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Air Pollution and Its Effects in the Respiratory System

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1. Introduction

1.1 Respiratory system structure and normal function

The respiratory system is the gateway for 15,000 liters of air that enter through the nostrils, and after its appropriate conditioning, arrives to the delicate net structured by the lung parenchyma. At this site gas diffusion takes place, and oxygen diffuses through the Pneumocyte I cytoplasm to reach the erythrocyte's hemoglobin, passing by the endothelial cell.

To make this possible, a well-structured conducting system leads the air (trachea, bronchi, bronchioles, alveoli) from the nostrils to the alveoli. A specialized epithelium blankets the tubes, with some local modifications (Fortoul et al., 2010). This epithelium is constituted by a variety of cells with different functions (Figure 1).

In the submucose under the bronchi, mucous and serous glands are located, and liberate its secretion to the surface of the epithelium (Figure 2). These glands, as well as the goblet cells, produce mucus that in normal situations is Alcian blue/ PAS+ (Davis & Dicker, 2008). The biochemistry of the mucus, produced by the goblet or the submucosal glands is important because they determinate their viscosity, pH, and charge, as well as its stain affinity (Figure 3) (Rose & Voynow, 2006).

With the help of intercellular junctions, this tubes system separates spaces between the epithelium, which is known as interstitial space and it houses connective tissue, fibroblast, lymphocytes, macrophages, and other cells that may migrate from the capillaries.

Along these tubes the air that enters through the nostrils becomes moistened, filtered and tempered, to arrive into the alveoli for gas diffusion. A change in the composition and function of the epithelial components will be associated with a variety of diseases which are associated to air pollutants exposure (Figure 4) (Mussali-Galante & Fortoul, 2008).

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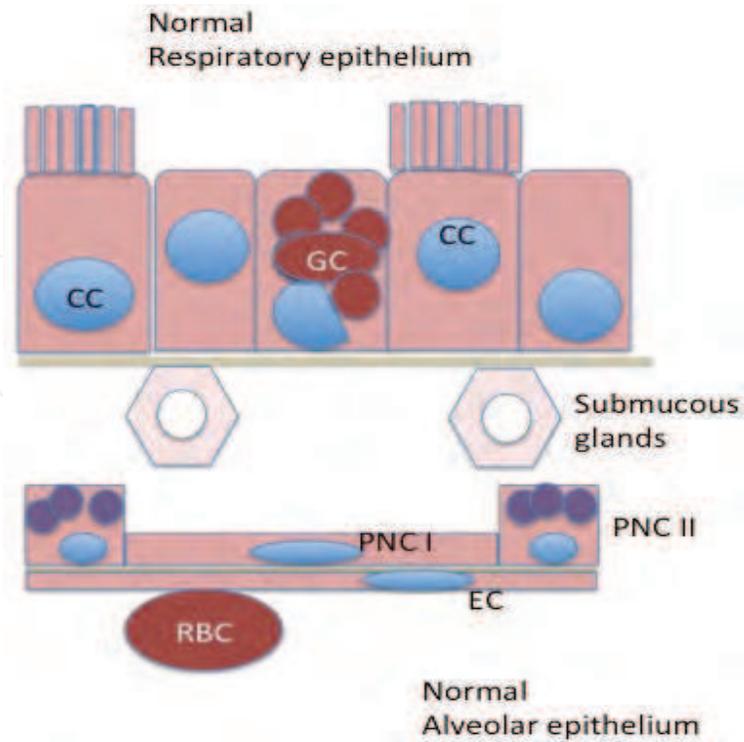


Fig. 1. Respiratory system epithelial cells. Ciliated Cell (CC), Goblet Cell (GC), Pneumocyte I (PNC I), Pneumocyte II (PNC II), Red Blood Cell (RBC), Endothelial Cell (EC).

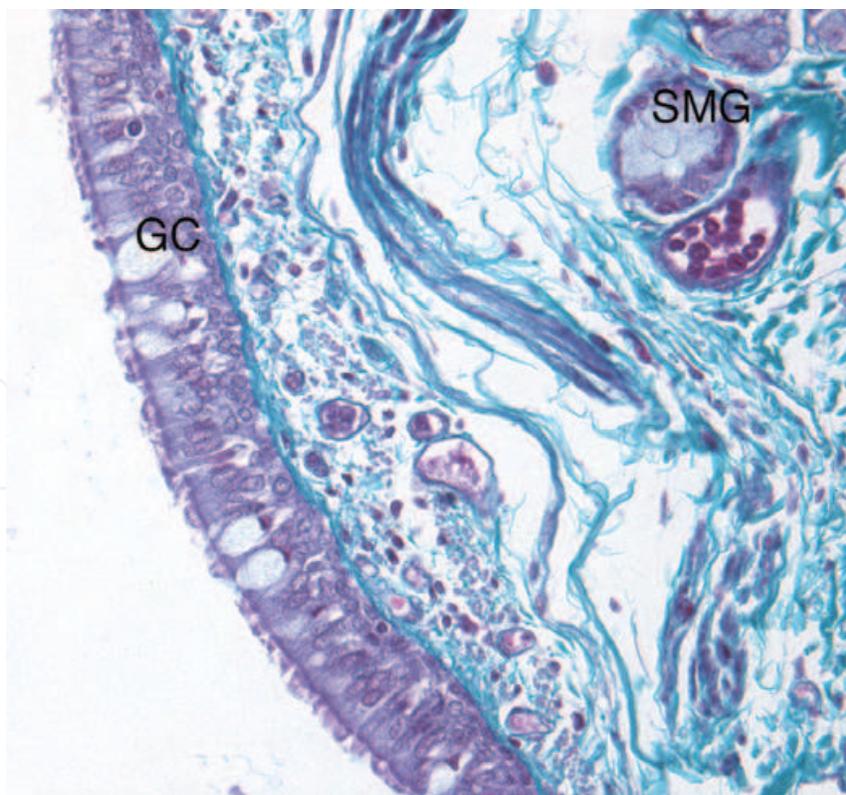


Fig. 2. Bronchial epithelium with Ciliated and Goblet Cells (GC). Submucose glands (SMC) with serous demilunes are also observed.

