_{2.5}$ levels in the air pollution and tear film osmolarity were significantly negatively correlated. For every 10 mg/m^3 increase of $PM_{2.5}$ in the air, the tear film osmolarity will decrease by 10.9 mOsm/kg. The study above suggested the adaptation mechanism of human ocular surface to $PM_{2.5}$ after long-term exposure.[25,26] Moreover, several researches revealed that ROS-NLRP3-IL-1β signaling pathway axis was upregulated in environment-induced ocular surface diseases such as dry eye and corneal toxicity.[10,27]

1.2. Conjunctiva induced by $PM_{2.5}$

Conjunctivitis is an inflammatory disease caused by infectious and non-infectious factors, which causes itchy eyes, conjunctival swelling, increased secretions and etc. Severe conjunctivitis can even make patients suffer from vision loss or blindness. As the most common eye disease in emergency department, conjunctivitis is a severe burden on public health and social economy. Previous Meta-analysis has found that air pollution is one of the pivotal causes that initiate conjunctivitis , among which NO_2, CO, O_3, SO_2, $PM_{2.5}$, and PM_{10} in the air are relevant to the morbidity of conjunctivitis in the population. Among them, women and adolescents are more sensitive to $PM_{2.5}$, NO_2 and O_3. Identifying the pathogenic factors existing in the environment and taking targeted measures to prevent them beforehand is of great significance to improve the public eye health.[28–31] A time series analysis conducted in Japan further pointed out that $PM_{2.5}$ levels are significantly related to the morbidity of allergic conjunctivitis. During the pollen-free season (May to July), the frequency of outpatient visits for patients with allergic conjunctivitis is positively correlated with $PM_{2.5}$ levels.[32] Above all , controlling air pollution, monitoring the concentration of $PM_{2.5}$ timely, and reducing the frequency of outing activities when the $PM_{2.5}$ concentration exceeds a critical level provide new ideas for the prevention and treatment of immune ophthalmopathy.

1.3. Blepharitis induced by air pollution

Blepharitis is a chronic inflammatory disease of eyelid margins , which mainly causes irritation, burning sensation, photophobia, red eyes and blurred vision. It may be related to a variety of systemic diseases, especially rosacea and seborrheic dermatitis, as well as other ocular surface diseases such as dry eye, conjunctivitis and keratitis.[33] A previous study have shown that long-term air pollution exposure significantly increases the morbidity of blepharitis in urban residents.[34] The palpebral margin is an essential structure to maintain the integrity of tear film, as well as the function of the ocular surface. Meanwhile, palpebral margin dysfunction is also an important factor in the development of dry eye disease. The importance of eyelid margins in maintaining ocular surface health and in the development of dry eye disease has been underestimated for so long.[35] Moreover, blepharitis takes a long time to cure and is prone to relapse. In clinical practice, eyelid hygiene is crucial to prevent blepharitis.

1.4. Keratitis induced by $PM_{2.5}$

So far, no research has shown that $PM_{2.5}$ has a direct pathogenic effect on the occurrence of keratitis. However, an animal experiment with mice as subjects showed that between two groups ($PM_{2.5}$-xeposed group and control group) of mice with keratitis induced by Pseudomonas aeruginosa, corneal perforation appeared earlier in the $PM_{2.5}$-exposed group than in the unexposed group. (confirmed by histology).[3]

2. Pathogenic mechanisms underlying $PM_{2.5}$-related ocular surface diseases

2.1. Inflammation and immune mechanism altered by $PM_{2.5}$

Inflammation plays a significant role in $PM_{2.5}$-induced ocular surface diseases.

