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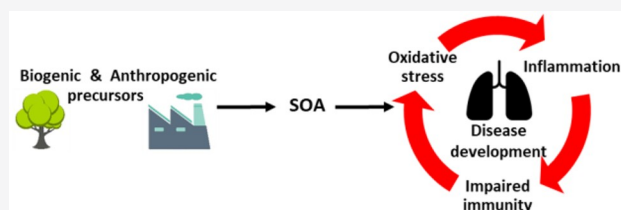
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Pathogenic Mechanisms of Secondary Organic Aerosols

Tanguy Déméautis, Marie Delles, Sophie Tomaz, Guillaume Monneret, Olivier Glehen, Gilles Devouassoux, Christian George, and Abderrazzak Bentaher*

ABSTRACT: Air pollution represents a major health problem and an economic burden. In recent years, advances in air pollution research has allowed particle fractionation and identification of secondary organic aerosol (SOA). SOA is formed from either biogenic or anthropogenic emissions, through a mass transfer from the gaseous mass to the particulate phase in the atmosphere. They can have deleterious impact on health and the mortality of individuals with chronic inflammatory diseases. The pleiotropic effects of SOA

could involve different and interconnected pathogenic mechanisms ranging from oxidative stress, inflammation, and immune system dysfunction. The purpose of this review is to present recent findings about SOA pathogenic roles and potential underlying mechanisms focusing on the lungs; the latter being the primary exposed organ to atmospheric pollutants.



1. INTRODUCTION

Air pollution represents a major health risk causing several million deaths worldwide,¹ not to mention the wide spectrum of associated chronic pathologies. Of note, nine out of 10 people breathe polluted air. Given such health impact and its associated economic burden,¹⁻⁴ a series of research studies have been developed with the aim to decipher the composition of our atmospheric air by identifying its constituents, their origin and potential impact on health. Accordingly, particulate matter (PM) emerged as an important component in terms of their predominance and health impact. Significantly, much interest has focused on fine particulate matter of $<2.5 \mu\text{m}$ in diameter (PM_{2.5}) as they seem to exhibit serious deleterious health effects. Indeed, a number of studies revealed a significant correlation between PM_{2.5} and mortality rate following either short⁵ or long exposure time.⁶⁻⁸

PM consists of a mixture of organic and inorganic components. Traditionally, they are classified according to their diameter, for instance, PM_{2.5} corresponds to particles with a diameter lower than $2.5 \mu\text{m}$ and are also called fine particles. Although, this classification is informative, it does not take into account the origin, composition, or the physicochemical properties of the particles. Nowadays, with technical and technological improvement, detailed information could be gathered about PM resulting in better categorization of particles. PM can be “primary PM” derived directly from the source of emission or “secondary PM” corresponding to a transfer of material from the gas phase to the particulate phase while reacting with other components in the atmosphere.

Organic aerosol (OA) represents a significant and variable part of PM_{2.5}.⁹⁻¹² OA can be primary or secondary (SOA), the latter being the product of multiple and complex gas- and

condensed-phase oxidation steps and vapor condensation¹³ of volatile (VOC) and semivolatile organic compounds (SVOC), coming from anthropogenic and biogenic sources. Investigation of SOA is challenging because their formation and relative importance within PM are not fully understood, as they are location and environmental conditions dependent. Of note, the contribution of OA is estimated between 20 and 90% to the total aerosol mass^{10,14-18} throughout the world. Of importance, it has been also reported that SOA represents approximately up to 80% of OA.⁹ As such and with the nonstop increase of particle emissions in the atmosphere, the awareness of SOA harmful impact on health becomes of interest and makes these types of particles a target for characterization and studies of action mechanisms. However, full characterization of SOA awaits further studies, and limited studies have addressed their deleterious effects. The purpose of this review is to present recent findings about SOA and their pathogenic roles on the lungs, the latter being the primary exposed organ to atmospheric pollutants. Also, our attempt is to speculate on potential SOA-mediated mechanisms of host inflammation and tissues injury.

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2. SOA: SOURCES AND CHARACTERIZATION

2.1. SOA Characterization. As alluded to earlier, SOA could raise from biogenic or anthropogenic emissions. In contrast to primary particles, SOA are formed in the air through a mass transfer from the gaseous mass to the particulate phase which can take place through multiple and complex reactions in the gas phase, aqueous phase, or multiphase, contributing to the SOA mass.¹⁹ These processes involve numerous reactions of multiple organic species. Indeed, SOA formation takes place in the atmosphere originating from a myriad of precursors, oxidants, and conditions, resulting in a complex mixture of organic species with different composition and properties.²⁰ Parameters such as relative humidity,^{21,22} temperature,^{23–25} solar radiation,²⁶ and time extent¹⁹ are very important in the formation of SOA. Moreover, as biogenic emissions represent a major part of SOA production, there is also a seasonal cycle that corresponds to the life cycle of plants,^{27,28} hence affecting more biogenic than anthropogenic sources. To help understand the mechanisms implicated in SOA formation, environmental chambers are used to replicate SOA that are derived from either a specific precursor, a complex mixture of precursors, or a selected source of emission. These chamber studies also allow to control for oxidants that are present as well as their concentrations.²⁹ Other parameters such as UV radiation, humidity, and temperature are purposely controlled, allowing for more realistic atmospheric mechanisms that lead to SOA but result in a high complexity of data collected. Noteworthy, analysis and modeling tools are constantly improving in this research field such as the new EESI-Orbitrap system.³⁰ Indeed, a better understanding of SOA formation and composition is necessary to apprehend their effects on health and provide useful information for efficient sanitary measures.