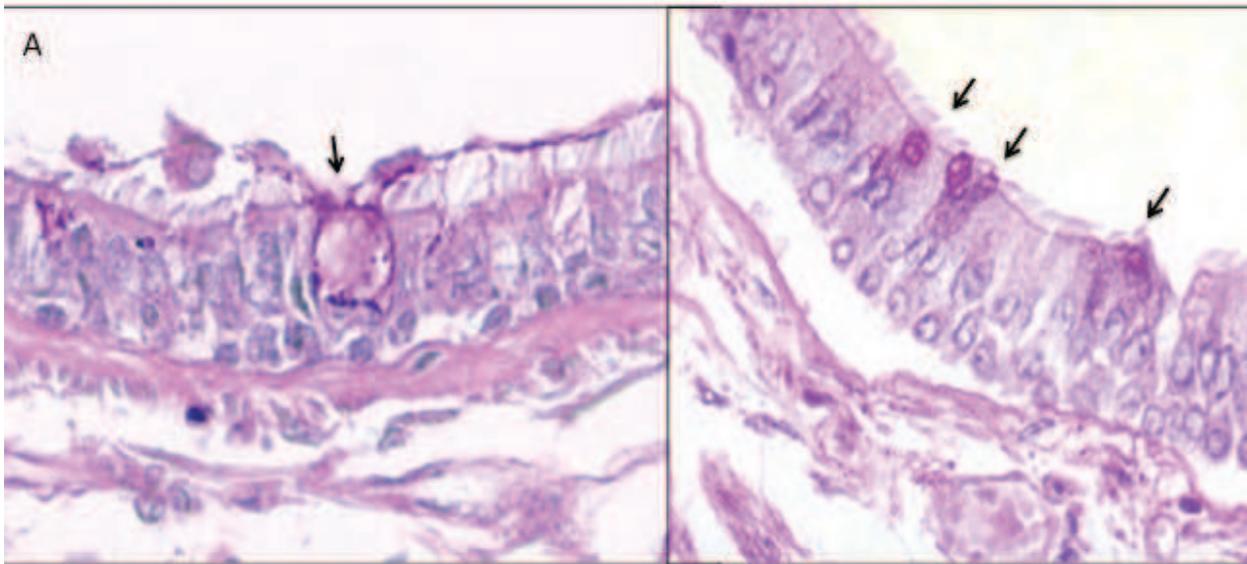


Fig. 3. Respiratory epithelium stained with PAS Schiff. (A) In normal situations, few PAS+ cells are observed (arrow). (B) In disease an increase in these cells is observed (arrows).

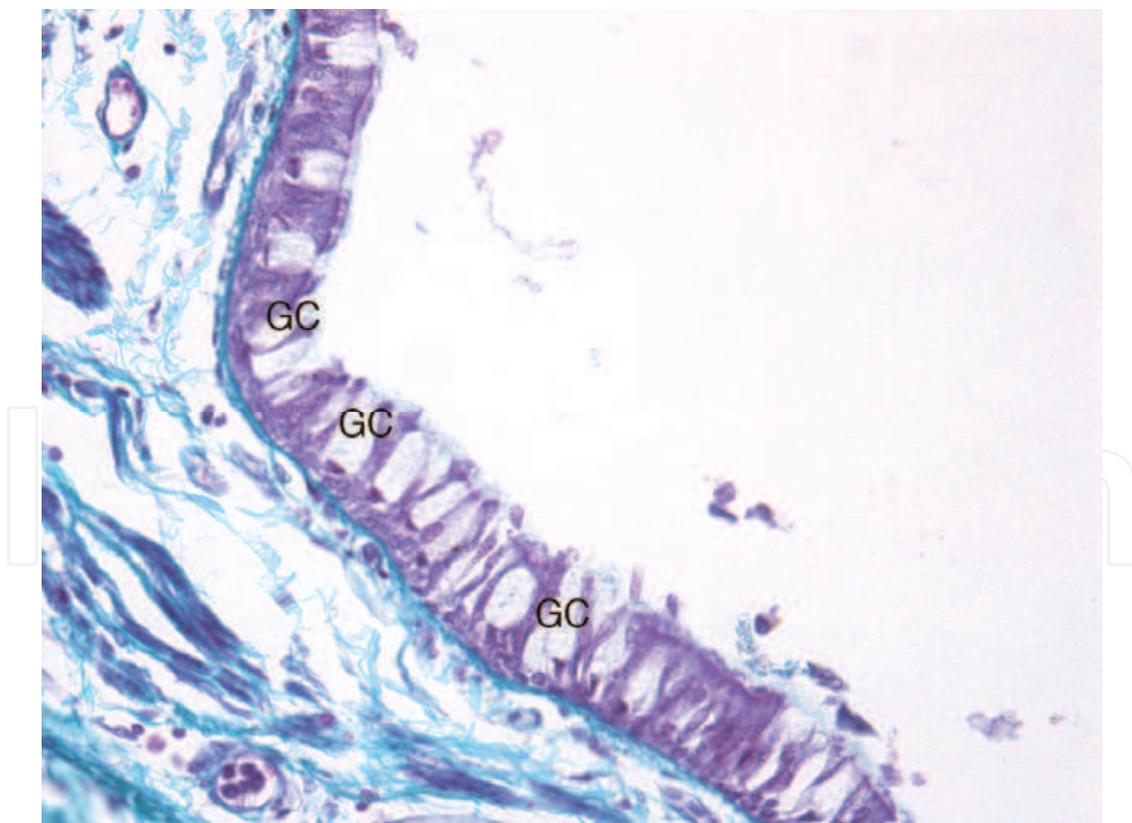


Fig. 4. The increase in the number of Goblet cells is a response of the respiratory epithelium to atmospheric aggressions.

1.2 Diseases associated with air pollutants (inflammation, fibrosis, COPD, asthma, cancer, immunologic modifications)

Air pollutants, described latter in this chapter, induce different reactions and diseases. Inflammation as a consequence of the exposure to irritants such as Ozone, NO_x, or particulate matter has been described (Yang & Omaye, 2009). Also, fibrosis as a consequence of the exposure to gases is explored with more detail in a next section (Figure 5).

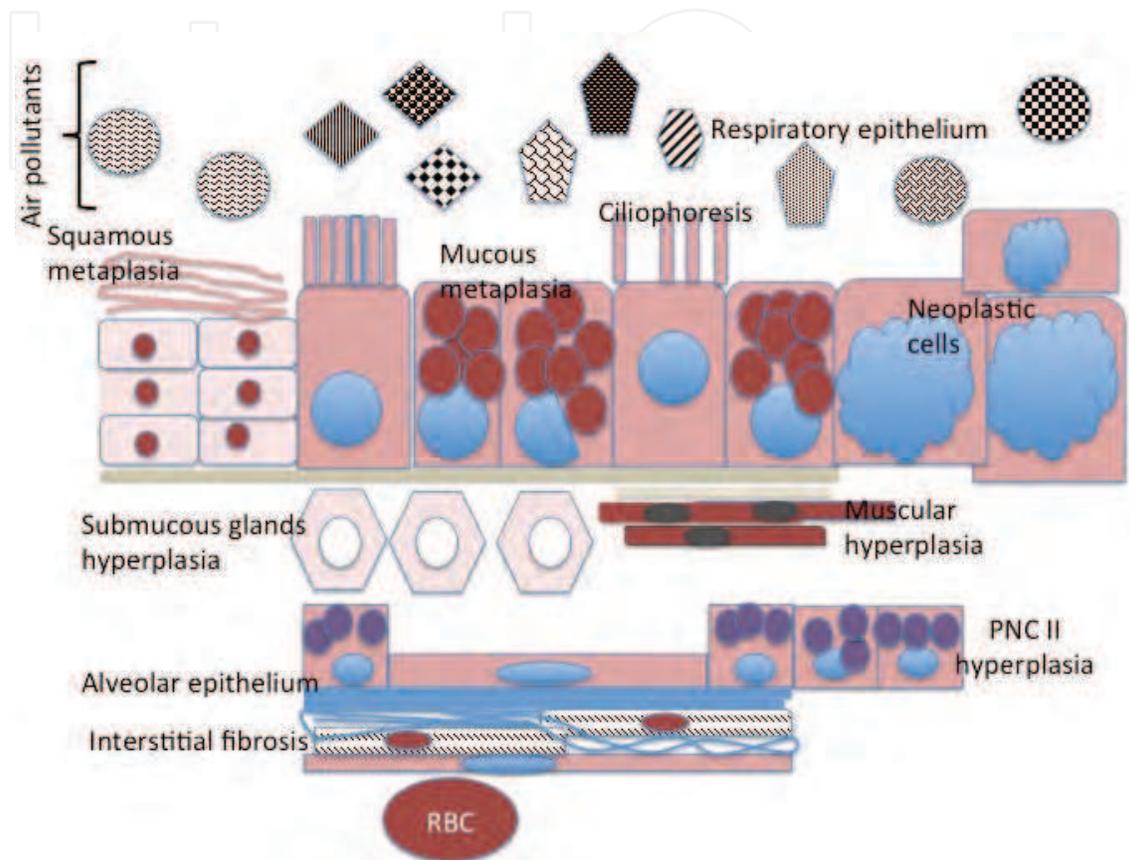


Fig. 5. Schematic representation of the changes that may be found in the respiratory epithelium, after its exposure to air pollutants.

