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Impact of Maternal Air Pollution Exposure on Children's Lung Health: An Indian Perspective

Pritam Saha[1], Ebin Johny[2], Ashish Dangi[1], Sopan B Shinde[1], Mathew Suji Eapen[3], Sukhwinder Singh Sohal[3], VGM Naidu[1], Pawan Sharma[4,5]

[1]Department of Pharmacology, National Institute of Pharmaceutical Education and Research, Guwahati, Assam; [2]Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Guwahati, Assam; [3]Respiratory Translational Research Group, Department of Laboratory Medicine, School of Health Sciences, University of Tasmania, Launceston, Tasmania, Australia, 7248; [4]Medical Sciences, School of Life Sciences, Faculty of Science, University of Technology Sydney, NSW, Australia, 2007; and [5]Woolcock Emphysema Centre, Woolcock Institute of Medical Research, The University of Sydney, Sydney, NSW, Australia 2037.

***Address for Correspondence:**

Pawan Sharma, PhD
The University of Technology Sydney
15 Broadway, NSW 2007, Australia
Tel: + 61 2 9514 3815
E-mail: Pawan.Sharma@uts.edu.au

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Abstract

Air pollution has become a growing invisible killer in recent years and is major cause of morbidity and mortality globally. India stands 10th among the highly polluted countries with an average PM_{10} level of 134μg/m^3 per year. It is also reported that 99% of India's population comes across air pollution level that exceed the World Health Organization Air Quality Guideline (AQG), $PM_{2.5}$ permissible levels of 10 μg/m^3. Maternal exposure to air pollution has a serious health outcome to the offspring because it can affect embryonic phases of development during the gestation period. Fetus is more prone to air pollution effect during embryonic developmental phases due to oxidative stress as antioxidant mechanisms are lacking at that stage. Any injury during this vulnerable period (embryonic phase) will have long-term impact on offspring health both in early and later in life. Epidemiological studies have revealed that maternal exposure to air pollution increases the risk of developing airways disease in offspring due to impaired lung development *in utero*. In this review, we discuss cellular mechanisms involved in maternal exposure to air pollution and how it can impact development of airways disease in offspring. Better understanding of these mechanisms in context of maternal exposure to air pollution can offer newer avenue to prevent development of airways disease in offspring.

Keywords

PM, Air pollution, maternal exposure, Airway disease

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Introduction

In recent years air pollution has become a leading cause of morbidity and death globally (1, 2). Air pollutant particularly particulate matter (PM) pose a major havoc to human health by causing serious respiratory illness such as chronic obstructive Pulmonary Disease (COPD), asthma and act as a trigger to various forms of chronic interstitial lung disease and lung cancer (ref). PM consist of fine and coarse particulate matter; fine $PM_{2.5}$ has an aerodynamic diameter of <2.5µM, while the coarse PM_{10} is <10µM. Both PMs primarily emanate from vehicles, industrial exhausts and household sources (3). It has been well established that both $PM_{2.5}$ and PM_{10} can cause serious respiratory damage (4). According to the World Health Organization (WHO) report in 2018, air pollution induces adverse health effects and as a result 8 million people undergo premature deaths every year. Air pollution contributes at least 23% of deaths from lung cancer, 43% occur through respiratory disease, 24% from strokes and 23% suffer from ischemic heart diseases related deaths (5). An interesting observation is that 91% of the world's population inhale poor quality air that exceeds WHO guideline of air pollution level. Further, increasing modernization also accounts for the increasing concentrations of airborne PM. Both short, and long-term exposure to air pollutants cause major respiratory associated pathological changes such as reduced pulmonary function, increase in respiratory infections and development of asthma and COPD (6).

One of the more important factors that is of concern is the effect of air pollutants during maternal gestational period. Indeed, increased presence of PM is associated with numerous adverse birth outcomes, such as pre-term delivery (7), low birth weight (8), small gestational age of births (9), congenital heart defects (10), intrauterine growth restriction (11, 12), stillbirth (13), and spontaneous abortion (14). Further, associated morbidities includes neurodevelopmental

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impairment leading to attention-deficit hyperactivity disorder (ADHD) and possible autism (15-17), neurological disorders such as impaired neurocognitive ability, nervous system sequelae (18), infant eczema (19). Increased maternal PM exposure is likely to increase the risk of childhood asthma as well (20).

