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Smog induces oxidative stress and microbiota disruption

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ABSTRACT

Smog is created through the interactions between pollutants in the air, fog, and sunlight. Air pollutants, such as carbon monoxide, heavy metals, nitrogen oxides, ozone, sulfur dioxide, volatile organic vapors, and particulate matters, can induce oxidative stress in human directly or indirectly through the formation of reactive oxygen species. The outermost boundary of human skin and mucous layers are covered by a complex network of human-associated microbes. The relation between these microbial communities and their human host are mostly mutualistic. These microbes not only provide nutrients, vitamins, and protection against other pathogens, they also influence human's physical, immunological, nutritional, and mental developments. Elements in smog can induce oxidative stress to these microbes, leading to community collapse. Disruption of these mutualistic microbiota may introduce unexpected health risks, especially among the newborns and young children. Besides reducing the burning of fossil fuels as the ultimate solution of smog formation, advanced methods by using various physical, chemical, and biological means to reduce sulfur and nitrogen contains in fossil fuels could lower smog formation. Additionally, information on microbiota disruption, based on functional genomics, culturomics, and general ecological principles, should be included in the risk assessment of prolonged smog exposure to the health of human populations.

1.   How smog is formed

Smog is an irritating mixture of gasses and particulates in the air formed by smoke and fog under the sun. Formation of smog is directly related to the weather and the topography of the land [1]. Air temperature decreases at about 6.4°C per kilometer in climbing altitude. Under normal conditions, warmer air on the ground rises to the upper atmosphere continuously. This constant air movement spreads pollutants around and thus prevent smog to accumulate on the ground. Sometimes, the temperature gradient is reversed; and the air on top is warmer than the air below it, a phenomenon called temperature inversion [2,3]. Temperature inversion can happen in many ways. When a warm and less dense air mass moves over a cold and dense air mass, or when warm air moves across a cold ground, the air temperatures near the

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ground, the troposphere, can be cooler than the air temperature above it. When an atmospheric inversion layer is closer to the ground, it works like a lid to prevent air upflow that spreads and dilute the pollutants. Temperature inversion explains why wintertime weather often favors smog formation on the ground [4]. The landscape of the land also plays a role in creating temperature inversion. When cold air from mountain peak flows down into valleys, the cold air pushes the warmer air in the valleys upward, creating an inversion. Because of their geographical location (they are built on low basins or valleys), cities such as Los Angeles [5], London [6], Taipei [7], Beijing [8], Tehran [9], and Mexico City [10] are prone to smog accumulation.

Smog can form naturally. Plants emit a plethora of volatile organic compounds (VOCs) as a defensive mechanism against herbivore attack [11]. Upon reaction with the sunlight, VOCs become a major source of ozone (O_3) in the atmosphere [12–14]. Volcano eruption produces airborne ash and gasses with high concentrations of SO_2 and H_2S [15,16], which can contribute to smog formation. Likewise, forest fire also produces a significant amount of smog [17,18]. The 2015 massive fires in Sumatra and Kalimantan in Indonesian Borneo, for example, has produced a persistently hazardous air pollution across downwind Indonesia, Malaysia, and Singapore. It was estimated that the toxic haze from this fire has caused more than 100,000 premature adult deaths in areas closest to the blazes [19]. These pollutants have been related to childhood leukemia [20].

Smog is also anthropogenic. The first and second industrial revolutions have replaced manpower with machines in many production processes. The increase in production of goods and expansion in human population has changed the ways we communicate. The transportation evolution allows massive and rapid transfer of humans and goods. The energy generated from burning coal and other fossil fuels have replaced the traditional source of energy provided by animals. However, coal burning causes the pollution of the air. In 1948, for example, severe industrial air pollution created a deadly smog in Donora, Pennsylvania, which made thousands of people sick [21]. Similarly, in 1952, smog from factories and home fireplaces killed at least 4000 people in London over the course of several days [22–24]. Nowadays, cars, trucks, trains, airplanes, and ships are the major means of transportation on land, air, rivers, canals, and seas. They have become major sources of air pollution [25–31]. Human population expansion also complicates the air quality. Treatment of human wastes, such as incinerators, landfills, and sewage treatment plants, produces various toxic gasses that are air polluting [32–35]. More than 100 toxic gasses are released from landfills [36,37]. Some of them, such as methane and hydrogen sulfide, are most abundant. Others, such as those polyaromatic hydrocarbons and polychlorinated biphenyl released in landfill fires and incinerators, are carcinogenic [38]. Toxins leachates from landfills are a potential pollutant to ground waters [39].

