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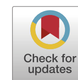
Review

The association of $PM_{2.5}$ with airway innate antimicrobial activities of salivary agglutinin and surfactant protein D



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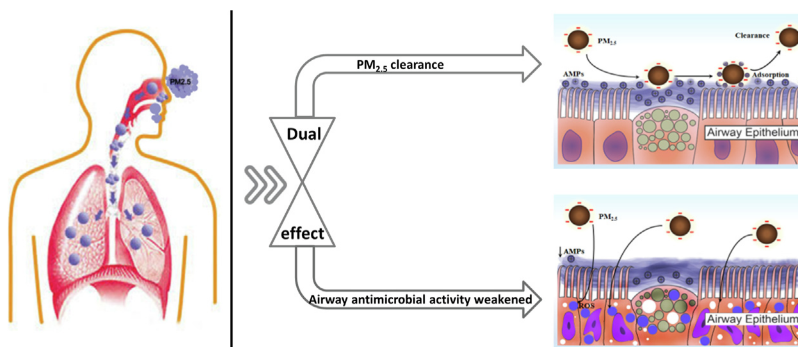
HIGHLIGHTS

- The first review about $PM_{2.5}$ and innate airway antimicrobial activity of soluble factors in human.
- There exists a dual effect between $PM_{2.5}$ and respiratory antimicrobial ability.
- $PM_{2.5}$ suppresses respiratory antimicrobial activity by downregulating airway AMPs.
- Airway AMPs accelerate $PM_{2.5}$ clearance by inducing $PM_{2.5}$ microbial aggregation.

GRAPHICAL ABSTRACT



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ABSTRACT

Fine particulate matter $\leq 2.5\ \mu m$ ($PM_{2.5}$) is a prominent global public health risk factor that can cause respiratory infection by downregulating the amounts of antimicrobial proteins and peptides (AMPs). Both salivary agglutinin (SAG) and surfactant protein D (SPD) are important AMPs in respiratory mucosal fluid, providing protection against airway pathogen invasion and infection by inducing microbial aggregation and enhancing pathogen clearance. However, the relationship between $PM_{2.5}$ and these AMPs is unclear. To better understand the relationship between $PM_{2.5}$ and airway innate immune defenses, we review the respiratory antimicrobial activities of SAG and SPD, as well as the adverse effects of $PM_{2.5}$ on airway innate antimicrobial defense. We speculate there exists a dual effect between $PM_{2.5}$ and respiratory antimicrobial activity, which means that $PM_{2.5}$ suppresses respiratory antimicrobial activity through downregulating airway AMPs, while airway AMPs accelerate $PM_{2.5}$ clearance by inducing $PM_{2.5}$ microbial aggregation. We propose further research on the relationship between $PM_{2.5}$ and these AMPs.
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Abbreviations: $PM_{2.5}$, fine particulate matter $\leq 2.5\ \mu m$; AMP, antimicrobial protein and peptide; SAG, salivary agglutinin; SPD, surfactant protein D; SRCR, scavenger receptor cysteine-rich superfamily; CRD, carbohydrate recognition domain.

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1. Introduction

Atmospheric particulate matter (PM) is a severe worldwide health problem, especially $PM_{2.5}$ (aerodynamic diameter ≤ 2.5 μm). This is a critical health risk factor, ranking fifth in mortality and contributing to approximately 4 million deaths in 2015 (Kelly and Fussell, 2015; Cohen et al., 2017; Lukowski et al., 2018; Shupler et al., 2018; Wang et al., 2018; Yin et al., 2018). $PM_{2.5}$ contains groups of chemicals (including minerals, inorganic ions and organic compounds) and microorganisms (such as bacteria, fungi and viruses) (Fang et al., 2016; Gonzalez-Delgado et al., 2017; Li et al. 2017, 2018a, b, c; Lu et al., 2018; Shao et al., 2018; Zeng et al., 2018). It causes serious adverse health effects, such as respiratory, endocrine and circulatory diseases (Hamra et al., 2014; Stafoggia et al., 2014; Mazidi and Speakman, 2017; Mbelambela et al., 2017; Stockfelt et al., 2017; Cong et al., 2018; Nie et al., 2018; Riant et al., 2018; Tavera Busso et al., 2018). Specifically, $PM_{2.5}$ is mainly responsible for lower respiratory infection (Cohen et al., 2017; Nie et al., 2018), which is the key cause of death in children under 5 years of age (Naghavi et al., 2015).

