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REVIEW

Inflammation, Immunity, Fibrosis, and Infection

Every breath you take: Impacts of environmental dust exposure on intestinal barrier function–from the gut-lung axis to COVID-19

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Abstract

As countries continue to industrialize, major cities experience diminished air quality, whereas rural populations also experience poor air quality from sources such as agricultural operations. These exposures to environmental pollution from both rural and populated/industrialized sources have adverse effects on human health. Although respiratory diseases (e.g., asthma and chronic obstructive pulmonary disease) are the most commonly reported following long-term exposure to particulate matter and hazardous chemicals, gastrointestinal complications have also been associated with the increased risk of lung disease from inhalation of polluted air. The interconnectedness of these organ systems has offered valuable insights into the roles of the immune system and the micro/mycobiota as mediators of communication between the lung and the gut during disease states. A topical example of this relationship is provided by reports of multiple gastrointestinal symptoms in patients with coronavirus disease 2019 (COVID-19), whereas the rapid transmission and increased risk of COVID-19 has been linked to poor air quality and high levels of particulate matter. In this review, we focus on the mechanistic effects of environmental pollution on disease progression with special emphasis on the gut-lung axis.

air pollution; COVID-19; gut; intestinal barrier; lung

INTRODUCTION

Ambient air pollution poses a major threat to human health with an estimated 4.2 million deaths per year due to the onset of cardiovascular disease and chronic respiratory illnesses linked to exposure to toxic air pollutants (1). Although there are regulatory policies to reduce air pollution, especially in urban areas where air quality levels exceed recommended restrictions for particulate matter (PM), communities continue to breathe air containing high concentrations of airborne toxins (1). Moreover, health disparities in the United States are seen among minorities and immigrants who account for the majority of seasonal farm workers frequently exposed to PM in agricultural dusts (2, 3). Strikingly, many farm workers live below the poverty level with limited access to healthcare services thus increasing their risk of developing respiratory disorders from exposure to airborne pollutants (4–7). Most air pollution is man-made and derived from fossil fuels including toxins from car exhaust and industrial waste (8–10). In addition, agricultural enterprises including concentrated animal feeding operations include a variety of dusts, vapors, and fumes that can promote and exacerbate respiratory diseases including chronic obstructive pulmonary disease (COPD), hypersensitivity pneumonitis (11, 12), and organic dust toxic syndrome (Fig. 1) (13, 14). More specifically, farmers who are in daily contact with livestock (e.g., pigs) are exposed to dust composed of microorganisms (Tables 1 and 2) originating from animal dander and fecal matter (31, 35). Although the inhalation of dust and other airborne pollutants are major factors in the development of cardiovascular and respiratory complications (48), recent studies have also shown that urban airborne particulate matter can have adverse effects on the gastrointestinal (GI) tract (e.g., barrier function and microbial composition) and immune system (Fig. 1) (18, 35, 56). In addition, the hazards of farming have been widely acknowledged with the primary environmental threat being exposure to pathogenic microbes and toxins generated during agricultural and swine farm field operations (57). Therefore, the purpose of this review is to examine the effects of airborne pollution, including agricultural- and concentrated animal feeding operation (CAFO)-associated particulate matter exposures, on the progression of gastrointestinal diseases through altered gut and lung bacterial and fungal communities. Moreover, we will emphasize the role of these microorganisms on immune responses through the gut-lung axis (GLA).

Swine Farm Building Environment and Clinical Ramifications

Concentrated animal feeding operations.

Because of the increasing demand for animal products worldwide, small livestock farms have been replaced with

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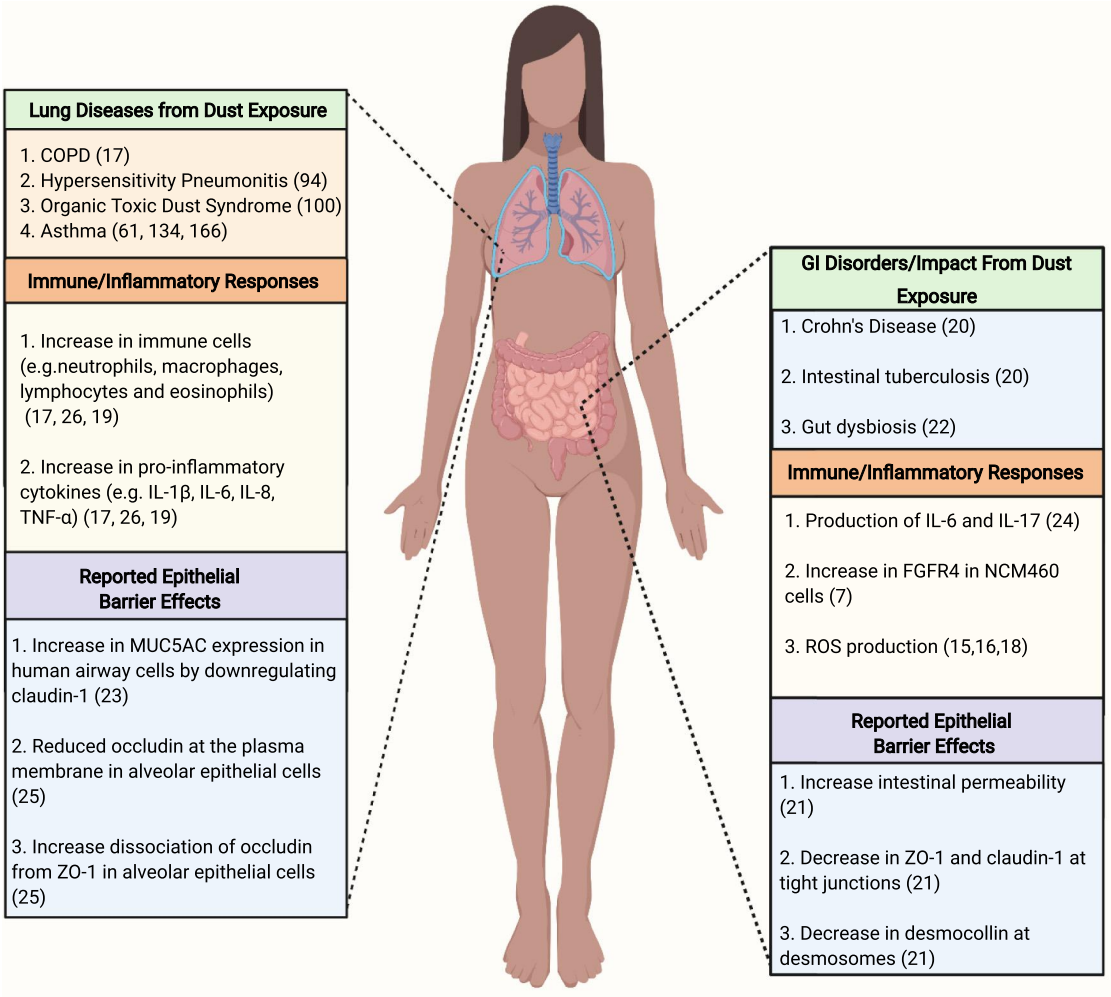