2. Sources of pollutants

It is important to identify where the pollutants are released to the air. Pollutants generated from stationary sources, such as

power plants, industrial and commercial boilers, paper and wood mills, smelters, refinery processing plants, chemical processing plants, and petroleum storage tanks, are considered point-source air pollution. The nonpoint source of air pollution includes some stationary and mobile sources that are individually small, but collectively, they generate a large volume of pollutants. Wood stoves, motor vehicles, ships and boats, and controlled burning of farm wastes by farmers are considered nonpoint sources of air pollution. Since 1972, The U.S. Environmental Protection Agency (EPA) has categorized information of different industrials and compiled them in its so-called AP-42 report [40,41] to regulate the emissions factors of the air of the United States.

The Clean Air Act passed by the U.S. Congress in 1970 and amended in 1990 sets limits on how much of a pollutant is allowed in the air in the United States [42]. The EPA has set national air quality standards for six major air pollutants: carbon monoxide (CO), lead (Pb), nitrogen oxides (NO_x), ozone (O_3), sulfur dioxide (SO_2), and particulate matters (PMs). Whereas CO, Pb, NO_x, and SO_2 are the results of direct emissions from a variety of sources, the formation of PMs is the result of direct emissions and aggregates of emitted gasses in the atmosphere. Most of the fine particle pollutants are aggregated through a complex interaction of VOCs and sunlight. Sunlight also activates the reaction between NO_x and VOCs, leading to the formation of O_3. Because O_3 is not produced directly from emission, O_3 in the troposphere is often referred as secondary pollutant [43].

The EPA refers to chemicals that cause serious health and environmental impacts as air toxics. Many chemicals (total of 187), such as benzene, chloroform, acetaldehyde, dioxin, polycyclic organic matter, chromium, lead, nickel, and mercury compounds, are recognized among the many air toxics. Air toxics can cause cancer and other serious health, including human reproduction, and birth defects. Air toxics also cause adverse environmental and many ecological problems [44].

We briefly introduce the six main air pollutants related to human health.

VOCs are produced from trees, plants, cars, or industrial emissions. VOCs react with nitrogen oxides in the presence of sunlight to form ground-level ozone, a primary ingredient in smog. Many VOCs have been linked to birth defects, cancer, and other serious illnesses [45]. For example, polycyclic aromatic hydrocarbons, a common product of biomass combustion [46], is highly genotoxic [47]. Benzene in the air is strongly correlated to childhood leukemia [20]. The EPA estimates that the air toxics emitted from cars and trucks—which include benzene, acetaldehyde, and 1,3-butadiene—account for half of all cancers caused by air pollution. VOC emissions are tracked by the National Emissions Inventory [48,49].

Nitrogen oxides (NO_x). Nitrogen can combine with oxygen in many forms, such as nitric oxide (NO), nitrogen dioxide (NO_2), and nitrous oxide (N_2O). NO_x is a generic term for NO and NO_2 [50]. While lighting, free-living bacteria and symbiotic nitrogen-fixing bacteria can produce NO_x naturally [51]; combustion of nitrogenous containing compounds, such as the burning of coal, oil, or natural gas, and during processes such as arc welding, electroplating, engraving, and dynamite blasting, can produce NO_x [52]. The toxicity of NO_x has been well studied [53–55]. NO_x not only causes lung irritation and

weaken the body's defenses against respiratory infections such as pneumonia and influenza [56], it is also found to be genotoxic [57].