Chronic Obstructive Pulmonary Diseases (COPD) included asthma, increases its frequency in cities with high atmospheric pollution (Olivieri & Scoditti, 2005). The epithelium in these cases may increase the release of IL-6, TNF α , PGE₂, PDGF, TGF β , VEGF, and a variety of chemokines, and other mediators capable of inducing proliferation of fibroblasts and mucus production (Holgate, 2008).

In addition other components of air pollutants, such as metals, Volatile Organic Compounds (VOCs) are carcinogenic; other pathologies are associated with the exposure (Yang & Omaye, 2009).

In the next sections the different responses of the lung to air pollutants will be explored.

2. Air pollutants

Air Pollutants are natural constituents of the air. Animals produce carbon dioxide as the end result of respiration, volcanic action produces sulfur oxides, and wind movement ensures

the presence of suspended particulates. Pollutants are part of our everyday life, and it is difficult to remove them from the respirable air. However, man has caused a severe imbalance, in the natural mechanisms for atmosphere clearance, increasing the discharges of pollutants in the atmosphere, resulting in severe effects on human health (Atash, 2007).

2.1 Classification of air pollutants

Atmospheric pollutants have been classified according to their source; chemical composition, size and release form into indoor or outdoor environments (Bernstein et al., 2004):

A. Primary - secondary pollutants

1. Primary: pollutants emitted directly into the atmosphere
2. Secondary: pollutants that form in the air as a result of chemical reactions with other pollutants and gases.

B. Indoor - outdoor pollutants

1. Indoor pollutants
 - 1.1 Sources: cooking and combustion, particle resuspension, building materials, air condition, consumer products, smoking, heating, biologic agents
 - 1.2 Products: combustion products, CO, CO₂, Specific volatile organic compounds, microbial agents and organic dusts, radon, manmade vitreous fibers
2. Outdoor pollutants
 - 2.1 Sources: industrial, commercial, mobile, urban, regional, agricultural, natural.
 - 2.2 Products: SO₂, ozone, NO_x, CO, PM, Specific volatile organic compounds

C. Gaseous - particle pollutants

1. Gaseous: SO₂, NO_x, ozone, CO, Specific volatile organic compounds
2. Particle: coarse PM (2.5 - 10 μm; regulatory standard = PM₁₀), fine PM (0.1 - 2.5 μm regulatory standard = PM_{2.5}); ultrafine PM (<0.1 μm; no regulated).

2.2 Gases

Problems in air pollution were associated with high concentrations of sulfur dioxide (SO₂) in 20th Century. Through controlled exposure, human studies to SO₂ (0.25 ppm) for only 5 minutes a rapid bronchoconstriction, in both healthy and asthmatic subjects was described. In patients exposed to inhalation of SO₂ a relationship with TNF-α promoter polymorphism was identified, which is known to be associated also with asthma (Winterton et al., 2001; Bernstein et al., 2004).

Ozone is formed in the troposphere through a complex series of reactions involving the action of sunlight on nitrogen dioxide and hydrocarbons. The global concentration of O₃ has increased due to an increase in nitric oxide emissions associated with the switch to fossil fuels during the industrial period. Nitric oxide is rapidly transformed into nitrogen dioxide by atmospheric oxidants such as ozone (Finlayson & Pitts, 1997). Exposure to ozone causes a decreased in forced vital capacity and FEV₁ associated with chest discomfort on inspiration and increased nonspecific airway hyperresponsiveness (Bernstein et al., 2004).

NO₂ is emitted directly into the atmosphere by combustion processes; however, the main source is the oxidation of NO by reactive species. Once NO is converted to NO₂, a variety of reactions can generate nitrate radical (NO₃), dinitrogen pentoxide (N₂O₅) (Finlayson & Pitts, 1997). NO₂ exposure (2 - 6 ppm) induces an inflammatory response in the airways characterized by neutrophil influx and reduced lymphocyte subpopulations, also it might play a more prominent role as sensitizing agent to inhaled allergens (Strand et al., 1997).

Carbon monoxide (CO) is produced by the incomplete combustion of carbon or carbon compounds. This gas can be bound to hemoglobin, forming carboxy hemoglobin and immobilizing hemoglobin function. Another compound of carbon, carbon dioxide is needed in plants' life cycle, in the reaction of photosynthesis. But its rise in the atmosphere in the presence of other gases such as methane and chlorofluorocarbons, is the cause of the greenhouse effect, (Raub et al., 2000).

2.3 Suspended particles

Particle air pollution is a mixture of solid, liquid or solid and liquid particles suspended in the air. The size of suspended particles varies, from a few nm to tens of μm . The PM 10 (thoracic) are particles smaller than 10 μm in diameter that can penetrate into lower respiratory tract; PM 2.5 (respirable) particles smaller than 2.5 μm that can penetrate into gas-exchange region of the lung, and ultrafine particles smaller than 100 nm which have a limited contribution to particle mass, but which in terms of numbers are more abundant than the other sizes, and offer a very large surface area, with increased degrees of lung penetration.

Major natural sources of particles include organic material terrestrial dust caused by winds, sea spray, biogenic emissions, volcanic eruptions and wild fires; the contamination through anthropogenic or technogenic is produced by combustion, industrial waste, nuclear energy, anthropogenic fire, and burning of household waste (Finlayson-Pitts & Pitts, 2000). Metal particles (mercury, cadmium, nickel and lead) are part of PM2.5.

3. Lung development modifications by air pollutants

The respiratory system begins its development at the 4th week of pregnancy, in the fetal larynx as a respiratory *primordium*. This structure is covered by endoderm that will differentiate into the respiratory epithelium, and the respiratory glands.

Other structures will be developed from the splanchnic mesoderm that surrounds the endoderm.

The regulation of the respiratory system morphogenesis is coordinated by different structures, in different time periods. It has been reported the expression of molecules such as Fibroblast Growth Factor (FGF), sonic hedgehog, Bone Morphogenic Protein (BPM), retinoic acid and Wnt signaling pathways, as well as various transcription factors as part of this regulatory network (Cardoso & Lü, 2006).

At the end of the 7-week, the lungs are already developed, but its maturation is extended during the pre and postnatal periods. 80% of the alveolar tissue ends its development until the end of adolescence. This large maturation time exposes the lung to suffer damage and modify its development; this also increases the risk for developing pulmonary diseases early in adulthood such as restriction or a decrease in lung function (Wang & Pinkerton, 2008; Rojas-Martinez, et al., 2007).