$PM_{2.5}$ directly attacks the respiratory tract, which is coated with mucosal fluid that provides protection against opportunistic pathogen colonization (Huttenhower et al., 2012; Morris et al., 2013; Bassis et al., 2015; Huffnagle et al., 2017; Li et al., 2017; Peters et al., 2017; Wang et al., 2017). Respiratory mucosal fluid, which is important for innate immune defense, contains numerous glycoproteins, such as β-defensins, lactoferrin, secretory IgA, sialic acid, SAG and SPD (Fabian et al., 2012; Boks et al., 2016; Esther et al., 2017; Okazaki et al., 2017; Vargas Buonfiglio et al., 2018). Both SAG (a scavenger receptor cysteine-rich superfamily molecule, SRCR) and SPD (a C-type collectin) are important for airway innate immunity because of their antimicrobial activities (Stoddard et al., 2009; Chu et al., 2013; Hillaire et al., 2013; Boks et al., 2016; Du et al., 2016; Gunput et al., 2016; Hu et al., 2016; Reichhardt and Meri, 2016; Li et al., 2017; Reichhardt et al., 2017; Sorensen, 2018; Wong et al., 2018).

To further understand the interaction between $PM_{2.5}$ and innate airway immune defense, this review emphasizes the respiratory antimicrobial activities of these two AMPs (SAG and SPD) and the harmful effects of $PM_{2.5}$.

2. Microorganisms in $PM_{2.5}$

$PM_{2.5}$ is related to human activities, such as urbanization and industrial development, and it is rich in minerals, heavy metals, organic compounds and microorganisms (Lemos et al., 2012; Alghamdi et al., 2014; Cao et al., 2014; Rivas-Santiago et al., 2015; Zhang et al., 2015; Bekki et al., 2016; Gao et al., 2016; Gonzalez-Delgado et al., 2017; Li et al. 2017, 2018a, b, c; Samek et al., 2017; Wang et al., 2017; Groulx et al., 2018; Lu et al., 2018; Lukowski et al., 2018; Shao et al., 2018; Morakinyo et al., 2019; Xu et al., 2019a) (Table 1). Although the hazards of $PM_{2.5}$ involve a combination of toxic effects, microorganisms are thought to be the main cause for the spread of respiratory disease (Cao et al., 2014; Wang et al., 2017).

Metagenomic analysis demonstrated that, during a severe smog event in Beijing, China, $PM_{2.5}$ contained more than 1300 species of microbes of which the most abundant was bacteria (Cao et al., 2014). This is consistent with Alghamdi et al. (2014) who found bacteria in higher concentration than fungi in $PM_{2.5}$ in Jeddah, KSA. Even though the majority of microbial populations in $PM_{2.5}$ remain stable, there are also seasonal and regional differences due to temperature, humidity, vegetation and wind speed (Bowers et al., 2011a; Bowers et al., 2011b; Bertolini et al., 2013; DeLeon-Rodriguez et al., 2013; Robertson et al., 2013; Alghamdi et al., 2014; Cao et al., 2014; Rivas-Santiago et al., 2015; Gonzalez-Delgado et al., 2017; Du et al., 2018a; Du et al., 2018b; Li et al., 2018a, b, c). Cao et al. (2014) pointed out that, in Beijing, the most abundant $PM_{2.5}$ bacteria was *G. obscurus*, whereas Bacillus and Zygomycetes were the common $PM_{2.5}$ microorganisms in Iztapalapa (Rivas-Santiago et al., 2015). On the other hand, *Alternaria*, *Penicillium* and *Fusarium* were the common fungi laden $PM_{2.5}$ in the United States whereas *Alternaria* and *Aspergillus* were the predominant $PM_{2.5}$ fungi in Mexico (Gonzalez-Delgado et al., 2017). Previous studies have implied that there is a positive correlation between microbial load and $PM_{2.5}$ concentration (Alghamdi et al., 2014; Cao et al., 2014; Gao et al., 2016). Even though most $PM_{2.5}$ microbes are soil-related and nonpathogenic to human (Bertolini et al., 2013; DeLeon-Rodriguez et al., 2013; Robertson et al., 2013; Cao et al., 2014), several pathogens have been identified, such as *S. pneumoniae*, *A. fumigatus*, and human adenovirus C, all of which can cause airway infection (Nierman et al., 2005; Shike et al., 2005; Alghamdi et al., 2014; Cao et al., 2014; Naghavi et al., 2015; Rivas-Santiago et al., 2015; Gonzalez-Delgado et al., 2017; Gotts et al., 2018).