Figure 1. Gut and lung diseases and the reported immune responses associated with agricultural and concentrated animal feeding operation (CAFO) dust exposure.

large-scale farming productions known as concentrated animal feeding operations (58). These industrial agricultural facilities that raise animals for the consumption of meat, eggs, or milk release toxic gases (e.g., ammonia, hydrogen sulfide) and particles that contribute to the development of respiratory diseases in farm workers (59) and people living in close proximity to CAFOs (60). Moreover, endotoxins found in the dust collected from CAFOs act as the primary factor in the onset of asthma and other respiratory conditions (61–63). A considerable amount of research has shown that exposure to endotoxins is especially prevalent in swine farm workers (64–66). Raising swine is a lucrative agricultural enterprise for US farmers with sales generating 26.3 billion dollars in 2017 (67). The success of swine farms depends on the large-scale indoor confinement of pigs and the commitment of full-time employees (68). Consequently, swine farm workers are frequently exposed to particulate matter in dust including microbial components (e.g., endotoxins, bacteria, and mites) and plant- and animal-derived materials (e.g., pollen and ammonia, respectively). Interestingly, swine farm laborers are reported to have a higher prevalence of occupational respiratory symptoms in comparison with other agricultural workers (11, 69). A clinical study reported that exposure to swine farm air for 2–5 h resulted in the thickening of nasal mucosa, lung function decline, an increase in immune cell infiltrates [e.g., neutrophils, macrophages (MΦ), lymphocytes, and eosinophils], and proinflammatory cytokines [e.g., interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNF-α), and IL-8] in the bronchoalveolar lavage fluid of healthy participants (11, 19, 70). These findings were also corroborated in animal studies by Charavaryamath et al. (71) which demonstrated that swine farm dust (SFD) exposure induced lung inflammation and the recruitment of neutrophils in Sprague–Dawley rats. A more recent study by Roque et al. assessed endotoxin levels in swine barn air. In comparison with pigs raised in barns with low-bacterial endotoxin levels, there was an increase of white blood cells in pigs exposed to high-endotoxin levels. In addition, peripheral blood mononuclear cells (PBMC) collected from high-exposure pigs had greater plasma immunoglobulin (Ig) G and IgE levels but lower IgA levels than that produced by PBMCs from low-exposure pigs (66). The inflammatory capabilities of SFD have also been demonstrated in various in vitro experiments using human bronchial epithelial cells and pulmonary carcinoma cell lines (19, 72). Similar studies have indicated that an increase in proinflammatory cytokines

Table 1. *Major bacterial composition of CAFO dust*

Bacterial Class	CAFO	Disease(s)/Impact	References
Staphylococcus spp. (*S. aureus*, *S. simulans*, *S. epidermidis*, *S. chromogenes*, *S. pasteuri*, *S. hyicus*, *S. haemolyticus*, *S. equorum*)	Swine farm	Pneumonia	(27–31)
Bacillus spp. (*Bacillus cereus*)	Poultry farm, swine farm	Respiratory infections, diarrhea, bacteremia	(27–32)
Mycobacterium tuberculosis	Swine farm	Pneumonia, Intestinal tuberculosis, Crohn's disease	(33, 34)
Methanobrevibacter, *Methanothermobacter*, and *Methanosphaera*	Pre-filtered SFD	Linked to inflammatory bowel disease	(35–37)
Ruminococcus	Swine farm	Associated with respiratory allergies and Crohn's disease	(31, 35, 15)
Lactobacillus	Swine farm	Pulmonary infections, Bacteremia, endocarditis	(31, 35, 38)
Eubacterium spp.	Swine farm	Associated upper respiratory tract infections and cystic fibrosis	(31, 35, 39, 40)
Clostridium spp. (*C. perfringens*)	Poultry farm, swine farm	Can assist the expansion of regulatory T-cellsPrevents growth of commensal bacteria found in the gut	(31,32, 35)
Betaproteobacteria	Swine farm	Low abundance associated with increase in serum IL-6 in acute respiratory disease syndrome patients	(32, 41, 42)
Actinobacteria (genus: *Micrococcus*)	Swine farm	Increase in gut associated with IBDPulmonary hypertension	(32, 43, 44) (27–30, 45)
Aerococcus (*Aerococcus viridans*)	Swine farm	Endocarditis	(27–31)
Enterococcus	Swine farm	Upper and lower airway infections	(27–30, 46)

CAFO, concentrated animal feeding operation; IBD, inflammatory bowel disease; IL-6, interleukin-6; SFD, swine farm dust.

following SFD exposure promoted the adhesion of lymphocytes through the upregulation of intracellular adhesion molecule-1 (73, 74), which contains five Ig superfamily domains (75). Although respiratory immune responses of SFD have been characterized in animal studies, the effects of particulate matter in SFD on the intestinal immune system continue to be an underdeveloped area of investigation.