Prenatal exposure to Environmental Tobacco Smoke (ETS) has been associated with an increased risk of asthma, and during the postnatal period, the exposure increases asthma exacerbations, as well as the risk for respiratory infections (Wang & Pinkerton, 2008). Studies in mice indicate that prenatal exposure to ETS increases allergic responses in postnatal period (Penn et al., 2007; Gern, 2010).

The exposure to outdoor pollutants such as Particulate Matter (PM), carbon monoxide (CO), sulphur (SO_2), nitrogen (NO_x), and ozone, decreases lung function during childhood

(Mortimer et al., 2008). Also O₃ exposures increase hyper-reactivity along with an increase in TNF-**a**, IL-1**b**, KC, IL-6, and MCP-1 with non-visible structural lung modifications (Auten et al., 2009).

4. Xenobiotic metabolism

4.1 Lung metabolic active cells

The lung is one of the main sites for xenobiotics metabolism and in some cases, biotransformation (Castell et al., 2005). Biotransformation is the process by which cells modify xenobiotics, with the ultimate goal of facilitating the elimination of lipophilic substances. These reactions are classified in three phases. Phase I: Enzymes encoded by cytochrome P450 (hemoproteins actively involved in the biotransformation of xenobiotics). Phase II: Reactions tend to render more water-soluble products and less active metabolites, and finally, Phase III: Elimination (Choudhary et al., 2005).

More than 40 different types of cells have been described in the lung (Pavek & Dvorak, 2008), and some are metabolically active. Immunohistochemical analysis has evidenced the presence of cytochrome P450 (Cytochrome Proteins) (CYP) in lung cells such as: macrophages (Pavek & Dvorak, 2008), endothelium, alveolar cells types I and II, ciliated cells (Castell et al., 2005) and Non-Ciliated Bronchiolar Cell or Clara cell. Clara cells are the leading cells for xenobiotic metabolism in the lung because its profuse cytochrome P450 mono oxygenase activity (Katavolos et al., 2009).

4.2 CYPs and lung metabolism (CYPs and cell metabolism)

CYP families and subfamilies are responsible of the oxidative metabolism of the majority of xenobiotics such as: drugs, environmental pollutants and carcinogens. The main families are: CYP1, CYP2 and CYP3 and comprise about half of the total CYPs. The subfamilies are classified according to the degree of nucleonic and amino acid sequence homology (Castell et al., 2005). All CYPs are localized in the cell's smooth endoplasmic reticulum. CYP 450 enzymes act as mono oxygenases, and use one atom of molecular oxygen to oxidase xenobiotics, requiring the aid of NADPH-cytochrome P450 reductase, to provide the electrons required for the reduction of the second oxygen atom to H₂O₂ (Ioannides, 2008). The lung contains a variety of subfamilies such as: CYP1A1, CYP1B1, CYP2A6, CYP2B6, CYP2E1, CYP3A5 (Castell et al., 2005), CYP2B1, CYP3A1 (Pons et al., 2000), CYP2F1, CYP2F2 (Carlson, 2008) and CYP2S1 (Deb & Bandiera, 2010).

4.3 Air pollution modification of CYPs

Air pollution increases or decreases the CYPs amount in the lung. Exposure to environmental factors such as: dioxins as 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), polycyclic aromatic hydrocarbons (PAH) as benzo [a] pyrene (BaP) and tobacco smoke (Chang et al., 2006), enhances CYP1A1 activity and has been reported to be a prognostic factor for lung cancer development. (Ioannides, 2008). CYP1B1 and CYP2S1 also increase its activity after the exposure to PAH and BaP (Deb & Bandiera, 2010), also CYP1A1 and CYP1B1 are localized in the Clara cell (Chang et al., 2006). PAH and BaP also bind to arylhydrocarbonyl receptor (AhR) that translocates to the nucleus and acts as a transcription factor that binds to a specific DNA recognition sequence, termed the xenobiotic responsive element (XRE) (Anwar-Mohamed et al., 2009) and all CYPs can generate ROS during NADPH-dependent CYP catalysis (Ioannides, 2008) (Figure 6).

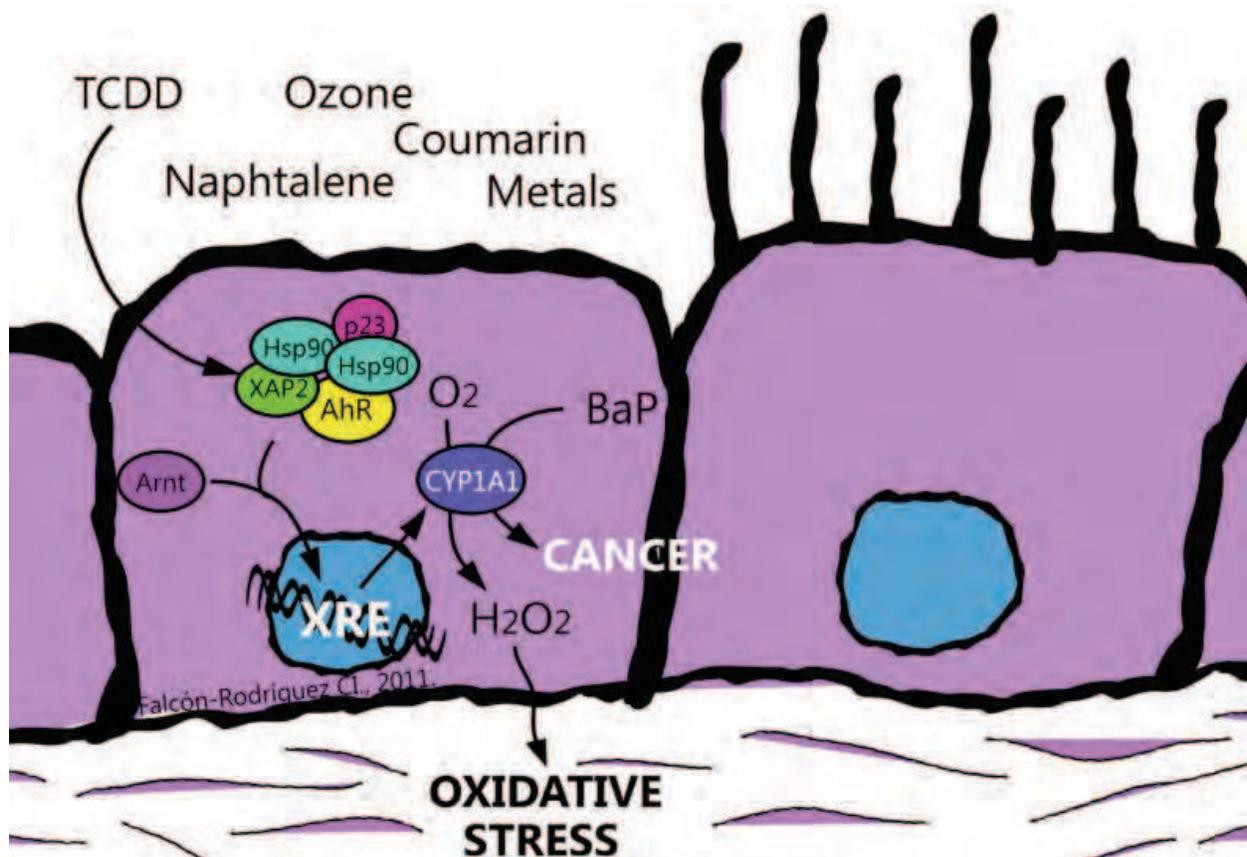


Fig. 6. Molecular mechanism of CYP1A1 activation by AhR signal transduction pathway in Clara cell (Bronchiolar epithelium). A ligand enters to the cell (TCDD) and binds to the cytosolic complex of AhR, chaperones hsp90, co-chaperone p23. Ligand-AhR complex translocates into the nucleus. AhR-ARNT heterodimer then binds to xenobiotic response element (XRE).