Essentially, PM is a mixture of solid and liquid particles consisting of inorganic and organic matter, dust particles, poly aromatic hydrocarbons (PAH), volatile compounds like sulphates, nitrates, ammonia and minute quantities of metals (TMs), as well as water and unidentified compounds (21). The source of PM can be divided into households (indoor) and commercial (outdoor). Indoor sources includes cigarette smoking, construction work, cooking with kerosene stove or conventional wood burning (chulas), burning of incense or mosquito repellent coils, pesticides and cleaning agents used at homes and room fresheners (aerosols) (22). Outdoor sources include industrial exhaust, diesel vehicles, burning of coals, wood, and road dust. Further sources of PM can be elucidated depending upon mode of emission, such as those from anthropogenic and natural sources (23). Anthropogenic PM source generally would include burning of coal, petroleum products, biomass, industrial processing, agricultural activities, vehicular exhaust, and friction between tires and road, while natural sources would include volcanic eruptions, dust storms, forest fires among others (24, 25). However, the adverse health effects of PM not only depend on the source of PM but also by the chemical composition that adsorb on its surface [27].

India stands among the ten most highly polluted countries with an average PM_{10} level of 134µg/m^3 per year. Sadly, out of 100 most polluted cities around the world, 42 Indian cities are listed as highly polluted. Of utmost concern is that 99% of India's population is exposed to air pollution level that exceed the WHO Air Quality Guideline (AQG) $PM_{2.5}$ permissible levels of 10 µg/m^3

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(26). Recent evidence also show that on an average $PM_{2.5}$ levels in India are found to be in the range of ~10-100 µg/m^3, a grave situation which needs urgent attention (27, 28). Because $PM_{2.5}$ comes under India's 10th health associated risk factors which causes premature death of approximately 1.67 million people according to estimates given by Global Burden of Disease (29, 30). In India higher concentrations of $PM_{2.5}$ are observed in northern parts rather than in southern region (28), and this is because northern India is landlocked. This geographical feature leads to poor wind circulation, thus causing air pollutants to dwindle in the atmosphere for longer periods. In contrast, southern India is surrounded by coastal region wherein sea breeze/wind plays a crucial role in pushing away the pollutants from the region. Moreover, during winters in North India, the creation of high-pressure zone obstructs wind generation, impacting the movement of the pollutants. Among metropolitan cities in India, New Delhi, Kolkata, Mumbai, and Hyderabad shows maximum $PM_{2.5}$ levels with an average concentration: 40-81 µg/m^3 per year, again exceeding the safe levels (40µg/m^3). Air pollutants in India contribute to the decrease in life expectancy on an average by 3.4 years in the general population (31). According to the reports published by Environmental Performance Index (EPI), approximately 3.5 billion people, i.e. half of the world's population are exposed to air pollutant of which three-quarters are of India's population (32). There are several descriptive studies conducted in India to find the impact of air pollution in neonates and children as represented in the Table 1 (33-35), however, these studies did not explore the underlying pathophysiological mechanisms. This review will provide an overview of all health issues concerning particulate matter exposure both indoor and outdoor with special emphasis on maternal exposure and its implications on children's health in India. It will also address the unwanted health effects and highlight some novel mechanisms that can be future targets for drug therapy.

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Evidence of maternal air pollution-induced health effects in offspring

Studies reveal that exposure to PM has been attributed for a large number of health issues in offspring including reduced lung function, increased chances of lower respiratory infections, cardiovascular diseases, exacerbation of chronic respiratory disease and premature mortality (32, 40). Birth weight is a foremost parameter to check for fetal growth. For example, it is now evident that maternal exposure to PM leads to lower birth weight (<2.5Kg), preterm deliveries and IUGR, which are likely factors associated with increased morbidity and mortality in offspring as well as heightened risk of other health complications later in life (41). PM exposure results in the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), both cause oxidative stress that triggers DNA damage leading to the development of placental DNA adducts formation (42). In addition, one of the PM components i.e. PAH binds to placental growth factor receptors resulting in an inadequate transplacental-nutrient exchange. Transplacental nutrient and oxygen transport are crucial during gestation period for regulating normal fetal growth and development (43). Moreover, PM also contain some inorganic metals like chromium, aluminum, silicon, titanium, iron, and copper that results in up-regulation of pro-inflammatory mediators contributing to pulmonary inflammation (44). Inadequate placental perfusion may also cause inflammation resulting in growth restriction *in utero* due to interference with the nutrient-oxygen transfer of the fetus leading to deoxygenation of maternal blood or both (41). It has been reported that maternal exposure to PM alters hematological parameters such as blood coagulation capacity, change in viscosity, levels of hemoglobin, platelets, and white blood cells, which further correlates to PM toxicity, leading to adverse fetal growth (45). In addition to the changes in hematological parameters, there is also endothelial dysfunction, which is attributed to maternal PM exposure during gestational period (46). It has been reported that systemic inflammation and oxidative stress