Carbon monoxide (CO). This odorless, colorless, and poisonous gas is formed by the combustion of carbonaceous compounds such as coal, gasoline, and diesel fuels. CO binds to the hemoglobin of the red blood cell and prevents oxygen transport to various parts of the body. CO also binds to the terminal oxidase of the electron transport chain of the cells in the mitochondria and stops respiration. The major target of CO in humans is the cardiorespiratory system of the human body [58].

Sulfur dioxide (SO_2) is created by coal-burning power plants and diesel fuels from motor vehicles. SO_2 dissolves in the rain and become sulfuric acid (acid rain), which is toxic to plants [59]. Sulfur dioxide can react in the atmosphere to form fine particles and poses the largest health risk to young children and asthmatics. A comprehensive review on SO_2 shows that exposure to relatively high levels of SO_2 resulted in decreased fecundability in humans. Among females, SO_2 interrupts fetal growth resulting in pregnancy loss. Among males, inhalation of SO_2 interrupts male reproductive parameters such as the testicular histology and biochemistry of sperms. SO_2 exposure also induces lipid peroxidation and interferes with the redox status in mouse organs [60].

PM, according to the EPA definition [61], is a complex mixture of extremely small particles and liquids that get into the air. Its sources include carbon dust, sulfates, and nitrates. Once inhaled, these particles can affect the heart and lungs, and cause serious health effects. PM_{10} is defined as particulates, such as dust, pollen, and mold, with a diameter smaller than 10 μm. $PM_{2.5}$ refers to particulates with a diameter smaller than 2.5 μm. The $PM_{2.5}$ particulates are the main cause of reduced visibility (haze) in parts of the United States [61]. Many trucks and ships use diesel engines. The burning of diesel engine is incomplete. Diesel engines running at its peak produce especially high concentrations of $PM_{2.5}$ [62]. $PM_{2.5}$ includes mainly combustion particles and organic compounds (27−40%) [63]. $PM_{2.5}$ particulates also carries a large portion (22−54%) of secondary organic aerosols [63,64] that are formed by complicated photochemical reactions between numerous sulfates, nitrogen oxides, and other inorganic and organic chemicals [65]. Heavy metals in $PM_{2.5}$ (~11−16%) often include Cd, Cr, Cu, Fe, Mn, Ni, As, and Pb [63,66−68]. The accelerated use of silver nanoparticles in many commercial products also raises concerns about the potential toxicity of Ag particles in the environment [69,70]. The sizes of some $PM_{2.5}$ particulates can be very small, close to the range of nanoparticles (<0.1 μm). These nano-sized metals are not just nuisance dust. In fact, these fine particles pose the greatest health risk [69,71−73]. Many of them are bioactive. These particles can attach to the lungs and transport into the bloodstream [74]; some are even found in the human brain [75].

3. Smog in China

As early as the 1970s, China has recognized that the lung cancer rate at Xuanewi City northeastern of Yunnan Province

was almost 5 times higher than that of the rest of the country [76]. The government attributed the mortality to exposure to indoor smoky coal emissions that contain very high levels of polycyclic aromatic hydrocarbons. Since then, the death rate from lung cancer had reached to 31 deaths per 100,000 population in 2004−2005 [77]. China's economic growth requires that massive labor forces concentrate in a few large cities. Industrial growth also consumes a huge amount of fossil fuels. In 2014, Chinese people living in urban areas accounted for about 54% of the total population and is projected to be ~70% by 2030 [63,78]. Air pollution has imposed a serious threat on public health in China. The 2010 Global Burden of Disease Study reported that $PM_{2.5}$ was one of the major public health risks to the Chinese people [77]. Air pollution also caused many social unrests in China [79]. In 2013, the Chinese government announced a plan to invest more than US$277 billion to reduce PM_{10} by 10% of the 2012 level in major Chinese cities. This plan also aimed to reduce $PM_{2.5}$ in the Beijing−Tianjin−Hebei area, Yangtze River Delta, and Pearl River Delta by 25%, 20%, and 15%, respectively. To date, it seems that the 2012 "11th Five-Year Plan" for emission reduction has generally met its goals [80]. The Greenpeace East Asia's 2015 annual city rankings show that $PM_{2.5}$ in 189 cities in China, including Beijing, Guangzhou, and Shenzhen (average, ~77.1 μg/m³), have fallen by 10% compared to the 2014 levels (average ~92.6 μg/m³) and was approaching the 2017 target of 73 μg/m³. However, most of the 366 targeted cities still failed to meet the national standard of air quality [81]. Whether this reduction in air pollutants were related to the slowdown of the world's economy, is still debatable [82].
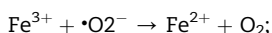
4. Smog and human health