Other hydrocarbons as toluene, occurs naturally in crude oil and in the tolu tree. It is also produced in gasoline process, fuels from crude oil, making coke from coal and it is used in paints and paint thinners. Toluene exposure enhances CYP2B1 activity in rat lung (Pons et al., 2000). Naphthalene, derived from petroleum, coal, and tobacco smoke (Morris & Buckpitt, 2009), increases CYP2F2 activity. In mouse lung CYP2F2 the metabolism rate was 107 nmol/min/nmol P450, whereas for human lung CYP2F1 was 0.045 nmol/min/nmol P450 (Carlson, 2008). Other products such as coumarin, a natural product used widely as a fragrance ingredient, and also been used clinically at high dosages in humans for the treatment of high-protein lymphedemas, and as an antineoplastic agent in the treatment of renal cell carcinoma and malignant melanoma. The Coumarin-Epoxidation increases the expression of CYP2F2, and shows a specific metabolism in mouse Clara cell (Born et al., 2002). Furthermore, Clara cell does not contain CYP2E1, but, when rats are exposed to ozone, the CYP2E1 is induced in the bronchiolar epithelium (Ioannides, 2008). In general Particulate Matter induces gene expression of CYP1A1 and CYP2E1 (Abbas et al., 2009). Finally, metals are components of Total Suspended Particles (PST). Scarce information is available on the metal effects on lung CYPs, although, demonstrated recently that V^{5+} was able to decrease the TCDD-mediated induction of CYP1A1 mRNA, protein and catalytic activity (Anwar-Mohamed et al., 2009).

5. Air pollutant effects on respiratory system

There are changes associated with atmospheric pollutants that are evidenced with different patterns and diseases. Changes in the local lymphoid tissue, carcinogenic and genotoxic changes, fibrosis, COPD, are some of the outcomes observed after air pollution. Inflammation is core event in all the changes observed after the contact of the epithelial cells with the air pollutants, so it will be the first described in this section.

5.1 Inflammation and air pollution

The first suggestion of the consequences of air pollution date back to the serious events that occurred in Belgium in 1948 in the so called “killer fog” incident, and in the so called “London fog” that happened in the first week of December 1952 and provoked 4000 more deaths than those expected. After those episodes air pollution control policies were introduced since it became clear that air pollution was associated with an increase in morbidity and mortality in individuals with cardiovascular disease or with chronic obstructive pulmonary disease (Mills et al., 2009). The root of this increased mortality lay in the lung chronic inflammation that affects the pulmonary vascular endothelium, the thrombotic potential and the fibrinolytic balance in exposed individuals. These processes favor atherosclerotic plaque rupture, thrombosis and translocation of particulate matter to the blood, through the pulmonary capillaries; the latter affects directly the body vascular endothelium leading to the loss of endothelium integrity thus initiating a pulmonary and a systemic inflammatory reaction (Mills et al., 2006). A fraction of the translocated particulate matters accumulates in the liver, the spleen, the thymus and others (Nemmar et al., 2002).

Ambient particulate matter (PM) is a mixture of inhalable particles that are considered as serious contaminants. These particles come from the combustion of biomass fuels used for cooking and heating homes, emissions from internal combustion motors and industrial machinery, and forest fires (Torres-Duque et al., 2008). This matter has been grouped in coarse (2.5-10 μ m) and fine (2.5 μ m or less) depending on their diameter.. Both types induce serious health consequences in exposed individuals. Both types of particles penetrate into the lung, however the coarse particles are more dangerous because of their mass (Hetland et al., 2005). Obviously there are many inherent conditions in the exposed individual that increase the risk to develop cardiovascular or pulmonary disease: α -1 antitrypsin deficiency, family history of chronic obstructive pulmonary disease or atherosclerosis, personal history of frequent upper respiratory tract infections, hypersensitivity to inhaled irritants, tobacco, asthma, and being female (Ekici et al., 2005). Also, we must consider the enhanced air pollution in overcrowded cities with serious traffic problems. These cities usually have a higher concentration of PMs in the air. An increase of 7 μ g/m³ in the PM_{2.5-10} concentration is associated with a 5% decrease in FEV1 and an odds ratio of 1.33 for chronic obstructive pulmonary disease in women compared with men (Schikowski et al., 2005).

Both types of particles recruit and activate neutrophils, but PM_{2.5-10} induces a higher proinflammatory activity (Wegesser & Last, 2009). There are important differences in the relative concentration and type of components (metals, organic compounds, ultrafine particles adhered to larger particles) (Donaldson et al., 2005) between coarse and fine particles that depend on the season and geographic site where the sample is collected (Seagrave et al., 2006).

Other constituents of ambient particulate matter are biological materials, especially β -glucans, fungi spores and endotoxins that derive from gram-negative bacteria (Schwarze et

al., 2006). It has been shown that PM constituent responsible for the pro-inflammatory activity induced by PM_{2.5-10} are endotoxins and particularly a soluble fraction known as lipopolysaccharides (LPS) (Schins et al., 2004). The concentration of endotoxin in PM depends on the site and season, as we have already mentioned, but environmental humidity is associated with endotoxin concentration in particulate matter (Spaan et al., 2008). One example of the impact of biological components in PM is the heat shock protein HSP60 derived from *Chlamydia pneumoniae*, detected in PM_{2.5-10} that promotes lung inflammation and pulmonary dendritic cells activation through the innate immune response receptor TLR4 and the MyD88 pathway. The inflammation induced by HSP is secondary to an increase in the number of immune-related cells in the broncho alveolar lavage (BAL), enhanced recruitment of neutrophils, increased synthesis of IL-6 and over-expression of CD80 and CD86 in BAL dendritic cells (Bulut et al, 2009). HSP60 also activate pulmonary macrophages and endothelial cells through TLR4 in a MyD88-dependent pathway (Bulut, 2002). Interestingly, and independently from its endotoxin content, PM_{2.5} per se activate macrophages through TLR-2 y TLR-4 (Shoenfelt et al., 2009). Similarly, the respiratory epithelium, the first point of contact for inhaled foreign organism, also express TLR4 and secrete, upon activation, pro-inflammatory cytokines and chemokines that recruit neutrophils and T lymphocytes to the infection site (Parker & Prince, 2011).