Respiratory and Systemic Responses to Particulate Matter

Particulate matter, found in ambient and urban air pollution, is a key pollutant linked to chronic airway inflammation, cardiovascular disease, and inflammatory bowel disease (9, 76–78). The components of particulate matter are defined by their aerodynamic equivalent diameter (AED), which determines the particles' potential to cause disease (79). Depending on particle AED, different regions of the human respiratory tract are penetrated by varying amounts of particulate matter (79, 80). Particle penetration into respiratory regions can be identified as either "inhalable fractions" or "respirable fractions" (80). Inhalable fractions are defined as the mass fraction of total airborne particles inhaled through the nose and mouth whereas respirable fractions can penetrate the unciliated airways (80). These categories recognize the important role of particle deposition and AED in the induction of disease in different regions of the respiratory tract. Ultrafine particles, with an AED of 0.1 μm ($PM_{0.1}$), pose a major health risk because of their size and their ability to absorb toxins. $PM_{0.1}$ is formed by the coalescence of ions and gaseous molecules produced by combustion (e.g., vehicle and power plant emissions) (81). These particles can easily penetrate the lungs and translocate through alveolar epithelial cells. This allows for the subsequent transport of toxic cellular fragments via the surface of $PM_{0.1}$ (82) that can enter the bloodstream and promote inflammation in distal organs (81, 83). Furthermore, the coalescence of ultrafine particulate matter can form larger particles such as $PM_{2.5}$ (2.5 μm). $PM_{2.5}$ is an indicator of "fine inhalable particles" which include combustion emissions, organic compounds, and metals (84, 85). "Inhalable particles," such as pollen, have a diameter of 10 μm (PM_{10}) or smaller and can typically be seen without the assistance of an electron microscope (86). Particles with an AED of 10 μm or larger directly impact the nasopharyngeal membranes (81) and can be swallowed following mucociliary clearance (87). Respiratory studies show that particles with a smaller AED may have the ability to infiltrate the terminal bronchioles and alveoli that are typically inaccessible to larger particles (78,

Table 2. *Major fungal/yeast composition of CAFO dust*

Fungi/Yeast	CAFO	Disease(s)/Impact	References
Aspergillus	Swine farm	Enterocolitis, appendicitis, colonic ulcers and GI bleeding	(16,17, 35, 47–50)
Acremonium	Swine farm	Colonize the lungs and GI tract	(35, 17, 48, 49, 50, 51)
Penicillium spp.	Swine farm	Associate with the onset of pneumonia	(35, 17, 48–50, 52)
Cladosporium	Swine farm	Respiratory infection; causes infection in immunocompromised individuals	(35, 17, 48–50, 53)
Filobasidium uniguttulatus (Yeast)	Swine farm	Meningitis	(31, 54)
Cryptococcus	Swine farm	Acute or chronic infection of the lungs	(31, 55)

CAFO, concentrated animal feeding operation; GI, gastrointestinal.

88). Thus, evidence suggests that the pathogenicity of particulate matter depends on their size (80, 89). $PM_{2.5}$ and PM_{10} have distinctive detrimental effects on respiratory and gastrointestinal health (55, 78, 86, 90, 91). To understand the pulmonary mechanisms involved in PM pathogenicity, Chan et al. (92) exposed mice to traffic-related PM_{10} for 3 wk and found a significant increase in lymphocytes, macrophages, IL-1β expression, and the apoptosis marker, caspase 3, in bronchoalveolar lavage fluid. Because of its small diameter, $PM_{2.5}$ can easily penetrate the lungs and activate inflammatory signaling cascades, triggering inflammatory cytokine expression and promoting systemic inflammation (93, 94). More specifically, when bronchial epithelial cells are exposed to extracts of swine dust representing $PM_{2.5}$ and smaller fractions, there is an increase in IL-6 and IL-8 release which is further dependent on the activation of protein kinase-α (PKCα) and -ε (PKCε) isoforms (94, 95). Similarly, C57BL/6J mice chronically exposed to different concentrations of $PM_{2.5}$ show distinct transcriptional profiles in the lungs associated with immune and cardiovascular disease pathways (96). Although fewer in number, there are studies that examined the mechanisms underlying the harmful effects of PM exposure in the gastrointestinal system. Kish et al. exposed wild-type 129/SvEv mice to PM_{10} for 7–14 days. This exposure altered immune gene expression, increased proinflammatory cytokine secretion, and barrier permeability in the small intestine (97). In addition, IL-10-deficient mice fed a chow diet supplemented with PM_{10} exhibited microbial dysbiosis and altered short chain fatty acid composition followed by elevated cytokine expression in the colon (97). In 2011, Mutlu et al. performed comparable in vitro studies in human epithelial colorectal adenocarcinoma cell (Caco-2) monolayers exposed to PM. PM exposure increased mitochondrially derived reactive oxygen species (ROS), intestinal permeability, the activation of nuclear factor-κB (NF-κB) and target gene IL-6, and Caco-2 cell death (98). They validated these findings in vivo by demonstrating that a single oral gavage treatment of PM (200 μg) decreased the colocalization and mRNA levels of zona occluden protein 1 (ZO-1), increased the levels of IL-6 mRNA, and induced apoptosis along the gastrointestinal tract of C57BL/6 mice (98). Overall, these data illustrate the disruptive effects of particulate matter on the respiratory and gastrointestinal systems, respectively. However, additional experimental research is needed to establish a well-defined gut-lung axis following exposure to airborne pollutants (99, 100).

Particulate matter and intestinal permeability.