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caused by PM exposure can increase plasma dimethyl arginine concentration (47). As dimethyl arginine is an endogenous nitric oxide (NO) synthase inhibitor (48) which decrease NO levels, as a consequence lead to endothelial dysfunction which is linked to impaired vascular function and increased risk of cardiovascular diseases. Studies also suggest that maternal exposure to PM leads to changes in hemodynamic parameter like increase in blood pressure, and this may be due to stimulation of sympathetic nerve and vasoconstriction (49). Pollutants derived oxidative stress in pregnant mothers can block the NO-mediated vasodilatation leading to increased blood pressure, which adversely affects offspring and leads to pre-term delivery and IUGR (50). Further, maternal PM exposure also results in inadequate fetal development (51) mainly due to abnormal blood flow to fetus. This decrease in blood flow triggers inflammatory signals to release parturition associated cytokines which results in membrane rupture, cervical ripening, myometrial contraction and ultimately contributes to premature delivery (52), plausible mechanism for PM exposure-induced complications in offspring.

Maternal air pollution and airways disease

Development of COPD and asthma

Though smoking is the greatest risk factor for the development of COPD, other exposures such as air pollution has emerged on the top as per WHO estimates, 14% premature deaths were a result of air pollution-induced COPD globally (53). COPD symptoms includes wheezing, breathlessness, chronic cough and further severe exacerbations, leading to reduced quality of life, with rapid decline in lung function (54-57) and risk of early mortality (58). Asthma is one of the most prevalent pediatric chronic inflammatory respiratory disease characterized by reduced airflow, airway hyperresponsiveness and airway remodeling (59). However, in case of asthma air

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flow obstruction is reversible while in COPD airflow obstruction is irreversible due to the extensive loss of the small airways and this has major implication on mortality in the later stages of the disease (60). Epidemiological studies have found strong association between air pollution and incidence of asthma in children (61, 62), though, many studies also indicate that these associations begin in *in utero* itself (63-66). There is a strong evidence to believe that the maternal immunity plays a pivotal role in the fetal-infant immune response development (67). Maternal allergies may delay the onset of transformation to a non-allergic immune response to inhaled allergens in children, thereby increasing the chances for the development of allergic sensitization and/or asthma to the offspring (67). Generally, lungs begin to develop during the canalicular phase i.e. 17^{th} –26^{th} week of embryonic development. During gestation period, as antioxidant defense functions are subdued, thus lungs are indeed more prone to oxidative stress. Further evidence of oxidative stress was observed in mouse model on day 16, which resembles canalicular stage of human pulmonary development wherein a decrease in number of peripheral airway branching, and alveoli formation was observed (67).

It has been established that air pollutants cause oxidative stress by impairing cellular endogenous antioxidant production capabilities and thus increasing in ROS generation (68). This increase in ROS leads to mitochondrial dysfunction and carbonyl stress which can further damage the tissue by modifying the function of vital proteins such as NADH-ubiquinone reductase, succinate-ubiquinone reductase, cytochrome c oxidase (69). Increases in ROS is also known to causes ER stress leading to the upregulation of inflammatory genes as well as impairment of autophagic process thus further aggravating the pathogenesis. Autophagy is a preserved protective catabolic process which facilitate lysosomal degradation or clearance of misfolded or unwanted proteins.

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Oxidative stress is the leading driver in the development of airway diseases in offspring. Because oxidative stress causes ER stress and lipid peroxidation which results in mitochondrial dysfunction, pulmonary and placental inflammation and thereby negatively affecting nutrient and fetal oxygen transport system, ultimately leading to impairment in fetal lung development (46, 70-73). Similarly, maternal exposure to air pollution causes oxidative stress and mitochondrial impairment in fetus which triggers pulmonary and placental inflammation and thereby negatively affecting nutrient and oxygen transport (73). Moreover air pollutants contains PM in which transitions metals get adsorbed which further aggravate ROS generation by the process of Fenton reaction (69). Fenton reaction lead to the subsequent activation of cellular signaling cascades, transcription and activation of inflammatory cells and release of pro-inflammatory cytokines and cause pulmonary and placental inflammation (46, 74). Rise in the ROS level can lead to oxidative modification of lipids, proteins and DNA thus causing further damage. Further, carbonyl stress also results in enhanced polyunsaturated fatty acids (PUFAs) and metabolites peroxidation (75). Collectively, ROS induce deficiency in pulmonary development in offspring as shown in Figure 1, increasing their susceptibility to acquire asthma and COPD in later in life.