Pulmonary inflammation induced by exposition to or inhalation of PM is closely related to particle processing by alveolar macrophages. Once these macrophages become activated a cascade of pro-inflammatory cytokines is initiated leading to endothelial damage. A recent study shows that in the presence of PM_{2.5-10} the amount of alveolar macrophages is duplicated and the amount of activated macrophages triplicates leading to persistent lung and systemic inflammation that were both associated with vascular endothelial dysfunction (Tamagawa et al., 2008). The increase in IL-6 serum concentration in PM_{2.5-10} exposed individuals was important during the first two weeks of exposure and was directly related to the amount of activated macrophages; afterwards, the concentration of IL-6 was similar in exposed individuals and controls. Alveolar macrophages activated with PMs secrete TNF- α , granulocyte-monocyte colony stimulating factor, and IL-1b (van Eeden et al., 2001). It is highly probable that these cytokines act not only locally but systemically thus generating a more organized inflammatory response that include the bone marrow. The acute exposure to PMs induces a rapid bone marrow response liberating leukocytes and platelets into the systemic circulation. As far as inflammatory cytokines in the pulmonary inflammation process, it has been shown that IL-6 inhibits directly the expression of eNOS thus diminishing nitric oxide production by the endothelium (Saura et al., 2006). Chemokine secretion is also altered in individuals exposed to particulate matter. Interleukin 8, a chemokine responsible for the recruitment and activation of pulmonary neutrophils in inflammation sites, binds to PMs (Seagrave, 2008). Activated neutrophils and macrophages secrete IL-8 and IL-1b. The excessive recruitment of neutrophils is clearly detected in BAL samples of individuals exposed to particulate matter.

A recent study analyzed the effect of daily changes in particulate matter air pollution upon the inflammatory cells response. The results showed that as the concentration of PM_{2.5-10} increases in the air the serum concentration of fibrinogen and the expression of E-selectin in exposed individuals increases whereas the concentration of prothrombin and von Willebrand antigen diminishes. The serum concentration of C reactive protein, coagulation factor VII, amyloid A and the soluble ICAM-1 fraction was not modified (Hildebrandt et al., 2009). Fibrinogen is an acute phase protein and a coagulation factor synthesized by the liver

in response to elevated IL-6 serum concentration (Gabay & Kushner, 1999). E-selectin reflects the activation of the vascular endothelium and it is well known that the increased expression of this adhesion molecule is associated with the serum concentration of inflammatory cytokines such as TNF- α , IFN- γ and IL-6 (Rice & Bevilacqua, 1989) as well as the recruitment of leukocytes and T lymphocytes in the inflammation zone. The presence of neutrophils in an IL-6 enriched environment enhances the expression of E-selectin in endothelial cells but also its apoptotic death thus perpetuating the inflammatory damage (Barnes et al., 2011). It has also been shown that prolonged exposure to PM_{2.5} is associated with an important plasmatic increase in endothelin-1 concentration and in an increased pulmonary artery pressure (Calderon-Garcidueñas et al., 2007). The contribution of all these processes in the lung keeps the inflammatory process alive.

Heat inactivation of PM_{2.5-10} diminishes the expression of CD14, CD11b/CR3 y HLA-DR and the phagocytic activity of alveolar macrophages (Alexis et al., 2006) but its influence in neutrophil recruitment into the airways is still controversial. Exposures to viruses, increase the serum concentration of INF- γ , previous to the inhalation of particulate matter induce a stronger pulmonary inflammation response that include oxidative damage to the lung. The result of these changes is a loss in the antibacterial function of neutrophils and alveolar macrophages and consequently, an increase in the local content of bacterial endotoxins (Sigaud et al., 2007) that perpetuates the pulmonary inflammation. Sigaud and coworkers (2007) also demonstrated that macrophages exposed to PMs have an enhanced expression of multiple inflammation-related genes: MCP-5, IL-9, IL-17B, IL-1b, MIP-1b, MIP-3b, IL-8R, C10, CCR-1, CCR-2 and MDC.

In summary, exposure to particulate matter induces excessive production of pro-inflammatory cytokines and chemokines by alveolar macrophages and lung dendritic cells, both of which are activated through TLR2 and TLR4 and the MyD88 signaling pathway. The excessive amount of these inflammatory molecules directly affect the pulmonary and systemic vascular endothelium by diminishing its capacity to regulate properly its vascular tone and permeability, triggering abnormal coagulation and fibrinolysis mechanisms, and increasing the adhesion of inflammatory cells to the vascular endothelium.

5.2 Bronchial associated lymphoid tissue (BALT) modifications

Bronchus-associated lymphoid tissue (BALT) is a constitutive mucosal lymphoid tissue adjacent to major airways. BALT is composed by B cells surrounded by a parafollicular region of T cells, dendritic (DCs) and macrophages. As the result of air pollution BALT can acquire antigens, allergens or contaminants from the airways, then complex interactions occur increasing its efficiency. For example, BALT can initiate local immune responses and the amount of BALT increases (Randall, 2010).

The presence of BALT in adult mammals depends on species, antigen stimulation and age. BALT is found in normal lungs of most healthy adult rabbits, rats, guinea pigs and old adult mice. In contrast, the presence and frequency of BALT in normal lungs of healthy adult humans is controversial (Kawamata et al., 2009).

In humans BALT is neither found at birth nor in healthy adults but transiently arises during childhood and adolescence. In both humans and mice, air pollution can induce BALT, data derives from splenectomized lymphotoxin α -deficient mice, which lack all secondary lymphoid organs but do develop BALT. This suggests that BALT can serve as induction sites for adaptive immune responses to contaminants. However, mechanisms that control the development and maintenance of BALT are largely unknown (Halle et al., 2009).

5.3 Carcinogenic and mutagenic effects

Lung cancer is the leading cause of cancer death worldwide. Smoking is the major risk factor for lung cancer. Although some subjects who have never smoked get lung cancer, smoking causes 9 out of 10 cases of this pathology. So there are other factors that promote the carcinogenic process. It has been reported that air pollution exposure may cause lung cancer. In a six US cities study, Dockery and coworkers (1993) found that the greatest effects were for lung cancer and cardiopulmonary disease, between the least and most polluted cities. Pope et al. (1995) found increased long-term effects on cardiopulmonary mortality and lung cancer in a 17-year follow-up (Naess et al., 2007). Also, Cao and coworkers (2011) analysis provides the first prospective evidence in China that air pollution (e.g., SO₂) may contribute to the increased risk for lung cancer mortality. In Europe, the proportion of lung cancers attributable to urban air pollution is estimated to be 11% (Molina et al., 2008). Likewise, it has been reported that the type of lung cancer is related to air pollution, for example, in a Spain study, individuals living near industries displayed an excess risk of lung cancer (OR=1.49; 95%CI=0.93-2.39), which attained statistical significance for small cell carcinomas (OR=2.23; 95%CI=1.01-4.92), residents in urban areas showed a statistically significant increased risk for adenocarcinoma (OR=1.92; 95%CI=1.09-3.38). In Aviles a health area, no differences in risk was found (López-Cima et al., 2011).

Urban air, particularly in densely populated urban environments, contains inorganic particulates (arsenic, asbestos, chromium, cadmium, lead and nickel), radionuclides (²¹⁰Pb, ²¹²Pb and ²²²Rn), gaseous and particulate organic species (benzene, benzo[α]pyrene, 1,3-butadiene and benzene-soluble organics), oxidants such as ozone and sulfur and nitrogen oxides in particle form. These substances are present as components of complex mixtures proceeding basically from industries emissions, combustion of fossil fuels for power generation or transportation, and all are related with carcinogenesis process (Naess et al., 2007).