2.2. Biogenic SOA. Biogenic SOA precursors come from natural sources like plants, a major source of VOC.¹³ These natural sources emit about 1700 substances.³¹ Their

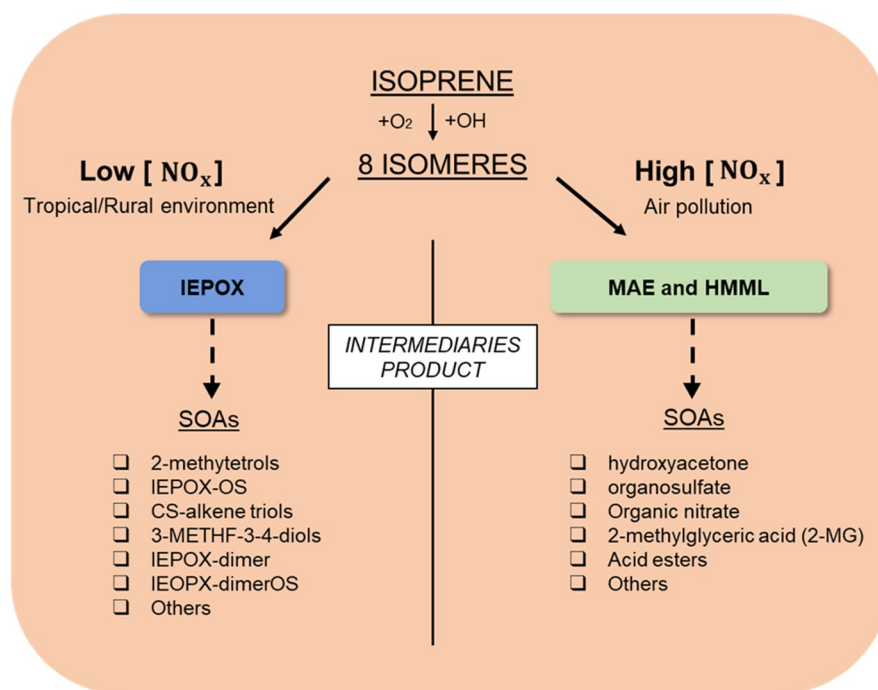


Figure 1. SOA formation from isoprene oxidation. Three main intermediate components following isoprene oxidation: IEPOX, MAE, and HMML and their ensuing SOAs.

contribution to local VOC concentration is contingent to the geographic environment (e.g., 10% in an industrialized city, up to 90% in central Amazonia)^{32,33} and its conditions, namely seasons. There are two types of plant-derived emissions: constitutive emission regulated by environmental conditions (e.g., sunlight, temperature, nutrition) and emission induced by stress. VOC are commonly used by plants for communication and stress response.^{34–37} Each plant will release a different “blend” of VOC according to the species and the environmental conditions, generating a mixture of primary VOC. These VOC are exposed to various oxidants and undergo transformation that leads to SOA production. Moreover, the ocean can also be source of SOA through VOC emission from phytoplankton and marine biota.^{38,39} Half of the total emission of biogenic VOC is estimated to be volatile terpenes.⁴⁰ For simplicity reasons, we will focus on terpene as representative of biogenic SOA (bSOA). Degradation products from terpene, like isoprene (2-methyl-1,3-butadiene, C₅H₈) with a global annual emission estimated at 600 Tg (1012 g), represent one-third of the VOC emissions⁴¹ and have a major role in SOA production.^{42,43} Isoprene is highly reactive due to its double carbon bond and is oxidizable in the atmosphere by hydroxyl, nitrate radical, and ozone.⁴⁴ Three main intermediates of isoprene-derived SOA are known: isoprene epoxydiols (IEPOX) mostly under low nitrogen oxide (NO_x) concentration,^{45–47} methacrylic acid epoxide (MAE),⁴⁸ and hydroxymethyl-methyl-lactone (HMML)^{49,50} under high NO_x concentration (Figure 1). Of interest, these same intermediates can have various isomeric structures that could potentially induce different health effects⁵¹ (Figure 1).

2.3. Anthropogenic SOA. Anthropogenic SOA (aSOA) come from precursors emitted by human activity and are transformed in the atmosphere through multiple reactions. At the global scale, the production of aSOA is estimated to be significantly smaller than bSOA.^{52–54} Known aSOA precursors are numerous and include toluene, xylene, naphthalene,

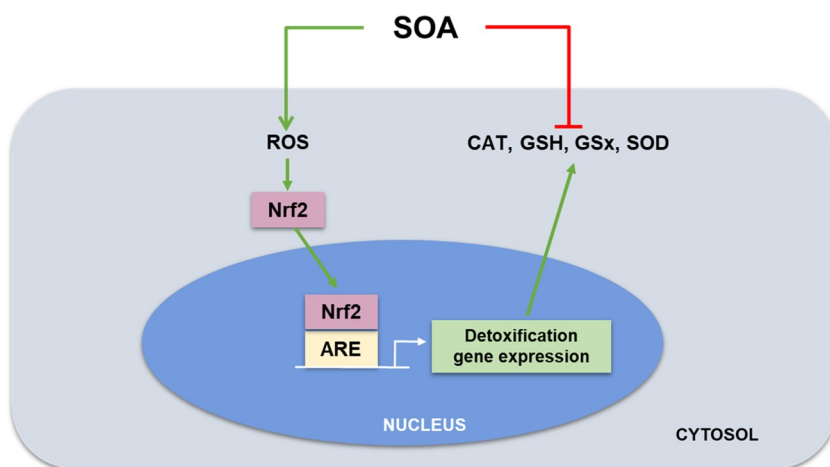


Figure 2. SOA-mediated double-edged effect. In SOA-induced oxidative stress conditions, Nrf2 translocates to the nucleus where it initiates the transcription of phase II detoxification enzymes, while at the same time, SOA inhibits antioxidant proteins activity.^{99,101,105,115,126,139}