3. $PM_{2.5}$ inhibits airway antimicrobial defenses by AMPs

$PM_{2.5}$ may directly influence the respiratory microbiome composition in a manner that could reflect potential tumor risk such as lung cancer (Peters et al., 2017; Pun et al., 2017; Andersen et al., 2018; Xu et al., 2019b). Additionally, $PM_{2.5}$ could increase the prospective risk of respiratory pathogen invasion and infection by suppressing airway antimicrobial effects (Nuorti et al., 2000;

Table 1
Microorganisms laden $PM_{2.5}$.

Sampling site/time	Group (relative abundance)	Reference
Jeddah, Saudi Arabia/Dec. 2012–Apr. 2013	Bacteria (170 ± 139.8 CFU/m^3) Fungi (9.21 ± 2.01 CFU/m^3) *Aspergillus, Alternaria, Penicillium, Rhizopus,* Sterile hyphae, *Emericella nidulans, Eurotium, Fusarium, Mucor, Trichothecium,* Yeast Actinobacteria (2.76 ± 1.13 CFU/m^3)	Alghamdi et al., 2014
Beijing, China/Jan. 8-14, 2013	Bacteria (86.1%) Phyla level: The most abundant were: Actinobacteria, Proteobacteria, Chloroflexi, Firmicutes, Bacteroidetes, and Euryarchaeota Species level: 1315 distinct bacterial and archaeal species were identified, and the 48 most abundant bacterial were: *Geodermatophilus obscurus*, *Modestobacterma rinus*, *Blastococcus saxobsidens*, *Micrococcus luteus*, *Kocuria rhizophila*, *Candidatus Nitrospira defluvii*, *Methylobacterium radiotolerans*, *Propionibacterium acnes*, *Thermobifida fusca*, *Nocardioides sp.*, *Nocardiopsis dassonvillei*, *Brachybacterium faecium*, *Arthrobacter phenanthrenivorans*, *Cellvibrio gilvus*, *Carnobacterium sp.*, *Microbacterium testaceum*, *Paracoccus denitrificans*, *Kytococcus sedentarius*, *Pantoea vagans*, *Pseudomonas stutzeri*, *Kineococcus radiotolerans*, *Sanguibacter keddieii*, *Thauera sp.*, *Pantoea ananatis*, *Cellulomonas fimi*, *Lactobacillus johnsonii*, *Deinococcus gobiensis*, *Lactobacillus crispatus*, *Lactobacillus salivarius*, *Lactobacillus reuteri*, *Clostridium perfringens*, *Bacillus megaterium*, *Psychrobacter cryohalolentis*, *Arthrobacter arilaitensis*, *Ramlibacter tataouinensis*, *Nakamurella multipartite*, *Streptococcus infantarius*, *Stenotrophomonas maltophilia*, *Arthrobacter chlorophenolicus*, *Mycobacterium gilvum*, *Methylobacterium extorquens*, *Methylobacterium chloromethanicum*, *Corynebacterium efficiens*, *Saccharomonospora viridis*, *Nocardiopsis alba*, *Psychrobacter arcticus*, *Leuconostoc mesenteroides*, *Streptomyces coelicolor* Eukaryotic (13.0%) The 2 most abundant fungal species were: *Aspergillus fumigatus* Af293, *Saccharomyces cerevisiae* S288c Archaeal (0.8%) Viral (0.1%) The 3 most abundant viral species were: Human adenovirus C, Pseudomonas phage F116, Enterobacteria phage P1	Cao et al., 2014
Beijing, Tianjin, Langfang, Beidaihe, Tangshan, and Baoding, China/May 21-Jun. 1, 2014	Ammonia oxidizing archaea, AOA (average cell numbers: 2.82×10^4 cell·m^{-3}) The most dominant was: *Nitrosopumilus subcluster* 5.2 Ammonia oxidizing bacteria, AOB (average cell numbers: 4.65×10^3 cell·m^{-3}) The most dominant were: *Nitrosospira Multiformis*, *Nitrosomonas aestuarii*	Gao et al., 2016
Beijing, and Baoding, China/Jan. 10-17, 2015	A total of 9 genera and 17 species of cultivable airborne bacteria were isolated and identified. The most abundant phylum was Firmicutes, and the dominant species was spore-forming Bacillus. Gram-positive bacteria (more than 90%): Firmicutes, *Bacillus atrophaeus*, *Bacillus cereus*, *Bacillus endophyticus*, *Bacillus kochii*, *Bacillus licheniformis*, *Bacillus megaterium*, *Bacillus niabensis*, *Bacillus subtilis*, *Lysinibacillus manganicus*, *Paenibacillus xylanilyticus*, Actinobacteria, *Arthrobacter oxydans*, *Brevibacterium frigoritolerans*, *Microbacterium sediminis*, *Streptomyces kurssanovii*, *Streptomyces silaceus* Gram-negative bacteria: *Paenibacillus provencensis*, α-Proteobacteria, *Sphingomonas dokdonensis*	Hu et al., 2017
Pretoria West, South Africa/Jan. 2-Feb. 29, 2016 and Jun. 1-Jul.31, 2016	Bacteria (168–378 CFU/m^3) *Staphylococcus* sp., *Bacillus* sp., *Micrococcus* sp., *Flavobacterium* sp., *Klebsiella* sp. and *Pseudomonas* sp. Fungi (58–155 CFU/m^3) *Cladosporium* spp., *Aspergillus* spp., *Penicillium* spp., *Fusarium* spp., *Alternaria* spp.	Morakinyo et al., 2019
Beijing, the Yangtze River Delta, and the Pearl River Delta, China/Spring 2016 to Spring 2017	Bacteria Phylum level: Actinobacteria, Bacteroidetes, Cyannobacteria, Deinococcus-Thermus, Firmicutes, Proteobacteria, others	Xie et al., 2019
Yucheng, China/Jun. 10-Jul. 10, 2014	Bacteria (1.20×10^5 cell·m^{-3}) Phylum level: Proteobacteria, Actinobacteria, Firmicutes, Cyanobacteria, Bacteroidetes Gram-negative bacteria (70.9%): Acinetobacter, Cyanobacterium, Janthinobacterium, Massilia, Pseudomonas, Stenotrophomonas, Sphingomonas Gram-positive bacteria (8.4%): Arthrobacter, Bacillus, Corynebacterium, Clostridium, Frigoribacterium, Rhodococcus Fungi (4.16×10^4 cell·m^{-3}) Phylum level: Ascomycota, Basidiomycota, no rank Eukaryota Genus level: Alternaria, Aspergillus, Cladosporium, Penicillium	Wei et al., 2019a
Mount Tai, China/Jul. 1-15, 2015	Bacteria Phylum level: Proteobacteria, Actinobacteria, Cyanobacteria, Firmicutes, Acidobacteria, Bacteroidetes, Chloroflexi	Wei et al., 2019b;