In utero **cellular mechanisms involved in the development of airway disease**

Maternal exposure to air pollution affects the developing foetus which can be deleterious in terms of impacting offspring's lung health and consequential development of airways disease later in life. These cellular mechanisms/pathways involved are shown in Figure 2, and some of the key pathways are described below.

ER Stress

The endoplasmic reticulum (ER) is one of the key cellular organelles which play pivotal role in biosynthetic and signaling functions in the cell. ER is associated with Ca^{2+} homeostasis as well as

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Ca^{2+} mediated signaling cascades. ER also provides the platform for the synthesis, folding, and modification of biomolecules which are to be secreted in the plasma membrane (76, 77). These processes are assisted by various intrinsic chaperones and Ca^{2+}-binding glucose-regulated proteins 78 (GRP78) or BiP (immunoglobulin heavy chain binding protein), calreticulin, calnexin, and protein folding enzymes, such as the thioredoxin-like protein disulfide isomerase (PDI) (78). Misfolded proteins are retro-translocated to the cytosol through a process known as ER-associated protein degradation (ERAD), followed by 26S proteasomal degradation. The imbalance between ER protein folding load and capacity, leads to the aggregation of misfolded proteins in the lumen, a condition that causes ER stress. ER having defensive or adaptive response called Unfolded Protein Response (UPR) elements that are mainly responsible to decrease the overloaded protein synthesis or to maintain ER homeostasis. The UPR elements regulate ER homeostasis by harmonizing the sensual shutdown in translation process of protein along with a programmed gene transcriptional process to increase ER folding capacity. If this co-ordinated gene transcriptional fails to provide proper ER homeostasis, then the consequential stress can induce intrinsic cellular apoptotic pathways (79). Proteasomes are essentially responsible to clear the accumulated misfolded protein aggregates in ER, however, when proteasome systems are dysfunctional, the UPR actively induces autophagy (79, 80). ER stress also induce the upregulation of inflammatory genes like NFkB and secretion of cytokines such as IL-23 and type I interferon (81, 82). It has been reported that GRP78 attune UPR activation and plays a pivotal role in embryogenesis (83). As evident from animal data that mouse pulmonary growth is initiated at Embryonic Day (E) 9.5 by the process of cell proliferation and differentiation from anterior foregut endoderm. However, lung maturation stage is at E16.5 to postnatal Day 5, characterised by decrease in cell proliferation and formation of newly differentiated cell types, including alveolar epithelial type-1 (AT-1) and

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alveolar epithelial type-2 (AT-2) cells in distal part of the lung (84). AT-2 cells are surfactant producing cells cuboidal in shape, having a lamellar bodies act as a precursor cells for AT-1 cells (which has the extensive surface area for gas exchange) during developmental stage (85, 86). During the saccular stage of embryonic development, enhancement of surfactant protein secretions by AT-2 cells allow lung to make it ready for postnatal respiration (87). As surfactant plays a crucial role in the reduction of surface tension, which allow the lung to inflate with maximum capacity by increasing the compliance, thus decreasing the work for breathing. However, AT-2 cells are regulated by ER homeostasis. So increase in ER stress results in apoptosis of AT-2 cells thereby, reduction in surfactant protein secretion. Thus, ER stress can lead to respiratory dysfunction in offspring (83). It has been reported that PERK and IREs regulate crosstalk between protective and apoptotic UPRs signalling (83). However, modulation of PERK upon ER stress regulates cell survival signalling by reduction of translational process *via* phosphorylation of Eukaryotic translation Initiation factor 2a (eIF-2a) and encourage apoptosis *via* the PERK-eIF-2a–ATF4–CHOP pathway (88). It has been reported that transforming growth factor (TGF)-β having a pivotal role in the regulation of apoptosis in lung epithelial cells apart from its role in bifurcation and septae formation during pulmonary development (89). It is also reported that ER Stress and TGF-β/Smad signalling pathways are tightly interlinked and accounts for apoptosis of AT-2 cells leading to decrease in surfactant secretion which in turn affect the alveolar epithelium formation in developing lung of offspring (83).