An *in vitro* study on corneal epithelial cells of mouse demonstrated that after $PM_{2.5}$ treatment, the mRNA expression of HMGB1 ($P < 0.05$), TLR2 ($P < 0.05$), IL-($P < 0.05$) were significantly increased.[3] Compared to control group, the protein production of IL-18, IL-22, IL-23, and MCP-1 in PM-treated group were also significantly increased in the conjunctiva ($P<0.05$) and cornea ($P>0.05$) tissues. The altered expression of inflammatory factors in the cornea and conjunctival tissues reflected that a specific regulatory mechanism induced by $PM_{2.5}$ may exists underlying the immune response of the ocular surface.[23] A recent study based on mouse model further demonstrated that $PM_{2.5}$ can induce inflammation and pyroptosis in mouse cornea,[10] and another study based on mouse model revealed that in the $PM_{2.5}$-treated group, CD11b (+) cells and mast cells increased significantly on the central cornea and in the conjunctiva of mouse. Compared with the control group, the expressions of IL-1β, IL-6, TNF and MUC5AC were statistically increased in the $PM_{2.5}$ exposure group, as well as the maturity of dendritic cells (DC) in draining lymph nodes (DLN). In addition, increased serum IgE levels and Th2 cytokine production were detected in DLN. In summary, $PM_{2.5}$ exposure causes ocular surface injury and inflammation, which leads to DC maturation and allergic immune response dominated by Th2 cells in the DLN.[36] The recent progress in dry eye study reveals that the pathological process of dry eye is a "vicious inflammatory circle". Comprehensive assessment of inflammation-based dry eye will help break the inflammatory process in the clinical condition and provide better options for treatment.[37] Epidemiological evidence revealed that $PM_{2.5}$ is one of the causes of allergic conjunctivitis, and the mouse model further confirms that $PM_{2.5}$ induces an increased goblet cell density in the upper eyelid conjunctiva and extensive eosinophil infiltration in the conjunctiva and meibomian glands.[32] Above all, inflammation and immune response play considerable roles in the incidence of $PM_{2.5}$-induced ocular surface diseases.[38]

2.2. Oxidative stress and autophagy triggered by $PM_{2.5}$

Although the mechanism underlying health hazards induced by $PM_{2.5}$ has not been fully elucidated, the oxidative stress response was experimentally confirmed to be one of the important mechanisms. Reactive oxygen species (ROS) is by-products of normal cell metabolism and plays an important role in signal transduction and maintenance of internal balance. Under specific environment or pathophysiological conditions, ROS will increase dramatically, resulting in an imbalance between the ROS production and the intracellular defense mechanism, which is called oxidative stress.[39] After exposure to $PM_{2.5}$ for 12h and 24h, increased cell

apoptosis and ROS production of human corneal epithelial cells (HCECs) were observed in a time and dose-dependent manner.[23] Meanwhile, a repeated-measure study performed in healthy students in Beijing pointed out that $PM_{2.5}$ was strongly related to the increase of antioxidant enzymes and the activation of systemic antioxidant activity.[40] Moreover, another study observed significant level changes in two antioxidant enzymes, glutathione peroxidase and total antioxidant status, in response to short-term changes in air pollution levels.[41]

Autophagy is regarded as a "self-phagocytic" process, which can be triggered by starvation, hypoxia, infection, aging and chemotherapy to protect the body and regenerate material and energy. The components of the autophagy process are highly and constitutively expressed in all parts of the eye, which makes autophagy closely related to ocular diseases such as corneal diseases, cataract, retinopathy and orbital diseases.[42,43] As observed in diabetic retinopathy (DR) and age-related macular degeneration (AMD), a high extent of autophagy can withstand external pressure, but excessive autophagy can lead to deterioration of eye tissues.[44] The expression levels of autophagy-associated markers ATG5, LC3B, and BECN1 proved that autophagy in HCECs was slightly suppressed in the early period of $PM_{2.5}$ exposure (before 4 h), but was notably activated in the late period (after 24 h). As an autophagy activator, rapamycin can reduce cell damage in HCECs induced by $PM_{2.5}$ in the early period and aggravate it in the late period, suggesting that autophagy effect on HCECs may change with the $PM_{2.5}$ exposure time. The results above elucidated the potential of autophagy in the therapy of ocular corneal diseases induced by $PM_{2.5}$ and directly demonstrated that $PM_{2.5}$ may influence the cytotoxicity of HCECs through autophagy process.[45,46]