The intestinal epithelium acts as a selective permeable barrier between luminal contents (e.g., intestinal microbiota) and the immune system (82, 101, 102). The barrier is supported by three distinct structural components: tight junctions that provide the first line of defense against toxins and enteric pathogens and selectively regulate paracellular permeability; the adherens junctions, which are protein complexes at cell-cell junctions that are linked to the actin cytoskeleton and combine with tight junctions to form the apical junctional complex; and desmosomes that form adhesive bonds between cells and provide mechanical strength to tissues (102, 103). Past studies have indicated that the gastrointestinal tract is exposed to high levels of pollutant particulate matter ostensibly from the inhalation of PM and the ingestion of contaminated food and water (9). As a result, studies have shown that particulate matter can obtain access to the gastrointestinal tract through several routes. After mucociliary clearance, particulate matter can pass via the esophagus, through the stomach, and enter the intestinal lumen where it can directly affect epithelial cells and be metabolized by commensal gut microbes causing the release of toxic metabolites (9, 82, 104, 105). Prior research also suggests that once deposited in the lungs, particulate matter behaves similar to gas molecules, moving through the alveoli via diffusion and translocating to the circulatory system (9, 106). Airborne microorganisms (bacteria, fungi, and viruses) are primary components of $PM_{2.5}$ (107, 108). When microorganisms are inhaled and reach the alveolar space, they are subsequently phagocytosed by alveolar macrophages that further stimulate immune cell activity (9). However, there are microbes that utilize alveolar macrophages to circumvent host defenses. For example, the airborne pathogen *Mycobacterium tuberculosis* can reside in the phagosomes of macrophages where it can gain access to the cytosol, control host cell death (33, 34), and increase the risk of granulomatous disorders such as intestinal tuberculosis and Crohn's disease (20). The bacteria and/or spores not destroyed by alveolar macrophages can move through the circulatory system to the intestines. In addition to inhalation, particles and microorganisms released by industrial waste and vehicle exhaust can contaminate food and water supplies, thereby suggesting another route of oral/gastrointestinal exposure (109, 110). Recent epidemiological studies have shown a direct link between particulate matter exposure and intestinal defects (111). Inflammation is a normative response to environmental stressors, even being important for wound healing (111). Commensal gut bacteria modulate the production of reactive oxygen species and various growth factors responsible for intestinal epithelial migration and proliferation (112). Therefore, dysbiosis of the gut microbiome induced by harmful pollutants (113) may severely impair critical processes necessary for intestinal epithelial wound healing (114–116). However, the protective or detrimental role of PM-induced inflammation on gut epithelial cells continues to be an active area of investigation (111). Chronic PM exposure for 12 mo in mice resulted in epithelial lesions and the confluence of inflammatory cells in murine colons (111). In addition, normal human colon epithelial cells (NCM460) exposed to PM for 48–72 h showed an increased expression of fibroblast growth factor receptor 4 (*FGFR4*) (111), which is associated with the development of colon cancer (117). In 2019, Li et al. (111) demonstrated that *FGFR4* activates the phosphatidylinositol-3-kinase (PI3K)/Akt pathway and the removal of *FGFR4* prevented PM-induced colorectal cancer in $FGFR4^{-/-}$ mice. Moreover, PM exposure has been suggested to increase the risk of inflammatory bowel diseases and colorectal cancer (118) by altering gut epithelial tight junctions via the production of reactive oxygen species (9, 27, 77) generated by Fenton's reaction of transition metals commonly detected in PM (119). More recently, a study has shown that levels of zona occluden protein 1 (ZO-1), claudin-1, and the desmosome protein, desmocollin, were decreased in enteroids following exposure to $PM_{2.5}$ culminating in increased intestinal permeability (21). Consequently, an increase in intestinal permeability allows for pathogenic bacteria, viruses, and fungi to migrate to the lamina propria and interact with