High death rates were observed in areas with elevated ambient pollution levels. It was estimated that more than 2 million premature baby deaths in China and in India are caused by smog [65]. The immediate effect was an increase in pneumonia deaths. The terms "acute respiratory distress syndrome" or "acute lung injury" are often used to describe many pneumonia deaths [74]. Numerous well-studied cases, including diseases of the heart [83], lung [84,85], skin and eye [86], reproduction [87], nervous system [88,89], inflammatory response [90], and cancer [91] are strongly related to smog exposure. Nanoparticles, because of their unique surface properties, may exhibit unexpected toxic biological effects [92,93]. Many heavy metal nanoparticles found in $PM_{2.5}$ can induce reactive oxygen species (ROS) [73]. The mechanism of nanotoxins in inducing apoptosis and cancer via an oxidative route has been thoroughly reviewed by Fu and associates [94]. The human lipoprotein apolipoprotein E is produced by the liver and white blood cells, and by astrocytes in the brain. A recent study suggests that interaction of $PM_{2.5}$ in the air and apolipoprotein E may cause brain aging and accelerates the development of Alzheimer's disease [89]. Oxidative stress has been identified as a unifying feature underlying the toxic actions of smog [47,88,95−103]. This conclusion should not be surprising, because O_3, VOCs, and the nanometal particles in smog can all induce free radicals [43,103−105]. Belyaeva and associates [106] proposed that the electron transport chain of
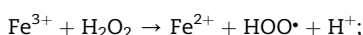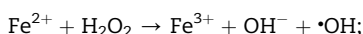
the mitochondria is the prime target for heavy metal-induced neurotoxicity.

5.   Smog induced oxidative stress

During respiration, foods are oxidized and the electrons in foodstuffs ultimately combine with molecular oxygen, producing water. Many reactive by-products of respiration, such as superoxide anion radicals, hydrogen peroxide (H_2O_2), and hydroxyl radicals (HO), are produced continuously in aerobically growing cells [107] through the Haber−Weiss reaction catalyzed by metals:

$$Fe^{3+} + \cdot O2^- \rightarrow Fe^{2+} + O_2;$$

The reaction is followed by the Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH;$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HOO\cdot + H^+;$$

The free radicals generated from the above processes rapidly take part in other secondary reactions. Free radicals can cause oxidative damage to the cell via covalent bonds modification of DNA, proteins, lipids, and other biomolecules (Figure 1). Additionally, covalent binding to an unsaturated lipid can induce lipid peroxidation. Lipid peroxidation is a chain reaction (propagation). The end products of lipid peroxidation are more reactive aldehydes, lipid radical, and other reactive products. If lipid peroxidation is not terminated, the reaction not only damages a single cell—free radical propagation will affect the cells surrounding the propagation site. Arachidonic acid, a polyunsaturated fatty acid, is abundant in the brain, muscles, and liver [108]. This fatty acid is most sensitive to lipid peroxidation and has played an important role in inflammation [109]. The end products of lipid

Figure 1 − Cytotoxic and genotoxic mechanisms induced by PM$_{2.5}$ via reactive oxidative species (ROS) in human cells. PM = particulate matter.

peroxidation, such as malondialdehyde, are mutagenic and carcinogenic [110]. The thiol groups of a protein are very sensitive to peroxidation. Protein damage by free radicals can induce cell death [111]. Peroxidation also causes DNA damage and formation of various DNA adducts [112,113].