Autophagy

Autophagy means “self-eating”. It is a fundamental and highly conserved process of lysosomal degradation and recycling of misfolded proteins or damaged cytoplasmic cellular organelles to maintain cellular homeostasis (90). Autophagic process includes engulfment of cell organelles

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within the vesicular membrane referred to as autophagosome followed by lysosomal degradation with the help of lysosomal degradative enzymes (91). It plays a crucial role in both pathological and physiological conditions such as cell survival, cellular energy production and metabolism as well as the innate and adaptive immune system (92, 93). Several studies demonstrate that hereditary association of genes involved in autophagic process such as ULK1, SQSTM1, MAP1, LC3B, beclin-1, and Atg5 in asthmatics, and also found an elevated number of double membrane autophagosomes in fibroblast and epithelial cells in asthma patients in comparison with healthy population (94, 95). It has been reported that an elevated number of autophagosome in lung sample derived from COPD patients in comparison with healthy volunteers (96). Under normal physiological conditions autophagy plays a protective role in the cell survival and clearance of damaged proteins whereas in stress conditions its regulation is impaired leading to development of various diseases. It is now known that an altered cellular autophagic process is seen in stress conditions like asthma and chronic obstructive pulmonary disease (90). However, dysregulation of autophagy cause breakdown of intracellular components to generate an energy source for extracellular matrix (ECM) production, and generation of inflammatory mediators and release of pro-fibrotic signalling molecules, consequently results in airway remodelling. Furthermore, it has also been reported that selective autophagy such as mitophagy (elimination of damaged or dysfunctional mitochondria) and ciliophagy (elimination of damaged cilia or components of cilia) also comes into play in airways disease (97, 98). The transmembrane proteins Atg9 and VMP-1 (99, 100) are pivotal for autophagosome formation and the assembly formed by Atg1, Atg13, and Atg17/FIP200 proteins are essential for relocation of protein Atg9 to the autophagosome leading to double membrane autophagosome formation, a key indicator for autophagy determination. However, the mammalian target of rapamycin complex1 (mTORC1) regulate autophagy by

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repressing the activity of assembly proteins Atg1-Atg13-Atg17/FIP200 and thus, inhibition of mTORC1 induces the initiation of autophagic process. Furthermore, rapamycin which blocks mTORC1 results in induction of autophagy. Bafilomycin A1 a molecule inhibits the fusion with autophagosomes as well as inhibits vacuolar type H^+-ATPase leads to impairment of lysosomal degradation capability (101). The kinase Akt, which is the upstream of regulators of mTORC1 phosphorylates and inactivates TSC2 and thereby Akt activation stimulates mTORC1 and inhibits autophagy. Increased autophagy in the context of airways disease act as a pro-survival factor required for the normal recycling process of damaged proteins or organelles and there is an increase in autophagic marker in sputum and peripheral blood cells in asthma (102).

Autophagy plays a pivotal role in embryogenesis as autophagic process initiates during the fertilization phase from two cell to eight cells division while defect in beclin-1 protein lead to embryonic death (E10–E14) with neural tube formation impairment (103). As evident from clinical data, during the early gestation period i.e 7–11 weeks interstitial extra-villous trophoblast (EVT) cells occupy placental side, and trophoblastic plug restricts the maternal blood flow, resulting in hypoxic condition. Moreover, during 12–16 weeks endovascular EVT dilates the blood vessels in spiral arteries leads to elevation in intervillous space blood flow (104). In normal physiology there is increase in autophagic markers such as autophagosomes as evident from lung tissue specimens whereas under pathological conditions decrease in autophagosomes results in impairment of lysosomal degradation. However, autophagic inhibition in trophoblasts induces inadequate placental blood supply in initial phase of gestation period lead to hypoxic condition in embryo. Furthermore, releases of anti-angiogenic factors from villi due to hypoxic conditions aggravate the dysregulation of trophoblasts by inhibiting autophagic process.

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Thus, autophagic inhibition causes impairment of homeostasis in trophoblast cells. However, controlled regulation of autophagic process is necessary for reproduction. On the contrary, dysregulation of functional autophagy negatively impact offspring health because inadequate placental blood flow affect lung development in offspring (46, 104). In this way, dysregulation of autophagy lead to impaired lung development, ultimately leading to development of airways disease.