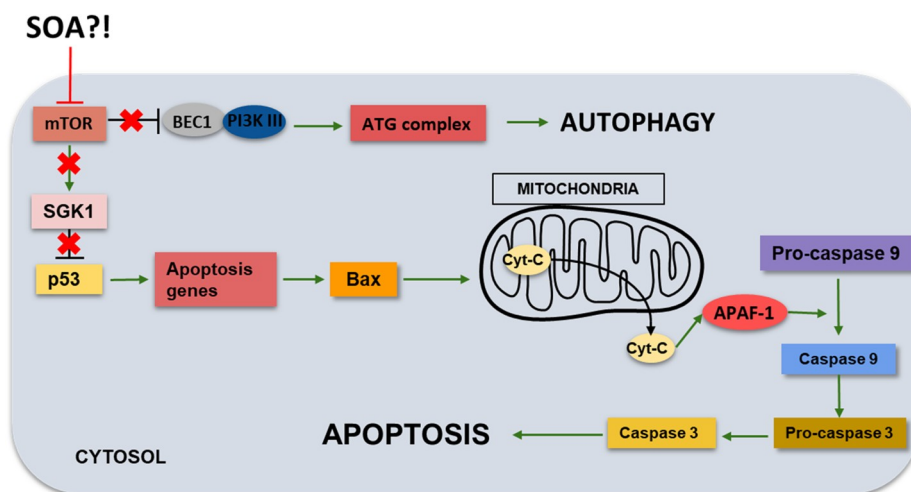


Figure 3. Possible SOA-mediated pathogenic mechanisms. SOA could trigger apoptosis and autophagy through mTOR inhibition resulting in a lack of SGK1 active form and thus a decrease of p53 inhibition. This increase in p53 protein^{112,126} will result in apoptosis genes transcription and survival genes inhibition. At the same time, mTOR inhibition causes a decrease of Beclin 1 inhibition resulting in ATG complex formation and autophagy.

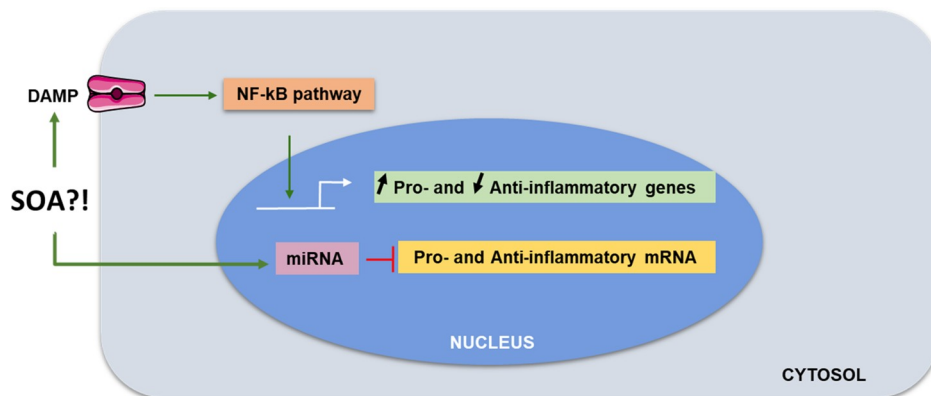


Figure 4. Examples of possible mechanism of SOA-mediated induction of inflammation. SOA could target DAMPs, thereby inducing pathways involving NF-κB and resulting in an increased production of pro-inflammatory cytokines. At the same, SOA might alter miRNA expression, impacting differential expression of a series inflammatory mediators.

benzene-derived molecules, and long-chain alkanes.^{55–58} As an example, an important SOA formation occurs after cold start^{59–61} and fuel exhaust. It can result from a too low catalyst

temperature, which induces a partial oxidation leaving it available for atmospheric oxidants.⁶² Like bSOA, aSOA formation is also regulated through NO_x concentration,

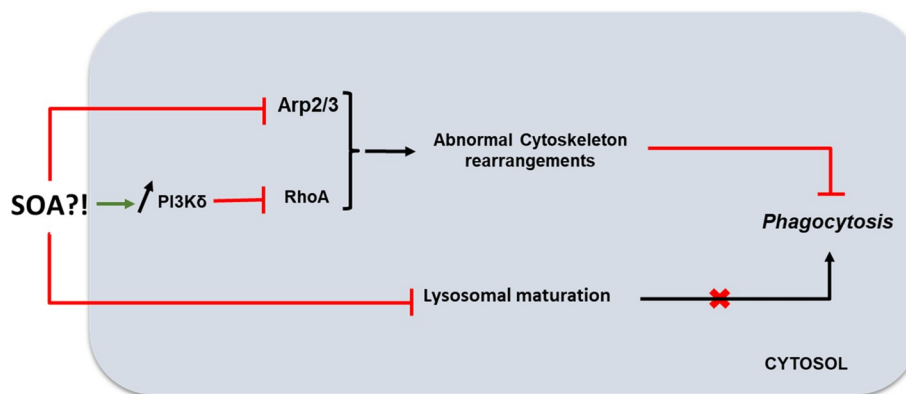


Figure 5. Possible SOA-mediated phagocytosis impairment. Impaired phagocytosis in cells exposed to SOA potentially induced by cytoskeleton disturbance or phagolysosome inhibition.

temperature, and relative humidity.⁶³ Importantly, aSOA can interact with bSOA which can enhance bSOA formation^{64,65} or suppress it.⁶⁶ This interaction between aSOA and bSOA could further complicate the prediction and analysis of SOA formation.