6.   Human microbiota and health

Microbes are found everywhere. Humans and microbes have evolved together for millions of years. Humans harbor 10 times more microbes inside or on their bodies than the total number of their somatic and germ cells. It has been known for decades that the human microbiota contribute many vital compounds and vitamins to humans [114]. The Human Microbiome Project [115,116] is a summation of projects launched in multiple areas of the world, including the United States, European Union, and Asia [116]. Results from the Human Microbiome Project studies show that we have greatly underestimated the diversity, prevalence, and persistence of the bacteria in our body, partly because more than 99% of the bacteria, the so-call biological "dark matter," cannot be cultured in the laboratory for detailed studies [117]. New methods that use the polymerase chain reaction approach to detect bacteria by their DNA or RNA sequences have allowed microbiologists to evaluate those otherwise unculturable bacteria in or on our body. Results from metagenomic studies show persistent and proliferate bacterial ecosystems in or on various parts of the human body. Gao et al [118] studied the microbiota of the forearms of some healthy individuals over a period of 10 months and described the bacteria as a "virtual zoo." Bjorksten [119] equated the bacteria in the human gut to a "forest" with more than 40,000 different bacterial species. Bacteria in or on different parts of our body form their own complex and yet distinctive communities. The oral microflora, for example, is rich in *Staphylococci, Propionibacteria, Streptococci, Enterococci, Pseudomonas*, and *Lactobacilli*, whereas the gut microflora is rich in *Lactococci, Lactobacilli, Bifidobacteria, Enterococci, Enterobacteriaceae, Clostridium*, and *Hellobacteira* [116,120]. The traditional concept of microbes as pathogens or innocuous commensals is mostly disputed. More advanced studies found that microbes are not just living on or in our body, they are actively engaged, or sometimes directly influence many of our physiological events. Microbes in or on our body form a complex mutualistic relation with us. For examples, the microbiota of the lung enable the expansion of the virus-specific CD8 memory T lymphocyte [121]. During gestation, the mother's microbes can influence her offspring's immune system [122]. On the human skin, the potential pathogen, *Staphylococcus epidermidis*, can be beneficial by producing antimicrobial peptide (bacteriocins) and pheromone that inhibits other bacterial cell−cell communications, and activates the innate immune response of keratinocytes of the skin [123]. The gut microbiota can influence the outcomes of gallstones [124], obesity [125], colonic inflammation [126], and even the behavior of autism patients [127]. Compounds such as beta-methyl-D-galactoside and N-acetyl-D-mannosamine produced by some oral bacteria can be used as prebiotics to stimulate beneficial bacteria in the oral cavity and prevent tooth decay [128]. Microbes in the oral cavity of newborn
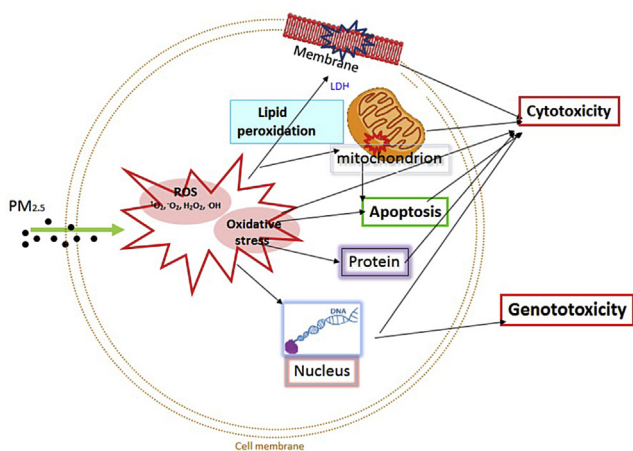
babies induce the expression of the Growth-Arrest-Specific-Protein-6 (GAS6) in oral tissues; GAS6, in turn, regulates the antibacterial function of the oral cavity [129]. Some authors even suggested that the adaptive immunity may have been evolved in vertebrates because of the need to interact with the beneficial bacterial communities [130]. All these findings suggest that human and its human-associated microbiota are inseparable. Gill et al [120] consider the human body as a "superorganism" with distinctive contributions from both microbes and the human host. The diversity of microbiota in humans fluctuates considerably, especially during disease and in young children [131,132]. Knowledge on the part of bacterial physiology, therefore, is important to appreciate human as a superorganism.