Mitochondrial damage

Mitochondria are the leading subcellular organelle from which ROS is generated under physiological conditions during catalyzation of ATP production, which is linked to electron transport chain that occurs in the inner mitochondrial membrane. The mitochondrial respiratory chain has four complexes in the inner membrane where electrons move in a synchronous manner i.e. move from a high to a low redox potential resulting in the generation of mitochondrial membrane potential (105-107). Air pollution which has both organic and inorganic compounds is capable of generating ROS which interferes in the electron transfer chain system by disrupting the Q cycle that operates between complexes I and III resulting in mitochondrial superoxide production (108, 109). Air pollutants also have the ability to disrupt mitochondrial permeability transition pore (110), a crucial molecule that regulates mitochondrial respiration and regulate the cellular apoptosis in a controlled manner (111, 112). However, disruption of the mitochondrial outer membrane by air pollutants, lead to release of several pro-apoptotic proteins such as cytochrome c, second mitochondria-derived activator of caspases (SMAC) and apoptosis inducing factor (AIF) into the cytosol where they activate apoptotic signalling pathways ultimately leading to programmed cell death (112, 113). Besides direct effects of air pollutants on mitochondria, the physiology of this organelle can also be altered indirectly by increasing ROS generation and Ca^{2+}

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flux in the cell. Even free intracellular calcium $[Ca^{2+}]_i$ plays an important role in regulating the opening and closure of the mitochondrial permeability transition pore (114). Moreover, ROS such as H_2O_2 can induce rise of $[Ca^{2+}]_i$ in a various cells by either inhibiting sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) or plasma membrane Ca^{2+}-ATPase (PMCA) leading to the activation of 1, 3, 5-trisphosphate (IP3) receptors (115, 116). Various constituents in air pollution can directly target mitochondrial membrane and cause structural damage (69). The process in which non-functional or damaged mitochondria are cleared *via* mitochondria-selective autophagy are known as 'mitophagy' and has been reported as pivotal mechanism in the development of airways disease (117).

Conclusion

Air pollution has become a growing concern in recent years in India and globally causing enormous burden to the society as well as loss of life. It has been well established that air pollutant particularly PM penetrate deep into the lungs causes pathological changes leading to impaired pulmonary function. Epidemiological studies demonstrate that exposure to PM increases oxidative stress leading to serious health effects. Similar mechanisms are involved in maternal air pollution exposure-induced health effects on offspring that is a result of increased oxidative stress leading to oxidative damage of biomolecules, placental inflammation and induction of autophagy. Moreover, oxidative stress also lead to mitochondrial damage, causing release of pro-apoptotic factors leading to cell death. Thus, a better therapeutic approach would be to target air pollution induced oxidative stress by enhancing endogenous antioxidant mechanisms in the cell. Further, targeting ER stress by autophagy inhibitors could also be a vital approach for future research into preventing the development of pollutant induced airways disease. Finally, air pollution induced

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adverse health outcomes could be prevented by comprehensive approached that eliminates or reduces the burden of PM both indoors and outdoors.

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Competing interests

The authors declare that there are no competing interests associated with the manuscript.

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S. No.	Author	Study Design	Sample Size	Exposure	Parameter studied	Comments and association	
1	Padhy et. al 2009 (36)	Case control	Control (n = 105) Biomass user (n = 115)	Biomass combustion smoke	Wheeze	OD=2.15 (1.80–4.75)	
					Sneezing	OD=2.47 (1.92–3.50)**	
						Control	Case
					Haemoglobin (g/dl)	13.5 ± 0.8	11.0 ± 0.5*
					RBC ($\times 10^{6}/\mu l$)	4.3 ± 0.6	3.8 ± 0.4*
					WBC ($\times 10^{3}/\mu l$)	6.2 ± 0.2	9.1 ± 0.2***
					Eosinophil ($\times 10^{3}/\mu l$)	0.2 ± 0.05	0.9 ± 0.1**
					Lymphocyte ($\times 10^{3}/\mu l$)	2.1 ± 0.2	2.5 ± 0.2*
					Monocyte ($\times 10^{3}/\mu l$)	0.18 ± 0.02	0.25 ± 0.02*
					Ascorbic acid (µmol/L)	12.0 ± 1.5	5.0 ±0.82***
					Superoxide dismutase(U/ml)	105.8 ± 20.5	63.8 ± 0.6***
					GSH/GSSG ratio	1.25 ± 0.21	0.52 ± 0.07***
2	Siddique et.al 2010 (37)	Case Control	Case=969 (school children of Delhi), Control=850 (students from rural area)	PM10	ADHD	OD=2.066 (1.079–3.958)	
3	Kumar et al 2015 (38)	Cohort	3104 children	Indoor SPM levels	Asthma	Indoor SPM level was significantly (p< 0.001) higher in the asthmatic children's houses.	
4	Murlidhar et. al 2015 (39)	Case report	11-year-old boy malnourished	Secondary exposure to sandstone mining	Silico-tuberculosis	Mother started working in the mines soon after her marriage and the family lives close to the mines	

Table 1. List of studies that has been carried out in Indian Population on air pollution