(*continued on next page*)

Table 1 (*continued*)

Sampling site/time	Group (relative abundance)	Reference
	Genus level: Pseudomonas, Acinetobacter, Stenotrophomonas, Janthinobacterium, Sphingomonas,, Delftia, Bacillus Fungi Phylum level: Ascomycota, Basidiomycota Genus level: Alternaria, Davidiella, Cryptococcus, Epicoccum, Aspergillus, Cladosporium	
Mount Tai, China/Jul. 2014–Aug. 2015	A total of 40 phyla, 78 classes, 154 orders, 286 families, and 724 genera were classified. Bacteria (40-1728 cell·m^{-3}, and the average of 490 cell·m^{-3}) Phylum level: Proteobacteria, Actinobacteria, Cyanobacteria, Firmicutes, Acidovacteria, Fusobacteria, and Bacterioidetes Genus level (dominating populations were gram-negative bacteria): Burkholderia, Delftia, Bradyrhizobium, and Methylobacterium Species level (5 g-positive potential pathogens): Bacillus subtilis, Rhodococcus equi, Streptococcus anginosus, Bacillus pumilus, and Rhodococcus fascians	Xu et al., 2019a

Neupane et al., 2010; Shang et al., 2011; Cheng et al., 2015; Psoter et al., 2015; Rivas-Santiago et al., 2015; Lewis et al., 2017; Chen et al., 2018; Gotts et al., 2018; Zhang et al., 2019).