7. Bioenergetic and ROS formation in bacteria

Bacteria must respond to their environment rapidly and effectively. The forms of nutrients provided to bacteria may differ from time to time. A bacterium must be able to adjust its trophic modes to satisfy its needs for carbon and energy [133–136]. However, the amount of carbons and energy in food sources are not necessarily the same [134,135,137]. Fermentation is a simple way for a bacterium to balance its redox by removing its surplus carbons (in forms such as lactic acid or alcohol) and to regenerate its oxidative capacity (NAD and FAD). When NADH is in surplus, some bacteria can regenerate its NAD via the formation of hydrogen gas [126]. Another way to regenerate the NAD is through the electron transport chain. The electron transport chains in bacteria are branched [133,138–141]. The electrons from various reductants (such as hydrogen gas [142], NADH, malate, and succinate [138,143]) are regulated by an energy-conserving electron transport pathway and by an energy-uncoupled pathway (Figure 2) [144]. Disruption of cellular metabolism, or uncoupling the electron transport chain, would likely interrupt the regulation of electron flow. Excessive electron flow through the uncoupled pathway could induce a futile cycle, leading to increases in ROS formation, and induce oxidative stress (Figure 3). All bactericidal antibiotics are known to induce cell death such as oxidative stress [145,146]. Lipid peroxidation [147,148], heavy metals (e.g., Cr, As, Hg) [106], and O_3 from smog can uncouple the electron transport chain readily, leading to bacterial mutation and death [45,149–152].

8. Perspective

Humans evolved with microbes for millions of years. These human-associated microbes have developed many remarkable strategies to sustain their alliances with each other and with us. Their physical locations on the epithelium also make them the first to be exposed to the harmful elements in smog. Chronic exposure to smog would undoubtedly disrupt the equilibrium of the microbial communities in the human body. How changes in the microbiota would affect the human health, especially among newborns and children, is unclear. Our understanding of human-associated microbiota is still in
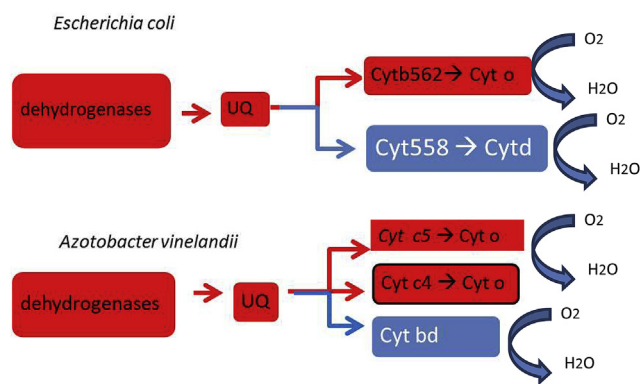

Figure 2 – Diagram of the electron transport chain of *Escherichia coli* and *Azotobacter vinelandii* with special reference to the energy-coupled (red) pathways and the energy-uncoupled (blue) pathways. Reductants such as NADH, succinate, and malate are oxidized by the dehydrogenases. Electrons from the dehydrogenase are transferred to the ubiquinone (UQ), which subsequently transfer the electrons to the cytochromes (cyt). There are two electron transport pathways, the energy-conserving pathway is coupled to a proton pump (red), whereas the energy-wasting pathway (blue) is not coupled to proton translocation. The diagram is compiled from published data [133,139,141,142]. Free radicals can generate via the Haber–Weiss reaction when electrons are passing the electron transport chain.
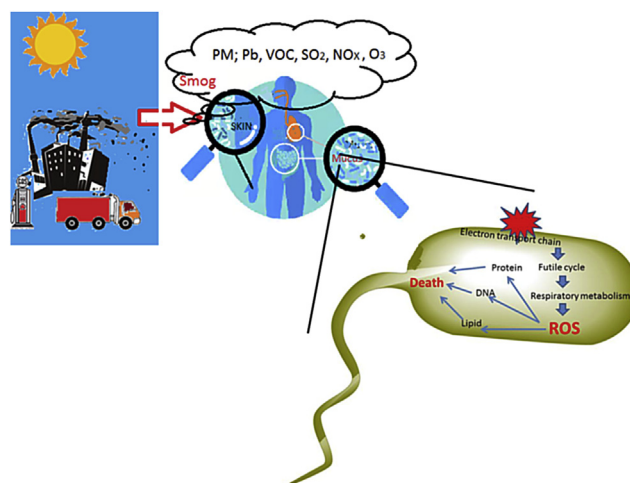