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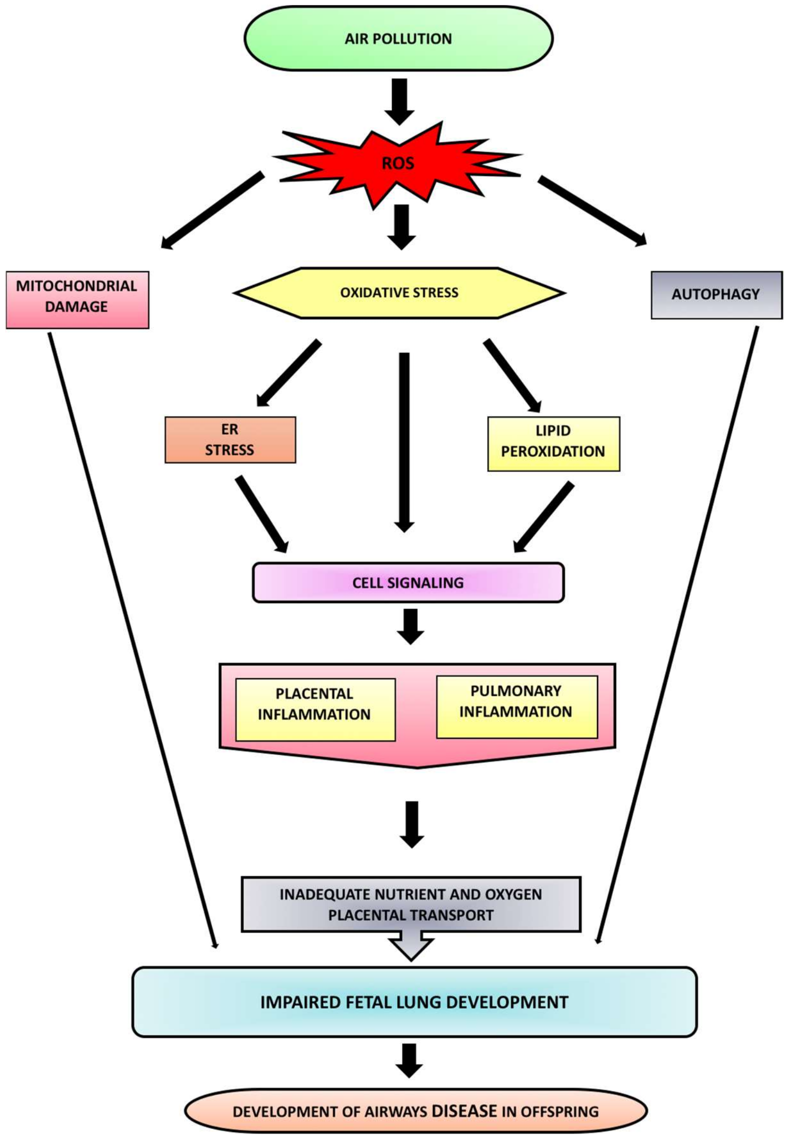

Figure 1. Plausible mechanisms for the development airways disease in offspring. Air pollution induces ROS generation which leads to oxidative stress followed by ER stress and lipid peroxidation resulting in up regulation of inflammatory genes. This causes pulmonary and placental inflammation and thereby negatively affect nutrient and fetal oxygen transport system. Excessive ROS generation also results in mitochondrial damage and induction of autophagy. Thus, oxidative stress, ER stress, autophagy and mitochondrial damage causes impaired fetal lung development leading to development of airways disease later in life.