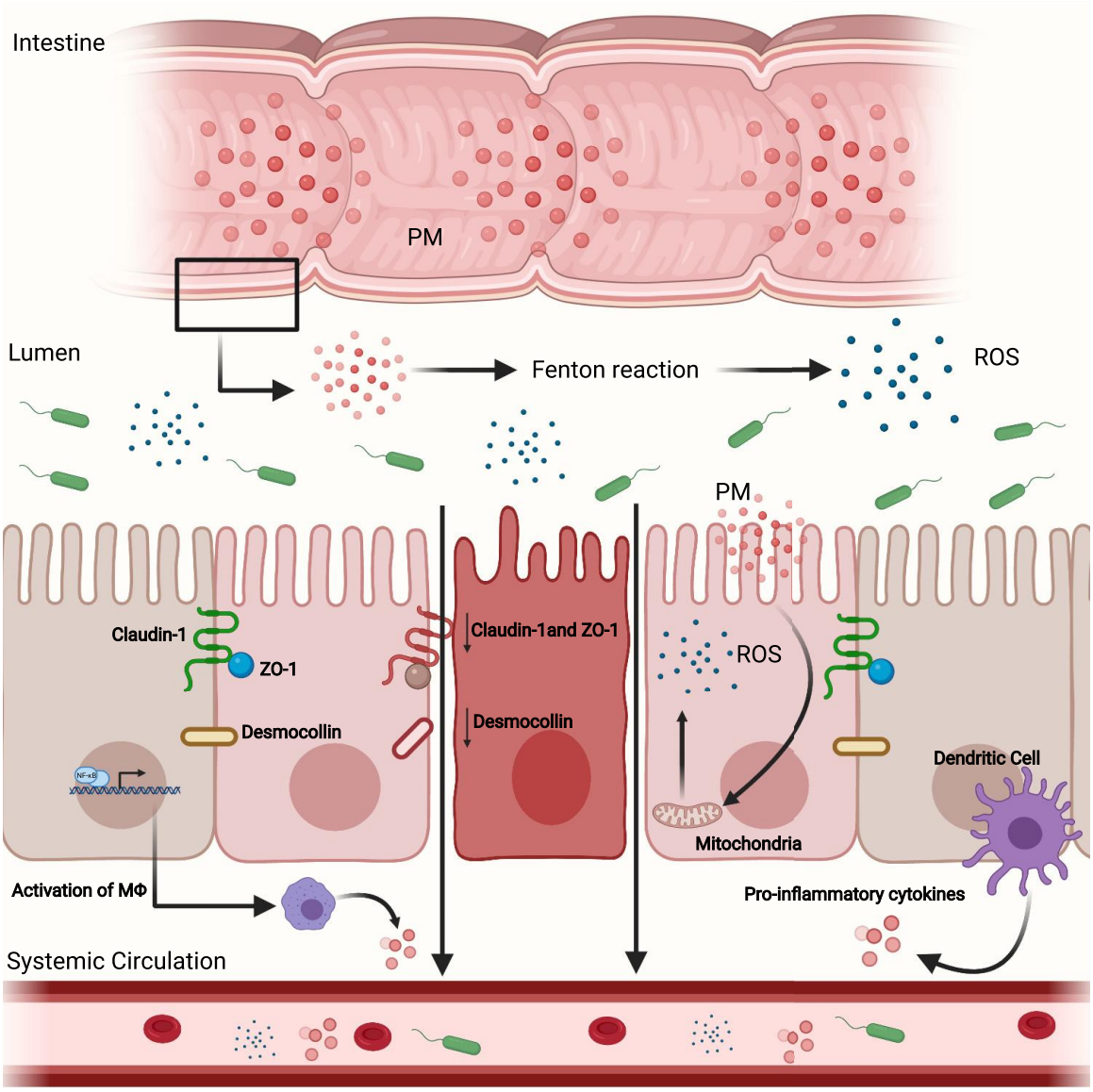

Figure 2. Particulate matter (PM) toxicity and reactive oxygen species (ROS). PM toxicity may come from the generation of hydroxyl radicals and ROS through Fenton's reaction. Following inhalation, particulate matter can reach the gastrointestinal tract, undergo a catalytic process, and promote systemic inflammation through the production of ROS and the subsequent release of proinflammatory cytokines/chemokines from macrophages (MΦ) and dendritic cells (9, 123–125). In addition, PM exposure can promote mitochondrially derived ROS in intestinal epithelial cells (98), thereby altering the expression of tight-junction proteins, intestinal barrier function, and increasing permeability which allows for the translocation and systemic migration of bacteria/bacterial products and proinflammatory cytokines/chemokines (21).

intestinal immune cells and commensal microbes (120–122). Ultimately, these interactions increase immune cell activity evidenced by proinflammatory responses from macrophages and dendritic cells, which worsen intestinal permeability and furthers dysbiosis (Fig. 2) (9).

Respiratory and Gastrointestinal Conditions Associated with Microbial Products in Agricultural Dust

Effects of microbial and fungal communities found in swine farm dust.

Agricultural workers are at extreme risk of developing chronic airway inflammation and severe respiratory illnesses when exposed to workplace dust (126, 127). These risks are further inflated by the absence of face respirators (57). Farmers who maintain crops may develop a type of hypersensitivity pneumonitis referred to as "farmer's lung" (128, 129). This severe respiratory condition is triggered by the inhalation of mold spores (e.g., *Micropolyspora faeni* and *Aspergillus fumigatus*; ~2–10 μm) that grow in hay and grain (129, 130). Mold spores have the capability of attaching to airborne dust particles (129, 130) and preventing normal lung function (131) such as gas exchange (132). Comparably, swine farm workers also increase their risk of lung function decline and chronic bronchitis from long-term exposure to swine farm dust (133, 134). "Feed particles" are the major component of agricultural dust and SFD (35); however, it is likely that microbes found in SFD provoke the proinflammatory responses linked to respiratory and gastrointestinal diseases. Metagenomic