Epidemiological studies have suggested a positive correlation between $PM_{2.5}$ exposure and increased vulnerability to respiratory pathogen infection, such as *S. pneumoniae*, *P. aeruginosa* and *M. tuberculosis* (Mushtaq et al., 2011; Psoter et al., 2015; Rivas-Santiago et al., 2015). $PM_{2.5}$ stimulates *S. pneumoniae* to adhere to airway epithelial cells via oxidative stress and platelet-activating factor, thereby resulting in airway infection (Mushtaq et al., 2011; Gotts et al., 2018). Chen et al. (2018) proposed that $PM_{2.5}$ reduces the expression of β-defensin-2 (hBD-2) through oxidative stress to promote *P. aeruginosa* invasion of airway epithelial cells. Rivas-Santiago et al. (2015) identified that $PM_{2.5}$-exposed airway epithelial cells attenuate the induction of hBD-2 and hBD-3, subsequently enhancing *M. tuberculosis* growth, and ultimately leading to cell senescence and increasing *M. tuberculosis* infection. In our previous study, although chronic $PM_{2.5}$ exposure did not alter child serum SPD concentrations, it could down-regulate child saliva SAG levels, which might increase the risk of respiratory infection (Zhang et al., 2019). Collectively, $PM_{2.5}$ could weaken the function of airway epithelial cells, by downregulating antimicrobial peptide expression, to modify innate airway antimicrobial defenses.

4. Airway antimicrobial activity of SAG

SAG, also known as lung scavenger receptor glycoprotein, is a major salivary glycoprotein (gp 340) encoded by *Deleted in Malignant Brain Tumors* 1 gene (*DMBT* 1), belonging to the SRCR family (Prakobphol et al., 2000; Bikker et al., 2002; Sonesson et al., 2011; Boks et al., 2016; Gunput et al., 2016). SAG is originally found in saliva and is present in many mucosal fluids, including amniotic fluid, bronchoalveolar lavage fluid, gastrointestinal mucus, tears, and vaginal mucus, but not in blood (Ericson and Rundegren, 1983; Holmskov et al., 1997; Reichhardt et al. 2014, 2016). SAG is important for host innate immune defense because of its antimicrobial activity, inducing microbial aggregation and clearance (Madsen et al., 2010; Chu et al., 2013; Reichhardt et al. 2014, 2016, 2017; Patyka et al., 2015; Boks et al., 2016; Gunput et al., 2016; Li et al., 2017).

The actions of SAG on microbes depend on its different phenotypes. Fluid phase SAG aggregates and removes microbes, thereby inhibiting pathogen infection, whereas surface bound SAG induces microbial colonization, consequently increasing the risk of pathogen invasion (Loimaranta et al., 2005; Malamud et al., 2011; Esberg et al., 2012). SAG binds and agglutinates large numbers of microbes, including *A. odontolyticus*, *B. lactis*, *C. albicans*, *E. coli*, *H. pylori*, HIV-1, IAV, *L. acidophilus*, *L. lactis*, *P. aeruginosa*, *S. enterica*, *S. aureus*, *S. gordonii*, *S. mutans*, and *S. pyogenes* (Edwards et al., 2008; Loimaranta et al., 2009; Madsen et al., 2010; Chu et al., 2013; Kukita et al., 2013; Brittan and Nobbs, 2015; Boks et al., 2016; Li et al., 2017; Reichhardt et al., 2017).