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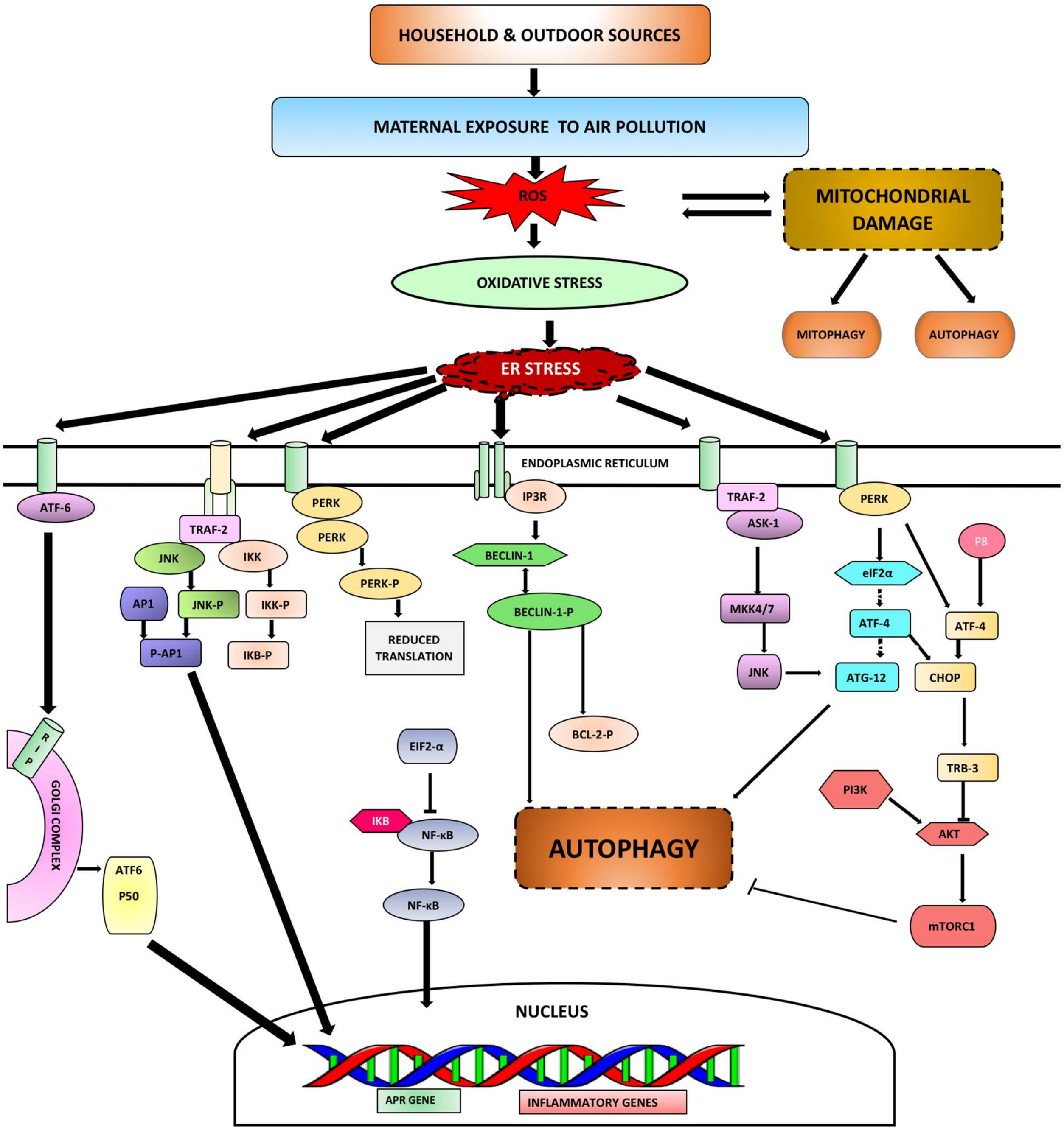

Figure 2. Cellular mechanisms involved upon maternal exposure to air pollution. Air pollutants enter into the lungs while breathing which increases ROS generation resulting in oxidative stress. Increases in ROS cause mitochondrial damage which further initiates cell death either by apoptosis or mitophagy. Oxidative stress induces ER stress leading to the stimulation of IRE1a kinase which interact with tumor-necrosis factor-a (TNF-a) and receptor-associated factor 2 (TRAF2) followed by interaction with Jun N-terminal kinase (JNK) thus stimulating several transcription factors and apoptotic factors. JNK also stimulate the inflammatory genes expression

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by phosphorylating the transcription factor activator protein-1 (AP-1) which enhances inflammation by regulating the transcription of cytokines and chemokines. Similarly, EIF2a interaction with IKK activates NFkB resulting in its transport to the nucleus, where it activates the inflammatory gene transcription. ATF-6 along with p50 protein activate the transcription of APR genes resulting in systemic inflammation. PERK protein upon phosphorylation lead to reduced translation. Inositol 1,4,5-trisphosphate receptor (IP3R) interaction with Beclin-1 protein upon phosphorylation inhibit autophagy. However, inhibition of IP3R initiates detachment with Beclin-1 leading to autophagy in absence of Ca^{2+}. Interaction of TRAF2 with ASK-1 protein lead to JNK activation which promotes Bcl-2 phosphorylation, leading to detachment with Beclin-1. PERK interaction to phosphorylated eIF2α can lead to autophagy thorough an interaction of ATF4 dependent Atg12 protein expression. Alternatively, P8 protein interaction with ATF4 stimulates the up-regulation of pseudokinase TRB3 which further leads to activation of autophagy by inhibition of the Akt/mTORC1 complex.