2.4. Tools and Models for SOA Analysis. The chemical characterization and quantification of SOA is challenging, requiring multiple analysis tools used individually and/or sequentially. These challenges have been recently reviewed.⁶⁷ Gas and liquid chromatography (CG or LC) associated with mass spectrometry (MS) are often used for the detection and molecular analysis of SOA. However, there are some limitations including separation of individuals entities and lack of standards.¹³ In recent years, sophisticated devices have been developed to overcome these concerns and can be identified as off-line and online tools. Off-line analysis requires SOA collection and separation (e.g., filters or cascades impactors), implicating a discontinuous analysis. Online analysis, on the other hand, gives time-resolved results but very often with reduced chemical resolution.⁶⁸ Significantly, high-resolution mass spectrometers, either long time-of-flights or Orbitrap MS, are currently deployed, thus opening new directions for simultaneous time-resolved and chemical species detection.³⁰

The modeling approach is important as well. It allows to simulate the formation and composition of SOA from a specific precursor or a set of precursors under known environmental conditions. It can also be used to predict their spreading in the atmosphere and concentrations in our daily environment.^{69,70}

3. PATHOGENIC IMPACT OF SOA

3.1. Epidemiology. Exposure to fine PM is associated with morbidity and mortality that is exemplified by a wide range of reported clinical manifestations. In fact, exposure of the lungs, first organs being targeted, to PM has been shown to be associated with airspace damages⁷¹ and alterations of lung function,⁷² resulting in a number of chronic pulmonary diseases^{73,74} such as chronic obstructive pulmonary disease (COPD).^{75,76} According to their sizes, PM “sit” in either bronchi or alveolar spaces where they could be internalized by local cells.^{77–79} PM_{2.5} have also the capacity to cross the alveolar–capillary barrier^{80–82} and reach other organs, contributing to the development of other pathologies like cardiovascular diseases, diabetes, or birth defects.

Few epidemiological studies have looked at the specific effects of SOA on health. However, a recent study by Pye et al.⁸³ reported a link between SOA exposure and cardiorespiratory-associated death rates in the U.S. It was shown that SOA were strongly associated with death rates independent of the total PM_{2.5} mass. Significantly, the study provided evidence that either per capita or per mass basis SOA had a higher rate of mortality by comparison to PM_{2.5}. Whether these observations could be extrapolated to other diseases and/or worldwide merits further studies.

If we bear in mind the above study and the fact that SOA are part of PM_{2.5}, we could infer that their effect on health could resemble the reported observations about the latter. Also, the observed clinical manifestations could be attributed to a number of mechanisms that alter host homeostasis. Below is a series of pathogenic pathways that could be potentially mediated by SOA, which await further investigations.

3.2. Imbalance of the Oxidative Homeostasis. A basal level of reactive oxygen species (ROS) is required for several physiological functions.^{84,85} However, an abnormal intracellular concentration of ROS might trigger cell structure damage and/or cell death.^{86–88}

Interestingly, one of the most reported mechanisms triggered by SOA is the induction of oxidative stress. There are multiple mechanisms, either endogenous or exogenous, that are involved in this imbalance of oxidative homeostasis. For example, one of the main mechanism concerns particle-bound ROS.⁸⁹ SOA may contain ROS or constituents that will react with thiols of host molecules and have a direct effect by increasing the level of exogen ROS like H₂O₂,⁹⁰ mainly from anthropogenic sources.^{91–93} Some organic compounds can produce oxygen species through redox and Fenton reactions.⁹⁴

According to few studies using a chemical assay to fast measure the oxidative properties of a compound, namely the oxidative potential (OP), bSOA might exhibit lower OP than aSOA.^{93,95,96} This could result from potential differences in their respective compositions (e.g., less quinone and metals in bSOA than in aSOA, known actors in PM_{2.5}-derived OP).⁹⁷ Alveolar macrophage (AM) exposed to aSOA had a greater oxidative response than AM exposed to bSOA.⁹⁸ Quite puzzling, other studies reported that the same response could be found in cells exposed to bSOA (α -pinene-derived SOA) and aSOA (naphthalene-derived SOA).⁹⁹ These discrepancies testify that the chemical compositions of both aSOA and bSOA are not completely established. Another

factor that merits careful attention is the structure of precursors. For example, the presence or absence of aromatic structures impacts OP of generated SOA.⁹⁶ It is worth mentioning a series of reported findings. Isoprene-derived SOA in highly polluted air, as judged by high NO_x level, presented higher OP.¹⁰⁰ Parallel studies confirmed a stronger oxidative stress in epithelial cells (BEAS-2B) exposed to MAE-derived SOA than IEPOX-derived SOA,¹⁰¹ which are both intermediates of isoprene-derived SOA (cf, biogenic SOA). MAE-derived SOA are mainly formed in air polluted, and IEPOX-derived SOA are more present in rural environment. These observations point to the importance of air pollution on SOA genesis and its ensuing impact on host ROS production. Finally, it must be noted that the impact of SOA aging on oxidative stress is still unclear. Chowdhury et al. has reported increased oxidative stress responses and toxicity in cells exposed to aged aSOA compared to fresh aSOA^{99,102} which could be explained by the higher carbon oxidation state found in aged aerosol.¹⁰³ Recently, Offer et al. corroborated this observation in an Air–Liquid Interface system.¹⁰⁴ Meanwhile Han et al. observed a stronger proteome-wide impact in cells exposed to fresh aSOA than aged aSOA,¹⁰⁵ and Fushimi et al. reported a weaker toxic potential from aged naphthalene-derived SOA.¹⁰⁶ These contradictory observations could be explained by differences in their experimental conditions (e.g., different conditions of SOA formation, A549 vs BEAS-2B cells, transcriptomic vs proteomic studies). This dilemma awaits further studies. Last but not least, if we admit that SOA is a major part of PM_{2.5},^{9–12,14–18} it might increase ROS production and oxidative stress via myeloperoxidase as does PM_{2.5} too, in vitro and in vivo.^{107–111}

Such SOA-mediated increase of oxidative stress could have a “double edged effect”. Regarding the physiopathologic role, SOA-mediated increase of ROS contributes to cell toxicity and damage.^{102–104,112–116} Of note, same observation has been made with PM_{2.5}^{117–122} suggesting that PM_{2.5} and SOA share common oxidative pathways.