Figure 3 – Sunlight activates the pollutants in the air and fog, causing the formation of smog. Bacteria on the surface of our skin and mucus are the first to encounter the harmful elements in smog. These elements could uncouple the electron transport chain of the bacterium and induce ROS formation, which subsequently damage protein, DNA and lipid, leading to cell death. ROS = reactive oxygen species; PM = particulate matter.

its infancy. Most of the available data are structural— they describe the species diversity, richness, and evenness of the community based on sequence homologies. Metagenomics data do not provide meaningful information on metabolic

capacities of these microbes, partly because only about 1% of the bacteria are culturable, and partly because a large number of genes have no known function [153]. How the inner working of the human and human-associated microbiota is less clear [154,155]. Functional genomics involves the use of various "omics" to predict the physiological dynamics of a biological system [156]. Research in functional genomics of human-associated microbiota should provide a better interpretation of diseases caused by smog. Culturomics [157–160], a new approach that uses high-throughput culture techniques and matrix-assisted laser desorption/ionization-time of flight mass spectrometry to grow and identify bacteria, should provide a more meaningful interpretation of microbiota successions and these biological dark matters. Although the consequence of smog-induced microbiota changes in human health is far from clear, general ecological principles should help to predict the consequences of population shifts in microbiota. Like a forest, ecological studies suggest that plants, animals, and the environment are interrelated. Species diversity is indicative of the healthiness of the forest; environmental changes can unbalance the equilibrium of the biocommunity, leading to the collapse of the ecosystem [153,161]. The successes in fecal transplant [162,163] show that it is possible to replace a collapsed microbial community. This implies that other forms of activity, such as exercise, diet, and a change in lifestyle, may alter the epithelium microbiota to prevent or mediate the harmful effects of pollution-induced changes in microbiota. Microbial succession can occur rapidly or gradually. The long-term effects of smog to the regime change of the human-associated microbes remain to be studied.

Obviously, reduction of fossil-fuel burning is the ultimate method to reduce smog formation. However, this goal is unlikely archived in countries with less economic wealth. Coal cleaning is a process by which impurities such as sulfur, ash, and rock are removed from coal prior to burning. Currently, both physical and chemical processes are available. Physical coal cleaning processes, the mechanical separation of coal from its contaminants using differences in density, are by far the major processes in use today [164,165]. Physical cleaning of coal is essentially based on the differences in either specific gravity or surface properties between the organic matter and the associated minerals, although a few separations that are conducted on the basis of their magnetic and electrostatic properties have been proposed. Chemical methods of cleaning coal [166], such as using molten caustic leaching, have been shown to remove more than 90% of the sulfur and ash from coal. The SNOX process is a very energy-efficient way to convert NO_x in the flue gas into nitrogen and SO_x into concentrated sulfuric acid of commercial quality without using any absorbents and without producing waste products or wastewater [167]. The SNOX technology is especially suitable for cleaning flue gasses from combustion of high-sulfur fuels in refineries. Biodesulfurization in fossil fuels [168] is an ideal alternative to remove sulfur in petroleum products. Many bacteria, both natural [169,170] and genetically altered [171], have shown promising results to remove SO_x and NO_x from fuels. However, the speed of bioconversion is still too slow to fulfill the industrial requirements. The remediation process could increase at the higher temperature. Some

bacteria, called thermophiles (optimal temperature ~70°C) and extreme thermophiles (optimal temperature above 100°C), can grow at high temperatures. More research is needed to isolate suitable strains to release sulfur and nitrogen from fossil fuels.

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