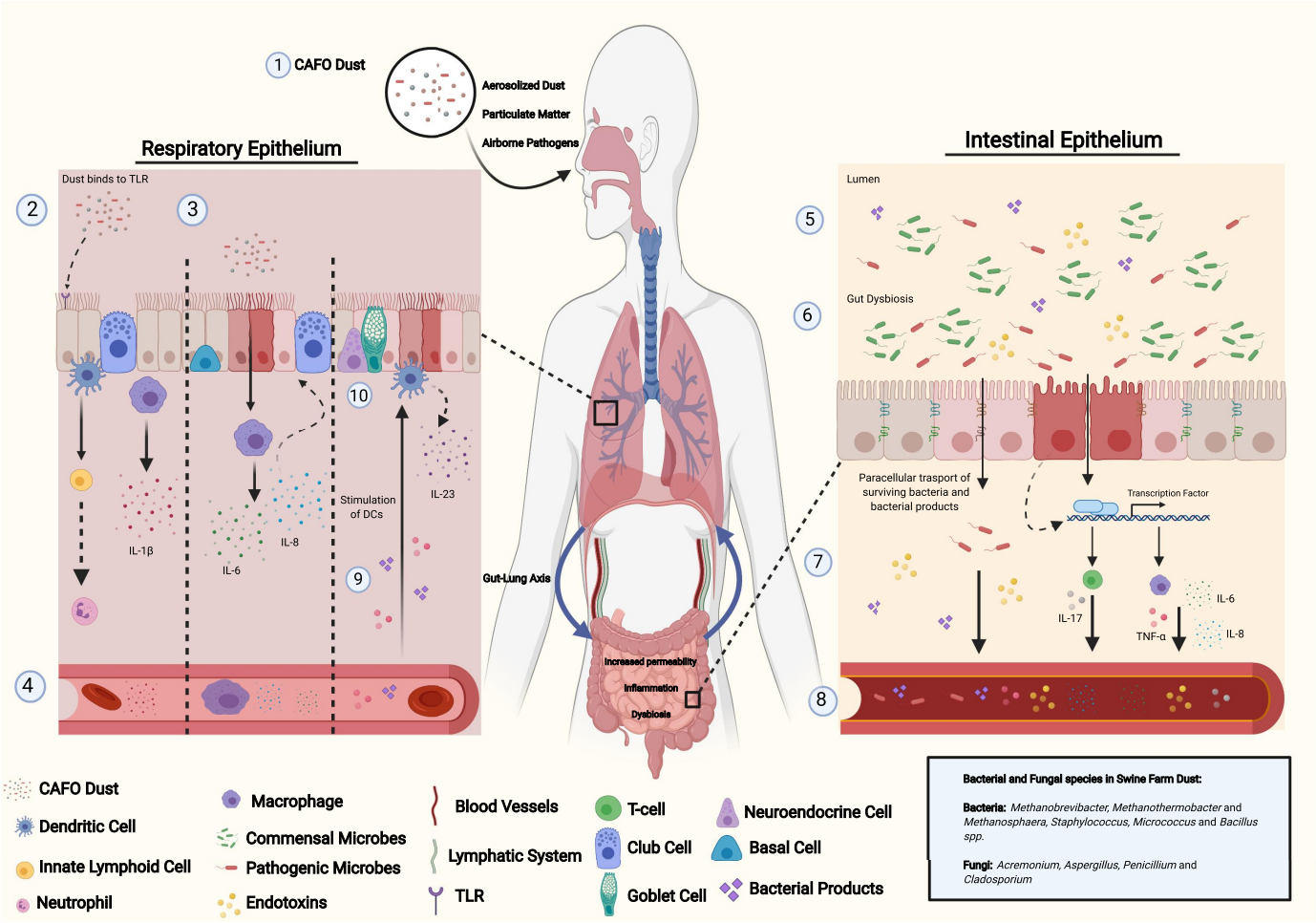

Figure 3. Particulate matter induction of inflammation along the gut-lung axis. (*1*) When inhaled or ingested dust can reach the alveolar space and promote immune responses. (*2*) Particulate matter in concentrated animal feeding operations (CAFO) dust, like swine farm dust (SFD), can bind to Toll-like receptors (TLR) on respiratory epithelial cells and activate innate lymphoid cells (ILC). ILCs recruit neutrophils, responsible for killing pathogens. In addition, ILCs such as ILC3 can differentiate into T-helper cells (i.e. Th17) and release interleukin (IL)-17A,F and IL-22. Furthermore, alveolar macrophages release IL-1B inducing pulmonary inflammation. (*3*) Particulate matter bypasses the respiratory epithelium and is phagocytosed by alveolar macrophages which release proinflammatory cytokines, IL-6, and IL-8. (*4*) The components of particulate matter (e.g., bacteria and fungi) and proinflammatory cytokines then travel through the circulatory and/or lymphatic system to the intestine. (*5*) Particulate matter can enter the gut via mucociliary clearance and/or circulation from the lungs. (*6*) Bacteria, endotoxins, and fungi from CAFO dust induces intestinal dysbiosis, increases permeability, the paracellular transport of pathogens, and promotes the activation of transcription factors such as nuclear factor-κB (NF-κB), which mediates the activation of macrophages in the intestine and releases IL-6, IL-8, and tumor necrosis factor α (TNF-α) (*7*). (*8*) Via the intestinal vasculature/mesenteric lymph nodes, proinflammatory cytokines, surviving bacteria, and bacterial products can reach the basolateral membrane of the respiratory epithelium (*9*) thus stimulating dendritic cells (DC) to produce IL-23 thus promoting further epithelial damage (*10*).

analyses on settled dust collected from two different swine confinement facilities have shown that "pre-filtered" SFD contains archaeal DNA (*Methanobrevibacter*, *Methanothermobacter*, and *Methanosphaera*) (35). However, swine farm dust is largely composed of *Staphylococcus*, *Micrococcus*, and *Bacillus spp.*, all of which can metabolize harmful environmental particles and promote bacteremia and ROS production (27–30). In addition to bacteria, fungal species ubiquitous to the environment have also been identified in SFD (*Acremonium*, *Aspergillus*, *Penicillium*, and *Cladosporium)* (Table 2) although they are less abundant and understudied (17, 35, 48, 50, 135). Past reports indicate infections caused by *Acremonium* species, although rare, affect immunocompetent individuals by colonizing the lungs and gastrointestinal tract (51). Clinical case studies in immunosuppressed patients have reported the ability of *Aspergillus* infections to develop into serious gastrointestinal complications including enterocolitis, appendicitis, colonic ulcers, and gastrointestinal bleeding (47, 136). Although the microbial composition of SFD has been characterized, the pathological features and mechanisms of SFD that are responsible for intestinal barrier dysfunction during chronic exposure remain an understudied area of investigation.

Gut-Lung Axis and Microbial Interactions

The gut-lung axis (GLA) describes a two-way interchange between the microbiota and immune system of the gut and lungs (137). In a healthy individual, the microbiomes of the respiratory tract and gastrointestinal system are comprised of distinctive genomes (archaea, eukaryotes, viruses, bacteria,

and fungi) that live symbiotically to maintain homeostasis in their respective organs (138). In 2019, Lee et al. (139) indicated that the lung microbiota, as assessed via sputum samples, is primarily composed of microbes from the phyla Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, and Fusobacteria. Further examination also revealed similarities between healthy sputum and saliva samples. However, in comparison with saliva, sputum is more abundant in the genera *Granulicatella* (phyla: Firmicutes) (139). A recent study examining the pharyngeal microbiota of outdoor farmers' market workers chronically exposed to smog with $PM_{2.5}$ and PM_{10} reported an increase in *Granulicatella* (140) that is directly linked to the onset of lung cancer and endocarditis (141). Interestingly, the lungs, once considered a sterile environment (142), have low-colony density but high-microbial diversity (16). Comparably, murine lung microbiome studies show a similar composition (143). Although the lung microbial community differs from the intestinal microbiota, similar phyla are found (e.g., Bacteroidetes, Firmicutes, and Proteobacteria) and play an important role in establishing the immune system (56). Previous studies have shown that the lung and gut microbiota are essential to the interactions between both mucosal sites and the development of disease. A recent study indicated that lung microbial dysbiosis and dysfunction was associated with the development of inflammatory bowel disease in patients who reported no history of smoking. However, no definitive pathogenic mechanism has been identified (144). In addition, respiratory diseases induced by environmental pollution promote dysbiosis of the pulmonary and intestinal microbiota indicated by an outgrowth of Proteobacteria and Firmicutes (39). It is well documented that changes in the pulmonary flora are directly associated with the onset of respiratory infections including pneumonia and influenza (106). Pulmonary research suggests $PM_{2.5}$ pathobionts can invade deeply into the lungs and release toxins that damage airway epithelial cells and selectively destroy pulmonary microbes (144, 145). Consequently, pathogenic bacteria and their toxins can translocate through endothelial cells and circulate in the blood to distal organs and tissues (93) including the intestines, culminating in altered gut flora, intestinal barrier dysfunction, and incitement of an immune response. Yet, alterations in the intestinal microbiota have been linked to changes in pulmonary immune responses, inflammation, and disease progression (Fig. 3) (137, 146). For example, the development of asthma, notably in children, has been associated with the reduced abundance of *Bifidobacteria* and an increase in Clostridia in the intestine (147). In addition, Arrieta et al. (148) have also shown that the over-representation of gut fungal species, specifically *Pichia kudriavzevii,* is associated with the development of atopic wheeze in children. Moreover, in human and murine models, modulation of the gut microbiota due to antibiotic intake increases the risk of lung diseases and allergic inflammation (149–152). Although the exact mechanisms continue to be examined, studies have shown that gut bacteria interact with the mucosal immune system via metabolites, including proinflammatory and regulatory signals (22, 137, 153, 154).