As mentioned above, PM- or SOA-mediated oxidative stress causes multiple adverse effects at cellular and tissue levels. These concern nucleic acid, proteins, and lipids. They both have the capacity to inhibit the activity of the antioxidant proteins such as catalase, glutathione, glutathione peroxidase, and superoxide dismutase (SOD).^{117,123–126} Mechanistically, among the involved signaling pathways are activation of mitogen-activated protein kinases and proinflammatory cytokines,¹²⁷ triggering of apoptosis activating factor (APAF-1) and interaction with cytochrome *c*, all of which will lead to apoptosome activation and cell death.^{126,128–130} At the protein level, ROS can also interact with amino acid residues and oxidize, for instance, cysteine that form disulfide bridge leading to loss of protein conformation hence its function(s).¹³¹ Moreover, unchecked superoxide can interact with NO forming peroxynitrite,¹³² known to impact DNA structure, protein conformation and function,¹³³ and mitochondria which in turn release mitochondria-free radicals in the cytosol.¹³⁴ With respect to the “physiologic” role of SOA, it has been reported that the latter can induce the activation of the antioxidative system. For example, increase of Heme Oxygenase 1 mRNA expression, which has a protective role against oxidative stress, was observed in mice exposed to aSOA (Diesel engine exhaust-derived SOA).¹³⁵

Another interesting example to illustrate SOA-inducing role of oxidative stress and biological consequences is the nuclear

factor erythroid-2-related factor 2 (Nrf2). Nrf2 is a key transcription factor for antioxidant systems and inflammation. In physiological conditions, Cullin3, Keap1, and Nrf2 form a complex in the cytosol, and Cullin 3 degrades Nrf2 through ubiquitination and proteasome pathway.^{136–138} However, under oxidative stress conditions, Keap1 releases Nrf2 that translocates in the nucleus, on the antioxidant responsive element and activates transcription of target genes (Figure 2). Cell exposure to aSOA (naphthalene, *m*-xylene, and TMB-derived SOA) and bSOA (isoprene and α -pinene-derived SOA) has been reported to correlate with genomic and protein upregulation of Nrf2 pathway, for example, *HMOX1* and *NQO1*.^{99,101,102,105,115,139}

However, these observations must be taken with caution as the chronic exposure to SOA and aberrant or prolonged antioxidant activity may have an adverse effect on the host in the long run.^{140,141} Indeed, the sustained Nrf2 activation might develop “Nrf2 addiction” phenomenon,¹⁴⁰ resulting in metabolic changes that contribute to disease initiation and/or progression via reductive stress as it has been reported in chronic diseases of organs other than lungs.¹⁴¹ Therefore, further studies are required to investigate the underlying signaling mechanism of chronic exposure to SOA.

3.3. Cell Toxicity. A series of cell culture studies reported the capacity of SOA to induce cell toxicity.^{99,105,112,139,142,143,143} Moreover, it has also been reported that SOA have the capacity to alter transcriptomic profiles of lungs cells (e.g., upregulation of tumor protein 53 (p53) signaling pathway).^{112,126} The latter, known as the guardian of the genome, regulates various processes in response to stress detection. Indeed, p53-targeted genes can induce cell cycle arrest, apoptosis, or autophagy in a dependent manner of SOA. Another study reported increased RNA oxidation in cells exposed to SOA resulting in transcript alteration and cell function disruption.¹⁴⁴ Some molecules namely cinnamic acid, hydroxybenzoic acid, and 1,4-naphthaquinone were found in SOA,^{145–151} and they or their derivatives have been reported to induce apoptosis and autophagy in multiples cancer cells lines.^{152–158}

Other potential SOA-mediated mechanisms could be envisioned if we reason that SOA are part of PM. It has been demonstrated that PM, especially PM_{2.5}, have the capacity to reduce cell proliferation^{159,160} through cell cycle arrest in different types of cells.^{119,121,159,161–163} PM are also known to induce apoptosis and autophagy.^{117,164–166} Interestingly, a crosstalk between the latter has been documented,^{167,168} and both can be explained by PM_{2.5} implication concerning a decrease of mRNA and protein level of mammalian target of rapamycin (mTOR).^{169–172} Quite relevant, PM_{2.5}-induced apoptosis was found to be mediated by an increase of known apoptotic factors like p53 and a decrease of its inhibitor, SGK1 usually activated by mTOR, resulting in a cascade of different steps and involving a series of molecules such as Bax, cytochrome *c*, APAF-1, and caspases (Figure 3).^{173–177} Of course, additional studies are required in order to determine the relevance of these speculations.

3.4. Inflammation. Inflammation is a physiologic mechanism in response to insulting agents, which becomes pathogenic following uncontrolled conditions as seen in many respiratory disorders.

Because of its capacity to induce oxidative stress, SOA could target directly or indirectly the host biomolecules, damage-