SAG is mainly responsible for microbial agglutination in saliva, and it supplies protection against pathogen invasion via inhibiting colonization. SAG can agglutinate *S. mutans* (Ericson and Rundegren, 1983). This specific function is mediated by the *S. mutans* surface protein antigen Ag I/II which binds to the consensus motif (VEVLXXXW) in the SAG SRCR domain (Oho et al., 1998; Loimaranta et al., 2009). Even though there are other proteins that contribute to microbial adhesion, such as the sialic acid-binding protein Hsa or GspB (Jakubovics et al., 2005), or leucine-rich proteins (Lrr) BspA and LrrG (Seepersaud et al., 2005; Kukita et al., 2013), streptococcal Ag I/II is identified as a common pattern that mediates the interaction between SAG and streptococci, thereby promoting streptococcal clearance (Jakubovics et al., 2005; Jonasson et al., 2007; Loimaranta et al., 2009). *S. aureus*, a major opportunistic human pathogen that can colonize asymptomatically over mucosal surfaces, including nasal and oral cavities (Luo et al., 2017), is capable of adhering to SAG through the lectin-like domain in SasA (Kukita et al., 2013) to facilitate *S. aureus* aggregation and clearance, thereby inhibiting *S. aureus* infection. As for viruses, SAG is known to interact with only two (HIV-1 and IAV) in saliva (Malamud et al., 2011). SAG inhibits HIV-1 infection via SRCR1 domain binding to the HIV-1 surface glycoprotein 120 (gp120) N-terminal V3 loop (Malamud et al., 1997; Nagashunmugam et al., 1998; Wu et al., 2003a, b; Chu et al., 2013), whereas SAG inhibits IAV by its SRCR interspersed domains (SID)-region sialic acid carbohydrate ligands binding to the IAV hemagglutinin (HA) (Hartshorn et al. 2003, 2006; White et al. 2005a, 2005b, 2009). Both gp120 and HA are susceptible target glycoproteins on the surface of these enveloped RNA viruses, which may be a common mechanism by which SAG prevents the invasion and infection of these two viruses. Also, SAG can competitively inhibit microbial adhesion to host cells, thereby promoting pathogen clearance. Boks et al. demonstrated that SAG is capable of binding to dendritic cells (DC) and Langerhans cells (LC) through C-type lectin receptors DC-SIGN and langerin, respectively, which effectively inhibits the adhesion of microbes (*C. Albicans* and *E. coli*) to DC and LC (Boks et al., 2016). In summary, SAG is notably important to the human innate immune defense because of its

ability to agglutinate microbes, including bacteria, fungi and viruses, subsequently promoting their clearance.

5. Airway antimicrobial activity of SPD

SPD, a multimeric C-type collectin, is secreted by alveolar epithelial type II cells and Clara cells, and is distributed in many mucosal surfaces and transported into the blood; however, its concentration in lungs is greater than other tissues (Madsen et al., 2000; Hartl and Griese, 2006; Kishore et al., 2006; Bratcher and Gaggar, 2014; Sorensen, 2018). SPD thus plays a critical role in human pulmonary innate immune defense, protects against pathogen invasion, inhibits microbial growth, and enhances pulmonary clearance (Takahashi et al., 2006; Sorensen, 2018; Wong et al., 2018).

The primary effect of SPD is identified to be the agglutination and removal of various microbes (including bacteria, fungi and viruses) via its carbohydrate recognition domain (CRD) (Restrepo et al., 1999; van Rozendaal et al., 2000; Allen et al., 2001; Ofek et al., 2001; Ferguson et al., 2002; Hartshorn et al., 2002; LeVine et al., 2004; Kishore et al., 2006; Douda et al., 2011; Pandit et al. 2012, 2014; Yokota et al., 2012; Hillaire et al., 2013; Du et al., 2016). The pathogenic microbes involved are *A. fumigatus*, *C. albicans*, *C. neoformans*, *E. coli*, *H. influenzae*, HIV-1, *H. pylori*, IAV, *K. pneumoniae*, *M. tuberculosis*, *P. aeruginosa*, *P. carinii*, RSV, *S. aureus*, *S. maltophilia*, and *S. pneumoniae* (Restrepo et al., 1999; van Rozendaal et al., 2000; Allen et al., 2001; Ofek et al., 2001; Ferguson et al., 2002; LeVine et al., 2004; Hartl and Griese, 2006; Pandit et al., 2012; Yokota et al., 2012; Heimer et al., 2013). As for gram-positive bacteria, such as *S. aureus* and *S. pneumoniae*, SPD binds to their cell wall lipoteichoic acid and peptidoglycan through its CRD domain, resulting in bacterial clearance (van de Wetering et al., 2001; Jounblat et al., 2004; Hartl and Griese, 2006). For *K. pneumoniae*, a gram-negative bacterium, SPD selectively agglutinates the unencapsulated phenotype through interaction with lipopolysaccharides (LPS) to increase membrane permeability (Ofek et al., 2001; Wu et al., 2003a, b). Similarly, SPD has been determined to bind and agglutinate *A. fumigatus* and *C. albicans* via its CRD, in a calcium-dependent manner, consequently inhibiting fungal growth and hyphal production, and subsequently inducing phagocytosis by alveolar macrophages and clearance from the lung (van Rozendaal et al., 2000; Allen et al., 2001; Geunes-Boyer et al., 2010). SPD, similar to SAG, also exerts antiviral activity by interacting with IAV and HIV-1 via binding HA and gp120, respectively (White et al., 2005a; Hartshorn et al., 2006; Pandit et al., 2014). Furthermore, SPD can bind the IAV neuraminidase (NA) via its CRD, which enhances the SPD inhibitory effect on IAV (White et al., 2005a). In addition, White et al. (2005a) suggested there is a cooperative antiviral effect between SPD and SAG in the innate respiratory immune system.