Particulate matter (PM), especially fine particles of less than 2.5 μ m in diameter (PM_{2.5}) is related with lung cancer (Perez-Padilla et al., 2010). Pope and coworkers (2002) reported that each 10- μ g/m³ elevation in long-term average PM_{2.5} ambient concentrations was associated with approximately a 8% increased risk of lung cancer mortality, although the magnitude of the effect somewhat depended on the time frame of pollution monitoring. Particulate matter contains a lot of compounds that are considered human carcinogens like heavy metals such as cadmium, cobalt, chromium and nickel. Several epidemiological studies have clearly demonstrated that exposure to metals has toxic and carcinogenic effects in animals and humans; some of them have been demonstrated to be lung carcinogenesis promoters (Salnikow & Zhitkovich, 2008). Human cadmium exposure is associated with lung cancer. Also in animal models, cadmium induces lung carcinomas after inhalation (Beyersmann & Hartwig, 2008). At the cellular level, this metal affects cell proliferation, differentiation, apoptosis, and other cellular activities and may cause numerous molecular lesions that would be relevant to carcinogenesis (Mates et al., 2010). Inorganic cobalt compounds, both soluble and particulate forms, caused lung tumors in animal experiments (Beyersmann & Hartwig, 2008). The IARC recently classified the mixture cobalt/tungsten carbide (Co/WC) as carcinogenic to humans (Mates et al., 2010).

Chromium is other carcinogenic metal. Epidemiological studies have consistently shown that the lower respiratory tract is the target organ of Cr(VI) compound exposure, and

occupational exposure to these compounds is strongly associated with a higher incidence of lung cancer. Chromium exists in the environment in two major valence states, Cr(VI) and chromium (III) [Cr(III)], and Cr(VI) is actively transported into cells by the anionic transport system. The reduction of Cr(VI) to Cr(III) can lead to the formation of DNA-chromium adducts, DNA-DNA and DNA-protein cross-links, DNA-Cr(III)-amino acid ternary complexes and radical-mediated DNA strand breaks. In addition, it has been reported that lung cancer from workers exposed to Cr(VI) has a high percentage of G to T transversion mutations in the non-transcribed strand of the p53 gene (Feng et al., 2003). Chromium compounds also are capable to induce oxidative stress and the deregulation of cell proliferation (Beyersmann & Hartwig, 2008). On the other hand, several epidemiological studies demonstrated a strong correlation between nickel exposure and risk of lung and nasal cancer, especially in the case of workers at nickel refineries. Evidence from experimental animals has demonstrated the carcinogenicity of metallic nickel, which is also classified as possibly carcinogenic to humans (Group 2B). Nickel carcinogenesis involves epigenetic alterations, disruption of cellular iron homeostasis (by interfering with iron-dependent enzymes), generation of ROS, and activation of the hypoxia-signalling pathway (Salnikow & Zhitkovich, 2008).

Sulfur oxide pollution (as measured by sulfate particles and/or sulfur dioxide) is significantly associated lung cancer mortality. Elevated mortality risks have been associated primarily with measures of fine particulate and sulfur oxide pollution (Naess et al., 2007; Pope et al., 2002). Inhalation exposure to air pollutants, e.g., SO₂, has been associated with the DNA damage of multiple organs including the lung, providing a possible biological pathway through which air pollution may affect lung cancer incidence (Cao et al., 2011).

Exposure to nitrogen oxide (NO_x and NO₂) also is related to lung cancer (Naess et al., 2007; Raaschou-Nielson et al. 2010). Studies have been shown that women had particularly large effects for lung cancer in the young age group, somewhat less so for the old exposed to nitrogen oxide (Naess et al., 2007). Moreover NO_x exposure has significant correlations with adenocarcinoma (AC) type cancer incidence rates for both genders (Chen et al., 2009), although women seem to be more susceptible (Liaw et al., 2010). NO_x may potentially trigger mutagenic and carcinogenic activity and play significant roles in the metabolism and behavior of AC type lung cancer (Fujimoto et al., 1998). It appears that the higher the NO_x concentration, the higher the AC incidence rate. Recent studies on the role of NO in tumor progression suggest that NO is an important bioregulatory and signaling molecule and may play a role in the process of carcinogenesis (Tamir & Tannenbaum, 1996). NO is an endothelial growth factor that specifically mediates tumor vascularization (Jenkins et al., 1995) and tumor blood flow (Tozer et al., 1997). Exposure of cells to high NO concentrations cause DNA damage and apoptosis. Moreover, recent results have shown that NO stimulates p53 accumulation (Forrester et al., 1996). In summary, according to previous literature, NO and its derivatives can cause DNA damages (Wink et al., 1993) and play important roles in human lung AC (Fujimoto et al., 1998) (Liaw et al., 2010).

Airborne polycyclic aromatic hydrocarbons (PAHs) are emitted when organic matter is burned. It has long been known that several PAHs can produce cancers in experimental animals, and epidemiologic studies of exposed workers, especially in coke ovens and aluminum smelters, have shown clear excesses of lung cancer (Bostrom et al., 2002; Ben et al., 2004). PAHs have been suggested as being responsible for the initiation and development of lung cancer. PAHs and their metabolites are involved in mechanisms of

carcinogenesis; produce early chromosomal changes, transformation of cells in culture, cytotoxicity and mutagenicity. The benzo(a)pyrene (BAP) for example, directly damages p53. In smoking-related lung cancer, 40% of the p53 gene mutations are G to T transversions, and 90% of this type of mutation can be attributed to the non-transcribed (coding) strand. G to T transversion has been regarded as a hallmark of PAH-induced mutations in smoking-related lung cancer. Activated metabolites of PAHs in cigarette smoke, including benzo[a]pyrene diol epoxide (BPDE), preferentially form DNA adducts at methylated CpG sites along the p53 gene corresponding to the afore mentioned major mutational hotspots in smoking-related lung cancer (Feng et al., 2003).

On the other hand, radon gas is a naturally occurring radioactive gas that can seep out of the soil into buildings, also emanates from uranium-bearing soil and porous rock. Radon is the second biggest cause of lung cancer after smoking. The cancer risk from radon increases the risk from smoking. Radon induces damage to a checkpoint tumor suppressor gene such as Tp53 (which codes for p53) since alpha particle radiation is a key mechanism for radon-related lung cancer (Harley et al., 2008; Bissett & McLaughlin 2010). Some studies suggest a relationship between the AGGARG-ATGMET transversion in codon 249 of P53 from people exposed to high radon concentrations (Ruano-Ravina et al., 2009). The damage done to epithelial cells of the lung occurs when radiation interacts either directly with DNA in the cell nucleus or indirectly through the affect of free radicals (UNSCEAR, 2000). Recently, *in vitro* studies of cells exposed to alpha-particle radiation gave evidence that more cells showed damage than those that were traversed by alpha-particles (Sawant et al., 2001; Alavanja 2002). Radon produces oxidative stress, although some similarities in the increased frequency of p53 mutations at a later stage in this process, DNA damage in the form of sister-chromatid exchange and mutations, have been observed for both smokers and those exposed to radon gas (Alavanja 2002). Other studies provided evidence of a GSTM1 and radon interaction in the increasing risk for lung cancer. Glutathione-S-transferase M1 (GSTM1) conjugates known carcinogens such as epoxides of polycyclic aromatic hydrocarbons (Risch & Plass, 2008). Other studies show that radon exposure in miners induces gene mutations and chromosomal aberrations. Numerous *in vitro* cytogenetic studies demonstrated that radon induces different types of genetic and cytogenetic damage that is likely to play a role in radon lung carcinogenesis (Al-Zoughool & Krewski, 2009).