associated molecular patterns (DAMPs), to initiate and/or perpetuate a noninfectious inflammatory response (Figure 4). Different DAMPs have been reported depending on the injured tissue and type of cells (e.g., epithelial cells). Two relevant DAMPs related to lungs that could be targeted by SOA are the high-mobility group box 1 (HMGB1) and heat shock protein 70 (Hsp70).^{109,178} Both Hsp70 and HMGB1 can lead to airway injury in stressed conditions.¹⁷⁹ They induce inflammation through mechanisms involving cell receptors (toll-like receptors, CDs), NF- κ B pathway, production of pro-inflammatory cytokines (e.g., IL-1, TNF- α , IL-6, IL-8),^{180–182} and increased expression of cell adhesion molecules (e.g., ICAM-1, VCAM-1).¹⁸³ It must be emphasized that the initiation, progression, and severity of inflammatory response are contingent of the type of SOA (anthropogenic versus biogenic) and the conditions of its production. Tumor necrosis factor alpha (TNF α) increases in rodents exposed to aSOA^{184,185} and bSOA.¹³⁵ In a separate study, an increase of TNF α was observed in cells exposed to aSOA from naphthalene but not in bSOA.¹⁸⁶ These discrepant observations stem from the nature of the precursor employed in the studies (limonene versus isoprene/ α -pinene/ β -caryophyllene) as well as the experimental conditions (rodents model versus cell culture systems). Another aspect of SOA-mediated inflammation which merits attention is the capacity of SOA to induce the expression of pro-inflammatory mediators while attenuating the anti-inflammatory mediators' expression. For example, an increase of neutrophil chemotactic factor IL-8 gene expression was reported in epithelial cells exposed to SOA from anthropogenic or biogenic sources.^{99,139,187} A downregulation of IL-4 and IL-13 was reported in epithelial cells exposed to SOA,¹¹² which are two mediators that inhibit neutrophil infiltration and accumulation.¹⁸⁸ Consequently, these opposing effects would lead to an accumulation of neutrophils in lung airways. Accumulation of these events will likely exacerbate lung inflammation and injury in diseases such as asthma, COPD, and fibrosis.^{189–193} Thus, SOA may trigger and/or worsen pulmonary diseases. Furthermore, the increased concentrations of pro-inflammatory cytokines for a prolonged time period could result in a systemic inflammation as reported in humans^{76,194} and animals,^{195,196} causing adverse effects on other organs like the cardiovascular system.¹⁹⁷ So, SOA not only can induce lung inflammation and tissue injury but could also impact other organs. However, SOA-induced inflammation is not that simple, as few studies reported a lack of inflammatory cell responses in mice exposed to naphthalene-derived SOA¹⁹⁸ and anti-inflammatory mechanisms through proteome inhibition¹⁰⁵ or IL-10 increase.¹⁸⁵

Of interest, Eaves et al. reported that SOA (isoprene-derived SOA) altered the expression of microRNA (miRNA), small noncoding RNA molecules whose function is mRNA silencing and degradation.¹⁹⁹ Consequently, this led to a differential expression of a series inflammatory mediators associated with SOA-induced inflammatory response¹²⁶ such as CCL5, IL23R, IL6R, and HMOX1. While this work highlights the miRNA pathway as new SOA-mediated pathogenic mechanism, it suggests also that miRNAs could potentially serve as disease biomarkers and echoes with Han et al.¹⁰⁵ Further studies are awaited to address this speculation.

3.5. Immune Cell Function Disturbance. Altered phagocytosis is detrimental to lungs as it will hamper physiologic respiratory functions. Decreased phagocytic activity was observed in human macrophages exposed to

bSOA and to a lesser degree with aSOA,²⁰⁰ but the potential underlying mechanism has not been commented. However, a number of articles have suggested PM2.5-mediated mechanisms of phagocytosis impairment. It is tempting to speculate that SOA, being part of the PM2.5 particles and causing oxidative stress, might hamper phagocytosis through similar mechanism(s) as those ascribed to PM2.5 (Figure 5). Impaired phagocytosis in PM2.5-exposed alveolar macrophages (AM)^{195,201} and decrease of *Staphylococcus aureus* phagocytosis by AMs in rats treated with PM2.5¹⁹⁶ were observed. This could be explained in part by a dysfunctional AM phagocytosis, which has been in fact reported in several inflammatory diseases.^{202–205} It could also be a direct consequence of abnormal cytoskeleton rearrangement induced by particles^{206–209} that targets specifically actin, a major component of the cytoskeleton implicated in phagocytosis.²¹⁰ Such alteration could be mediated by inhibition of the actin-related protein 2/3 (Arp2/3) complex, a finding that was documented in a mouse COPD model exposed to PM2.5.^{207,211} The complex Arp2/3 is indeed vital for actin polymerization, which is necessary for phagocytosis. Another possibility is the over activation of phosphoinositide 3-kinase delta isoform (PI3K δ), which inhibits Ras homologue family member A activity, also implicated in actin polymerization.²⁰⁹ SOA could inhibit lysosomal maturation which is required in phagocytosis.^{212,213} Other alterations mediated by these particles could involve: a decrease of interferon-gamma (IFN γ)²¹⁴ and interferon- β ²¹⁵ during the immune defense against viral infection;² and a decrease of natural killer (NK) cell recruitment into the airway after *S. aureus* infection¹⁹⁶ that may be explained by CCL5 and IFN γ diminution,^{214,215} as they play an important role in proliferation and accumulation of NK cells.^{216,217} Whether SOA mediates the above mechanisms and its associated immune function alterations warrants further studies.

3.6. Impact on Lung Health. The above proposed pathogenic mechanisms of SOA suggest that exposure of lungs to this insulting agent will undoubtedly result in inflammation and tissue injury. Cell culture studies and animal experimental models support this assumption. Furthermore, a recent series of reported works show the deleterious effect of PM2.5, hence SOA, knowing it represents a major part of PM2.5.^{76,218–222} Among these effects are septal thickening leading to a decrease of lung capacity and development of fibrotic tissues due to the massive recruitment of macrophages/monocytes and release of their protease arsenal involved in tissue remodeling^{76,220} which may induce fibrosis.^{223,224} Based on the literature, although scanty, the impact of SOA on lung tissues seems to translate in different pathologies. In a mouse model, we provided compelling evidence that exposure to nanoparticles led to granuloma formation in lungs.²²⁵ Other studies have reported that chronic exposure to fine PM increased the susceptibility to pulmonary diseases, including acute respiratory distress, asthma, COPD, and lung cancer.^{226–228} Of relevance as well, the capacity of SOA to alter the host immune system may predispose to exacerbation episodes of patients with diseased lungs. The argument for this would be the recently published reports about PM2.5 and pneumonia^{229,230} or COVID-19.^{231,232} Finally, it must be emphasized though that quantitative and/or qualitative comprehension of SOA impact on lung health demands a detailed knowledge of the particle source(s), composition, and atmospheric transformation.