Immune cell contributions to the gut-lung axis.

It has been suggested that the respiratory microbiome acts as a "gatekeeper," providing colonization resistance against environmental pathogens (119) and metabolizing pollutants (142). These preventative measures, along with the respiratory mucosa (e.g., mucus production) (119) and ciliary clearance (155), block pathogens and particulate matter from reaching the airway epithelium (70, 144, 156, 157). However, if bacteria or foreign materials invade this barrier, airway epithelial cells express pattern recognition receptors, secrete antimicrobial peptides, and incite an inflammatory response through the activation of mitogen-activated protein kinases (155), thereby serving as the primary line of defense (135). Together, interactions between the respiratory microbiota and the epithelial barrier influence pulmonary immune responses. Of note, prior studies have shown that long-term exposure to urban particulate matter can have severe effects on lung microbial composition and immunity (158, 159). In murine models, Li et al. (89) demonstrated T-helper (Th) 2 cell-mediated immune responses and acute inflammation are linked to toll-like receptor (TLR) 2 and TLR4 activation following exposure to $PM_{2.5}$. More specifically, urban particulate matter-activated dendritic cells (UPM-DC) are responsible for Th1, Th2, and Th17 differentiation through major histocompatibility class II availability (93). Th1, Th2, and Th17 effector phenotypes are directly implicated in the exacerbation of asthma and chronic lung inflammation (158, 160, 161). In addition, particulate matter also activates dendritic cells to release the proinflammatory cytokine, interleukin-23 (123, 124). IL-23 incites T-cell immunity and stimulates innate lymphoid cell (ILC) (100, 162) production of cytokines responsible for the defense against extracellular bacteria and fungi (23, 163, 164). Moreover, Th17 cells play a significant role in host defense against extracellular pathogens by recruiting neutrophils and macrophages to infected tissues and provide compensatory support in response to epithelial barrier defects (165, 166). In addition, there is evidence that suggests respiratory infections not only alter the lung microbiome but are also responsible for directing signals of infection from the lungs to the gut causing alterations in gut microbiome dynamics (137, 167). This interaction is seen in Balb/c mice infected with aerosolized *M. tuberculosis* where they exhibit a rapid shift in gut microbial diversity which may indicate these alterations are as a result of *M. tuberculosis* infection and immune signaling from the lungs (167). During a respiratory infection, bacteria and immune cells can translocate across lung epithelial cells and reach the gastrointestinal tract via lymphatic or blood circulation to activate local intestinal immunity (65, 137, 168). Prior studies have reported that swine farm dust is primarily composed of *Ruminococcus*, *Lactobacillus*, *Eubacterium*, and *Clostridium* species (31, 35). *Clostridium* species have been reported to assist in the expansion of regulatory T-cells, which are linked to the suppression of immune responses in the colon of germ-free mice (169). Likewise, spore-forming *Clostridium perfringens* (*C. perfringens*) demonstrate rapid proliferation while secreting membrane and cytoskeleton disrupting, pore-forming, and tight-junction disintegrating toxins that prevent the growth of commensal bacteria found in the gut (31). Enterotoxin is linked to food poisoning and nonfoodborne diarrhea through the disruption of claudin tight-junction proteins in gut epithelial cells (31). The disruption of tight-junction proteins in response to environmental pathogens has a direct impact on commensal gut microbes and the pulmonary immune system (170). An increase in intestinal

permeability allows for the systemic migration of gut bacteria and their metabolites (short-chain fatty acids; SCFA) to the lungs (168, 171, 172). More specifically, gut-derived metabolites can pass systemically to the bone marrow and promote hematopoiesis (137, 173). Under inflammatory conditions, hematopoietic stem cells can differentiate and give rise to dendritic cell precursors that disseminate to the lungs and mature into $CD11b^+$ dendritic cells (21, 136, 172) that have been shown to be responsible for inducing allergic airway hypersensitivity (174). SCFAs can also affect lung immunity by enhancing $CD8^+$ T-cell activity (22), promoting forkhead box P3 (FOXP3) expression (175) and regulating the production of proinflammatory cytokines (TNF-α, IL-2, IL-6, IL-10) through the activation of free fatty acid receptor 3 (122, 176). Together, these findings demonstrate the level of communication between the gut and lungs in response to alterations of the gut microbiota and intestinal permeability. The gut-lung axis is a two-way system that involves the interactions between their respective microbiota and immune cells. There has been increasing evidence of host-microbe and microbe-microbe interactions shaping immune responses in respiratory diseases and the development of subsequent effects in the gut (177–179). Nevertheless, further investigation is needed to explore the potential pathogenic effects of the gut-lung interaction following agriculture and CAFO exposure.

Air Pollution and COVID-19

An additional and highly topical example of a pathogenic influence on the lung also manifesting symptoms in the gastrointestinal tract is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The outbreak of coronavirus disease 2019 (COVID-19) in December 2019 has led to a global pandemic affecting over 90 million individuals and leading to more than 1.9 million deaths (as of January 14, 2021) (www.who.int) with most patients suffering from respiratory symptoms. It has been reported that SARS coronaviruses infect immune cells and the lung epithelium thereby enhancing proinflammatory cytokine and chemokine production and leading to severe acute respiratory syndrome (180). However, there is increasing awareness of the high prevalence of extrapulmonary symptoms, in particular, those arising from the gastrointestinal tract. Viral infections, such as influenza, can promote dysbiosis in the gut microbiota and increase gut permeability (181). Indeed, studies identified that 46% of patients had GI symptoms, diarrhea (29.3%) being the most frequent (114, 127, 182). More specifically, SARS-CoV-2 activates angiotensin-converting enzyme 2 (ACE2) and promotes enteritis and the risk of diarrhea (183, 184). SARS-CoV-2 uses transmembrane protease serine 2 receptors (TMRPSS2) and TMPRSS4 to gain entry into small intestinal epithelial cells and has been shown to promote enterocyte dysfunction and increase intestinal permeability (185–188). In a manuscript recently deposited in *medRxiv*, preliminary evidence, generated using multiomics screening approaches on serum samples, suggests that severe COVID-19 may be associated with increased intestinal permeability to microbial products (e.g., lipopolysaccharides/lipopolysaccharide binding protein, β-glucan), altered amino acid metabolism, and compromised gut enterocyte function (189). Moreover, hospitalized patients diagnosed with severe COVID-19 displayed higher levels of plasma zonulin. In the gut, elevated levels of zonulin increase intestinal permeability, microbial-mediated myeloid inflammation, and allow for the translocation of microbes and their products (e.g., lipopolysaccharides/lipopolysaccharide binding protein, β-glucan) from the gut into the systemic circulation (189). Although these data are not yet published, they do begin to identify a mechanism by which GI symptoms and effects of COVID-19 on gastrointestinal function contribute to more severe COVID-19 outcomes.