2.3. Cell migration suppressed by $PM_{2.5}$ exposure

A previous study confirmed that cell migration plays a crucial role in corneal epithelium repair and corneal homeostasis maintenance. Both animal experiments and cell experiments elucidated that $PM_{2.5}$ exposure obviously suppressed the migration of corneal epithelial cells. The FAK/paxillin phosphorylation and FAK-paxillin interaction were vital for the formation of focal adhesion complex, which was crucial for the cell migration process. As confirmed by immunofluorescence and Immunoprecipitation, the phosphorylation activity and interaction activity of HCECs were both suppressed after $PM_{2.5}$ treatment. Meanwhile, the RhoA activity and stress fiber formation were significantly inhibited. It was demonstrated that $PM_{2.5}$ exposure significantly damaged the FAK/Rho signal pathway and inhibited the actin reorganization to suppress the migration process of corneal epithelial cell. In addition, *in vitro* experiment conducted in mice further pointed out that $PM_{2.5}$ treatment may delay the wound healing of corneal epithelium through inhibiting cell migration. The results above suggested that it may be significant to pay attention to corneal infection and corneal epithelium defect in patients who were exposed to $PM_{2.5}$. Further researches can be conducted to protect the corneal epithelium from the harm caused by $PM_{2.5}$ exposure.[47]

2.4. Epigenetic alterations induced by air pollution

$PM_{2.5}$ can cause DNA damage and cellular senescence in HCECs, probably through stimulating the ROS formation.[39] Several studies pointed out that air pollution, especially NO_2 and $PM_{2.5}$ exposure, are positively correlated with proliferation of human conjunctival goblet cells (GC), and therefore increase the mRNA level of MUC5AC on the ocular surface as adaptation to environmental pollution.[48,49] Moreover, a study focused on respiratory system elucidated that lncRNAs took part in the toxicology of $PM_{2.5}$ via stimulating the epithelial-mesenchymal transition (EMT) process and inflammation process.[50] In addition, another research on lung carcinogenesis revealed that $PM_{2.5}$ led to ROS formation, which stimulated the expression of loc146880. This lncRNA in turn up-regulated the level of autophagy and promoted the further deterioration of lung cancer cells.[51] There is so far no study to investigate the role of lncRNAs in $PM_{2.5}$-induced ocular surface-related diseases, and studies above suggests that it is a good research direction.

3. Conclusion and discussion

$PM_{2.5}$ is intimately associated with ocular surface diseases. Long-term exposure to $PM_{2.5}$ will increase morbidity of ocular surface diseases in individuals, thereby affecting the quality of life in the population. $PM_{2.5}$ exposure concentration and exposure time will influence the occurrence and development of ocular surface diseases. The current studies have shown that $PM_{2.5}$ may promote the appearance of conjunctivitis, keratitis, blepharitis, dry eye, MGD and other ocular surface diseases through regulating a series of mechanisms such as inflammation, immune reaction, oxidative stress, autophagy, cell migration, and epigenetics. However, further clinical studies and experimental researches using cellular and animals models are still needed to be conducted to fully clarify the underlying mechanisms in $PM_{2.5}$-induced ocular surface diseases. As air pollution becomes increasingly serious, improving standardized procedures to monitor the $PM_{2.5}$ level in the air is of great significance to ocular surface diseases. Moreover, in cities with severe $PM_{2.5}$ pollution, taking screening and protection measures for susceptible populations are cost-effective ways for the prevention and treatment of $PM_{2.5}$-induced ocular surface diseases, which is also a significant focus of clinical researches.

Study Approval

Not applicable.

Author Contributions

QLF and KY conceived and designed the study; FS, SJH searched references of the study; FS and YZG selected the references; SJH and YZG wrote the original paper; QLF and KY re-wrote the final paper and submitted the pape. All authors have read and approved the manuscript.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Editorship Disclosure

Given their role as Editor-in-Chief, Ke Yao had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Simin Ding.

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