Table 1. Summary Table Listing Studies about SOA Effects^a

precursors	SOA formation conditions	experimental model	SOA-mediated response	refs
isoprene/IEPOX/MAE	photooxidation under natural sunlight in presence of nitric oxide and acidified sulfate aerosols	BEAS-2B cells	↑ IL-8 and PTGS2 expression and altered transcriptomic profile of treated cells	47
toluene/isoprene/TMB/ α -pinene	oxidation in presence of NOx under various conditions (humidity, temperature, Nox concentrations)	human small airway epithelial cells	only toluene-derived SOA induced IL-8 expression	95
naphthalene/ α -pinene	photooxidation under 35–38% humidity at 22.2 °C	A549 epithelial cells	aged SOA induce more toxicity than fresh SOA increased IL8 and protective gene expression in cells exposed to aged SOA	99
IEPOX/MAE	photooxidation in presence of acidified sulfate seed aerosols under natural sunlight and humid conditions (50–70%) at 27.4 °C	BEAS-2B cells	↑ Nrf2-mediated genes expression MAE-derived SOA induce a higher oxidative stress than IEPOX-derived SOA	101
naphthalene/ α -pinene	photooxidation with high hydroxyl radicals exposure (36 ± 2% humidity at 22 °C)	A549 epithelial cells	aged SOA induce more toxicity and ROS than fresh SOA	102
naphthalene/ β -pinene	precursors vapors are mixed with soot particles photooxidation under humid conditions (40%) and sunlight	A549 epithelial cells and/or EA hy926 endothelial cells in an air–liquid interface	↑ toxicity, oxidative stress, angiogenesis and inflammation naphthalene-derived SOA induce higher response than β -pinene-derived SOA	104
naphthalene	photooxidation with hydroxyl radicals under 30–40% humidity at 22–25 °C	BEAS-2B epithelial cells	downregulated proteomic profile except Nrf2-mediated proteomic profile, which is upregulated	105
dimethyl selenide	photooxidation with either hydroxyl radicals or ozone under <25% humidity	BEAS-2B epithelial cells	p53 signaling and genotoxicity pathway-mediated genes were upregulated genes from inflammation and glucose metabolic regulation were downregulated	112
ISOPOOH	oxidation with hydroxyl radical and ammonium sulfate under dark conditions	BEAS-2B epithelial cells	↑ oxidative stress-associated gene expression	113
exhaust emissions from vehicles using gasoline or gasoline-ethanol blend	photooxidation under UV for 3 h under 40% humidity at 20 °C	adult male Sprague–Dawley rats	early acute inflammatory response with massive macrophages and neutrophils recruitment	114
isoprene	photooxidation in presence of acidified sulfate seed aerosols under natural sunlight and humid conditions (50–70%) at 27.4 °C	BEAS-2B epithelial cells	↑ Nrf2 activity and a genes expression associated with inflammation and oxidative stress	115
<i>trans</i> - β -IEPOX/MAE	oxidation with acidic sulfate aerosol under dark conditions	BEAS-2B epithelial cells	IEPOX-derived SOA downregulate miRNA expression implicated in Nrf2 inhibition	126
D-limonene	ozonolysis under 21.4 ± 5.3% humidity at 25.5 °C	female F344 rats (2 and 18 months)	↑ TNF- α , COX-2, and Cu/ZnSOD in rats exposed to SOA ↓ p38, p44/42, and JNK MAP kinase in AM and TH with differences between younger and older animals ↑ NF- κ B and C/EBP DNA binding activity in AM but not TH	135
α -pinene	ozonolysis for 15 min	BEAS-2B epithelial cells	no effect on BAL protein and cell number	139
<i>m</i> -xylene/trimethylbenzene	photooxidation for 5h with NO (ratio: VOC 2:1 NO) under UV	BEAS-2B epithelial cells	↑ HMOXI and ↑ ILB	139
α -pinene	ozonolysis under dry (<5% humidity) and dark conditions.	BEAS-2B and A549 epithelial cells	↑ proliferation and ↑ toxicity in BEAS-2B after 24 and 48 h treatments; no change in A549	143
ACR/MACR/ α -pinene	ozonolysis under 35–60% humidity and dark conditions at 37.9 °C	BEAS-2B cells	↑ RNA oxidation resulting in a cholesterol metabolic alteration and defective cellular morphology	144
diesel exhaust	ozonolysis under 50 ± 5% humidity at 22 °C	pregnant BALB/c mice	↑ NDMA Receptor subunits and CaMKII expressions in the hippocampi	184
isoprene/ α -pinene/ β -caryophyllene/pentadecane/ <i>m</i> -xylene/naphthalene	photooxidation under various conditions: H ₂ O ₂ vs HONO; <5% humidity vs 40–45% humidity	MH-5 macrophage cells	↑ Iba1 and TNF- α in mice exposed to SOA, but no change of COX2 and IL-1 β isoprene, α -pinene and <i>m</i> -xylene-derived SOA-induced similar inflammatory response	186

Table 1. continued

precursors	SOA formation conditions	experimental model	SOA-mediated response	refs
isoprene	photooxidation with acidified sulfate seed aerosol and NO during sunny days under high humidity	BEAS-2B epithelial cells	high level of IL-6 was observed for pentadecane and naphthalene-derived SOA formed under humid conditions ↑ IL8 and COX-2	187
naphthalene	photooxidation with hydroxyl radicals and 30–40% humidity at 22–25 °C	female BALB/c mice (B-10 week)	no inflammatory cell recruitment observed, but increased respiratory resistance to methacholine at 100–150 µg/m ³	198
TMB/ α -pinene	oxidation with various gas concentration of NO ₂ /NO/SO ₂ under 50% humidity at 20 °C	pigtracheal explants and epithelial cells; pig and human macrophages; A549	↓ phagocytic activity and ↑ IL8	200

^aAM, alveolar macrophages; BAL, bronchoalveolar lavage; CaMKII, calcium/calmodulin-dependent protein kinase II; IEPOX, isoprene epoxydiols; ISOPOOH, isoprene hydroxyl hydroperoxides; MAE, methacrylic acid epoxide; NDMA, N-methyl-D-aspartate receptor; PTGS2, prostaglandin G/H synthase 2; TII, type II alveolar epithelial cells; TMB, 1,3,5-trimethylbenzene.