6. Interaction of SAG and SPD

In addition to adhering to and agglutinating microbes, SAG binds to a number of endogenous molecules in a calcium-dependent manner to play key roles in innate defensive immunity (Madsen et al., 2010; Reichhardt et al. 2012, 2017; Purushotham and Deivanayagam, 2014; Reichhardt and Meri, 2016). Significantly, the interaction between SAG and SPD has been characterized in detail. SAG directly binds to SPD in a calcium-dependent manner through protein-protein interaction (Holmskov et al., 1997; Ligtenberg et al., 2001). This interaction cooperatively enhances viral aggregation, as well as hemagglutinin inhibition and viral neutralization (White et al., 2005a; Hartshorn et al., 2006). Interestingly, the higher affinity between SAG and SPD will reciprocally inhibit their antiviral activity via binding each other and thereby block adhesion to IAV due to steric hindrance, although there are non-overlapping binding sites in the CRD domain of SPD between SAG and carbohydrates (Holmskov et al., 1997; White et al., 2005a; Hartshorn et al., 2006). This phenomenon demonstrates that the cooperative effect more likely relies on the individual agglutination activity of each, and not the interaction between SAG and SPD. Additionally, the cooperative effect of SAG and SPD could enhance neutrophil uptake of IAV and limit respiratory injury and increase viral clearance by reducing a detrimental respiratory burst (White et al., 2005b; Madsen et al., 2010). This could be a significant and additional pathway of SAG and SPD to remove microbes while restricting a deterioration of immunological response.

7. Conclusion

In the present review, we summarize the microbes associated with $PM_{2.5}$, inhibition of airway antimicrobial activity by $PM_{2.5}$, as well as the predominant role of SAG and SPD in respiratory innate antimicrobial immune defensive system. We speculate there may be a dual effect between $PM_{2.5}$ and respiratory antimicrobial activity (Fig. 1). On the one hand, SAG and SPD can induce microbial agglutination, promote $PM_{2.5}$ uptake by alveolar macrophages (Kendall et al., 2013), and enhance $PM_{2.5}$ as well as its microbe clearance from airways, which affords a protection against $PM_{2.5}$ invasion and pathogen infection. On the other hand, $PM_{2.5}$ can inhibit airway antimicrobial peptide expression and facilitate pathogen adhesion to airway epithelial cells, resulting in host

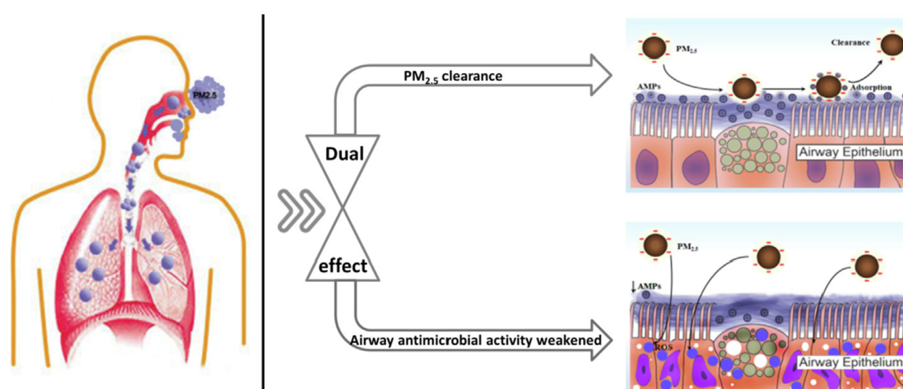

Fig. 1. Dual effect between $PM_{2.5}$ and respiratory antimicrobial activity by AMPs. AMPs: antimicrobial peptides and proteins. ROS: reactive oxygen species.

pathogen infection. The binding of microbes to $PM_{2.5}$ required for enhanced infection, and the relationship between $PM_{2.5}$-associated microbes and SAG and SPD, remain poorly understand. Further research on the relationship between $PM_{2.5}$ and SAG with SPD will enable a better understanding of the interaction of $PM_{2.5}$ and airway innate antimicrobial immune defensive system.

Conflicts of interest

We declare there is no conflict of interest.

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