Risk factors for infection and more severe disease include age, with the elderly (>65 yr old) being most vulnerable, and individuals with underlying medical conditions including respiratory disease, cardiovascular disease, and chronic inflammatory conditions such as obesity and diabetes (190). Obesity, the most common metabolic disease and global epidemic characterized by chronic low-grade inflammation, is implicated in COVID-19 severity in patients with a body mass greater than 40–45 kg/m^2 (191–193). Obesity can significantly influence the respiratory system by reducing lung volume and capacity via mechanical changes (e.g., patterns of fat distribution particularly along the chest wall, abdomen, and upper airway). Nevertheless, there is also risk of systemic inflammation through the production of inflammatory cytokines (e.g., TNF-α, IL-1B, IL-6) by excess adipose tissue. In addition, metabolic dysregulation in obese patients promotes intestinal barrier dysfunction (194–197). Reports also state that adipose tissue has higher expression of ACE2 in comparison with the lungs, therefore, serving as a reservoir for viral infections. Increased *ACE2* mRNA expression in the ileum of patients with inflammatory bowel disease (IBD) and non-IBD subjects was associated with a higher body mass index (BMI), whereas obesity is also associated with a higher risk of infections that can underlie or exacerbate many conditions that have more severe outcomes in obese subjects (198). Moreover, ACE2 is upregulated in visceral and subcutaneous adipose tissue in obese patients, thereby increasing the risk of ACE2 shedding and the redistribution of the receptor to other tissues (199) via transcriptional upregulation and activation of a disintegrin and metalloproteinase domain 17 (ADAM17) (200, 201).

An additional vulnerability appears to be the association between increased deaths from COVID-19 in areas with high levels of air pollution, more specifically, elevated exposure to the toxic component nitrogen dioxide (NO_2). Anthropogenic activity, such as fossil fuel combustion, releases NO_2 into the atmosphere and exposure has been linked to metabolic disorders (96), COPD (202), and lung injury (203). Moreover, NO_2 promotes the production of proinflammatory cytokines and lung epithelial cell death (204). In 2020, Ogen (205) assessed long-term exposure to NO_2 in European countries and found a strong correlation between high levels of NO_2 (>100 $\mu mol/m^2$) and COVID-19 fatalities. Nitrogen dioxide can also react with other chemicals and produce secondary pollutants such as ozone and PM (206). A recent nationwide cross-sectional study revealed that an increase of just 1 $\mu g/m^3$ of PM corresponded to an 8% increase in COVID-19 deaths (207). Although the mechanisms by which air pollution modifies severity of COVID-19 responses have yet to be determined, very little is known about the host factors that determine mild or even asymptomatic responses

compared with life-threatening or fatal outcomes. As with many inflammatory diseases, it is the combination of specific host and environmental factors in certain individuals that provokes more severe disease outcomes. What does appear to be emerging from evidence generated thus far is that environmental air pollutants have a positive correlation with overall COVID-19 severity (207). Furthermore, members of racial and ethnic minority groups are at a greater risk of contracting COVID-19 because of social inequalities and health disparities (208). This increased vulnerability is also seen among seasonal agricultural workers in COVID-19 high-risk rural counties in the US (209) because of factors including confined group housing conditions as well as limited access to healthcare and personal protective equipment (44, 209, 210). Moreover, although the specific influences of aerosolized agricultural dust on COVID-19 are unknown, it is not unreasonable to suggest that given its causal role in many respiratory conditions, agricultural dust may represent a potential additional risk factor for COVID-19 infection, or more severe outcomes, in agricultural workers. This may be particularly relevant to the high levels of COVID-19 in Imperial County, California (149). This rural and agriculture-intense inland county has a number of disadvantages as it battles the pandemic including limited access to healthcare, high levels of poverty, obesity, and asthma hospitalizations (209, 211), as well as poor air quality with higher levels of particulate matter exposure than the state or national averages (24, 119, 212).

CONCLUSIONS

Farmers and farm workers are regularly exposed to agriculture dust (57). Adverse respiratory health effects including reduced lung function and shortness of breath (213, 214) are directly linked to the components of agriculture particulate matter such as chemicals, bacteria, fungi, and viruses (35, 76). Interestingly, chronic lung disorders and respiratory infections as a result of particulate matter exposure are often accompanied by gastrointestinal diseases (appendicitis, bowel infections, and irritable bowel disease) (47, 215, 216). The source of these GI disorders has been linked to lung microbial alterations followed by a robust immune response of the respiratory system. In parallel, gastrointestinal diseases have also been shown to be a comorbidity for respiratory disorders. Although the respiratory effects of air pollution and agriculture dust have been well investigated, there is a lack of studies that examine the consequences of inhaled particulate matter from agriculture and CAFO dust on intestinal barrier function and immunity. Further investigation is especially important for minority populations who are generally employed as seasonal farm workers with limited healthcare access. Thus, identifying the mechanistic properties of the interactions seen between both mucosal sites is an important area of exploration and imperative to understanding the physiological consequences of chronic exposure to harmful environmental pollutants while also promoting awareness of the health disparities in minority and immigrant populations.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.S.C. prepared figures; M.S.C. and D.F.M. drafted manuscript; M.S.C., T.M.N., and D.F.M. edited and revised manuscript; M.S.C., T.M.N., and D.F.M. approved final version of manuscript.

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