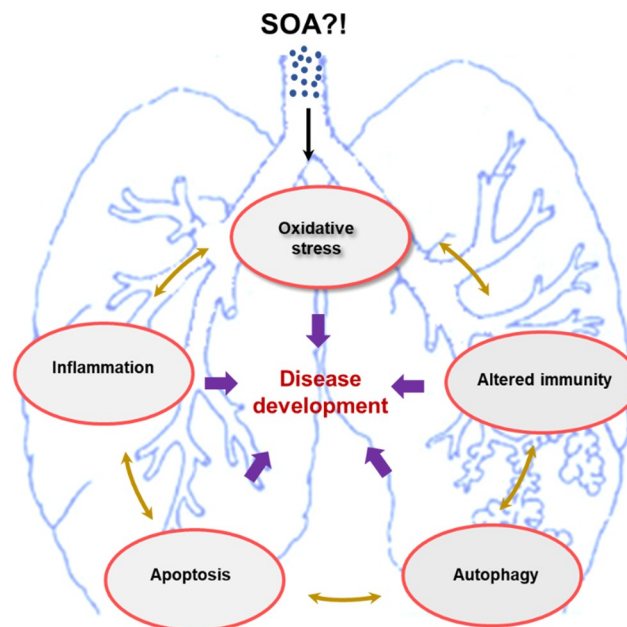


Figure 6. Possible SOA vicious cycle of lung inflammation and injury. SOA-mediated pathogenic mechanisms that might contribute to the development of lung diseases.

4. CONCLUSION AND PERSPECTIVES

A great deal has been learned about the impact of air pollution on health. While there are studies that report conflicting findings, it must be emphasized that it is somewhat expected. Indeed, working with atmospheric pollutants (biogenic or anthropogenic), and for that matter SOA, is challenging. A number of criteria, some of which were beyond control, will dictate the physicochemical composition and properties of the particles of interest and the ensuing impact on the cell and/or tissue responses. These include precursor types, a myriad of chemical species, humidity, temperatures, solar radiation, and exposure time. More perplexing are the experimental conditions (Table 1), namely the use of cell lines (immortalized cells) versus primary cells and acute versus chronic treatments. One has to bear also in mind that primary cells have usually short life spans. Altogether, these factors in addition to unlisted others will contribute to the generation of discrepant data. Interestingly, advances in air pollution research are being pursued and have allowed particle fractionation and identification of SOA. The latter might have a deleterious impact on health by initiating and/or amplifying morbidity and mortality of chronic inflammatory diseases. As suggested above, the pleiotropic effects of SOA could involve different and interconnected pathogenic mechanisms ranging from oxidative stress, inflammation, and immune systems dysfunction, all of which converge to the development of chronic lung pathologies (Figure 6).

Recent technological tools (e.g., EESI-Orbitrap system) will allow SOA synthesis and physicochemical characterization, taking into account SOA precursor's identity and environmental/atmospheric parameters. Advances in such studies will help in the identification of "SOA markers" that could potentially be incorporated into air quality measurements and perhaps set the stage for SOA-related epidemiological studies. Importantly, the development of sophisticated cell culture systems (e.g., lung-on-chip) and clinically relevant experimental animal exposure models that mimic human

conditions will better our understanding of SOA-mediated pathogenesis of diseases of interest, especially pulmonary diseases, and potentially pave the way for efficient therapeutic strategies to protect populations at risk.

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■ ABBREVIATIONS

AM, alveolar macrophages; APAF-1, apoptosis activating factor 1; ARE, antioxidant responsive element; aSOA, anthropogenic secondary organic aerosol; BAL, bronchoalveolar lavage; Bax, bcl-2-like protein 4; bSOA, biogenic secondary organic aerosol; CaMKII, calcium/calmodulin-dependent protein kinase II; CAT, catalase; CCL5, chemokine (C–C motif) ligand 5; COPD, chronic obstructive pulmonary disease; DAMPs, damage-associated molecular patterns; GSH, glutathione; GSx, glutathione peroxidase; HMGB1, high-mobility group box 1; HMML, hydroxymethyl-methyl-lactone; HMOX1, heme oxygenase 1 gene; Hsp 70, heat shock protein 70; IEPOX, isoprene epoxydiols; IFN γ , interferon-gamma; IL-1/4/6/8/13, interleukin 1/4/6/8/13; ISOPROOH, isoprene hydroxyl hydroperoxides; Keap1, Kelch-like ECH-associated protein 1; MAE, methacrylic acid epoxide; MPO, myeloperoxidase; mRNA, messenger ribonucleic acid; mTOR, mammalian target of rapamycin; NDMA, N-methyl-D-aspartate receptor; NF- κ B, nuclear factor kappa-light-chain enhancer of activated B cells; NQO1, NAD(P)H dehydrogenase [quinone] 1; Nrf2, nuclear factor erythroid-2-related factor 2; NOx, nitrogen oxide; OA, organic aerosol; OP, oxidative potential; P53, protein 53; PI3K δ , phosphoinositide 3-kinase delta isoform; PM, particulate matter; PM2.5, particulate matter of <2.5 μ m in diameter; PTGS2, prostaglandin G/H synthase 2; ROS, reactive oxygen species; SGK1, serum/glucocorticoid regulated kinase 1; SOA, secondary organic aerosol; SOD, superoxide dismutase; SVOC, semivolatile organic compound; TII, type II alveolar epithelial cells; TMB, 1,3,5-trimethylbenzene; TNF- α , tumor necrosis factor alpha; VOC, volatile organic compound

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