5.4 Genotoxic effects

Generation of DNA damage is considered an important initial event in carcinogenesis. Multiples assays exist for the detection of different genotoxic effects of compounds in experimental systems, or for exposure investigation for genotoxic agents in environmental or occupational settings (Moller 2005). Cells with DNA damage are more susceptible to develop mutations after exposure to xenobiotics (Olive et al. 2001). For this reason, genotoxic evaluation of environmental pollutants is necessary in the respiratory system, because it is the first contact for inhaled xenobiotics.

Studies on environmental pollution (and their components), genotoxicity and respiratory tract, have been carried out *in vivo* and *in vitro*. Table 1 summarizes the results obtained in the last years.

A number of studies have considered DNA damage as an endpoint for the effects of air pollutants (Vineis & Husgafvel- Pursiainen 2005). In this report, we evidence the results

obtained by genotoxic profiles, indicating that air pollutants cause alterations in the genetic material of the tested cells (strand breaks [illustrate in Figure 7], oxidative damage, adducts and micronucleus). DNA damage could provoke mutations in any cell from the respiratory tract and, may facilitate the development of neoplastic events.

	Exposure	System/Tissue	End Point	Results	Reference
<i>In vivo</i>					
	DEP Inhalation	Big Blue rats Male Lungs	Mutant frequency Mutation spectra DNA adducts 8-OHdG levels	+ + + +	Sato et al., 2000
	DEP Inhalation	Mice Female Lungs Bronchioalveolar lavage cells	8-OHdG levels DNA strand breaks (comet assay)	+ +	Risom et al., 2003
	DEP Inhalation	Mice	DNA adducts DNA strand breaks (comet assay) DNA oxidative damage Mutation frequency	+ + + -	Dybdahl et al., 2004
	Environmental Pollution	Human Females/males Nasal epithelial cells	DNA strand breaks (comet assay)	+	Fortoul et al., 2010
<i>In vitro</i>	DEP	A549 cells	DNA strand breaks (comet assay)	+	Dybdahl et al., 2004
	Particulate Matter (PM _{2.5} and PM ₁₀)	A549 cells	DNA strand breaks (comet assay)	+	Gutierrez-Castillo et al., 2006
	Particulate Matter (PM ₁₀)	A549 cells	Micronucleus	+	Roubicek et al., 2007
	Fine Particles	A549 cells	DNA strand breaks (comet assay)	+	Sharma et al., 2007
	Nitrogen dioxide (NO ₂)	Nasal epithelial cells	DNA strand breaks (comet assay) Micronucleus	+ -	Koehler et al., 2010

DEP: Diesel Exhaust Particles. A549 cells: human lung epithelial cell line. +Positive results. - Negative results. PM_{2.5}: Particulate Matter with aerodynamic diameter $\leq 2.5 \mu\text{m}$. PM₁₀: Particulate Matter with aerodynamic diameter $\leq 10 \mu\text{m}$.

Table 1. Genotoxic damage studies associated with air pollutants.

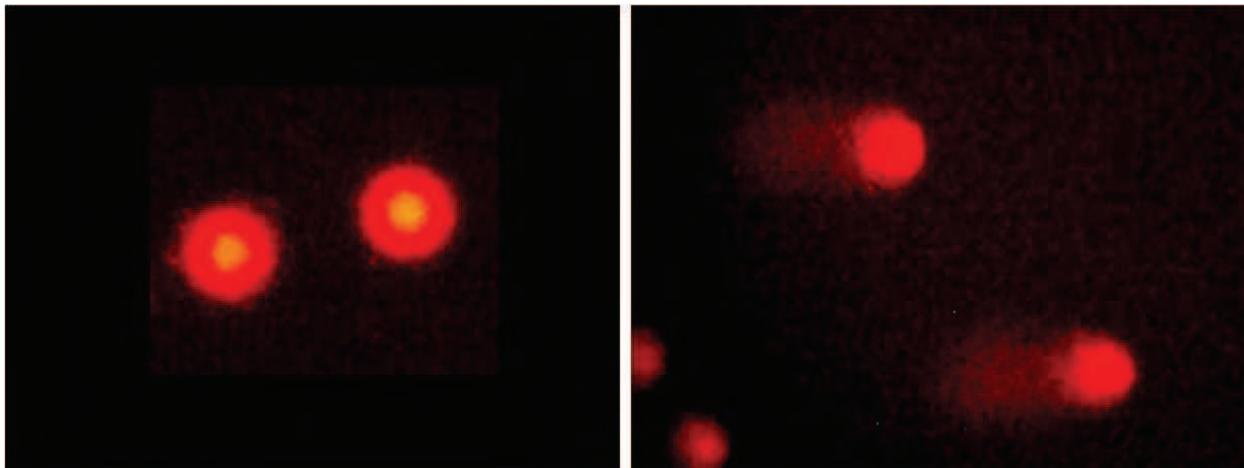


Fig. 7. Comet assay in nasal epithelial cells. Left: Undamaged Cells. Right: Damaged Cells (comets).

5.5 Pulmonary fibrosis and atmospheric pollution

Pulmonary fibrosis is the end result of a diverse group of lung disorders. Although there are multiple initiating agents for pulmonary fibrosis, including toxins, fibres/particles, autoimmune reactions, drugs and radiation, the etiology of the majority of cases of pulmonary fibrosis is unknown and these cases are referred to as Idiopathic Pulmonary Fibrosis (IPF). The harmful effects of environmental pollution on the respiratory system are undeniable. The combustion of fuels and its derivatives are the main cause for pollutant emission through engines and industrial plants (Zuurbier, et al., 2011). Chronic exposure to particulate matter, ozone and cigarette smoke can produce long-term effects on the lungs. This source of pollutants sets the lungs in a situation of constant aggression that result in a state of chronic inflammation, which could lead to pulmonary fibrosis (Churg & Wright, 2002).

5.5.1 Fibrotic lung reactions due to air pollution

The etiology for lung's fibrotic reactions is still unknown and it has been proposed a variety of environmental stimuli, such as metals, cigarette smoke, drugs and infectious agents (Araya & Nishimura, 2010). The degree of fibrosis will depend on the response of each individual, even with similar exposures, indicating that host genetic factors influence the fibrotic response of the patient (Westergren-Thorsson, et al., 2010).

Diesel exhaust particulate matter in polluted environments derived from internal combustion engines, increases the transcription of inflammatory cytokines and antimicrobial peptides, contributing to increased inflammatory response of airways in patients with chronic obstructive pulmonary diseases (COPD) (Nam, et al., 2006). This induces an oxidative state caused by lung macrophages that increase pulmonary responses and could result in irreversible lung fibrosis (Figure 8).

It has now been implicated the Transforming Growth Factor β 1 (TGF- β 1) as a key factor in the lung fibrotic response (Datta et al., 2011; Koli et al., 2008). The changes caused by TGF- β 1 could be observed in repeated injuries of the airways, as occurs in asthma, chronic obstructive pulmonary disease and pulmonary fibrosis (Araya & Nishimura, 2010).

Exposure to cigarette smoke produces a large amount of reactive oxygen species and activates latent TGF- β 1. The inhalation of this smoke promotes the recruitment of macrophages and neutrophils that are important sources of reactive oxygen species and also

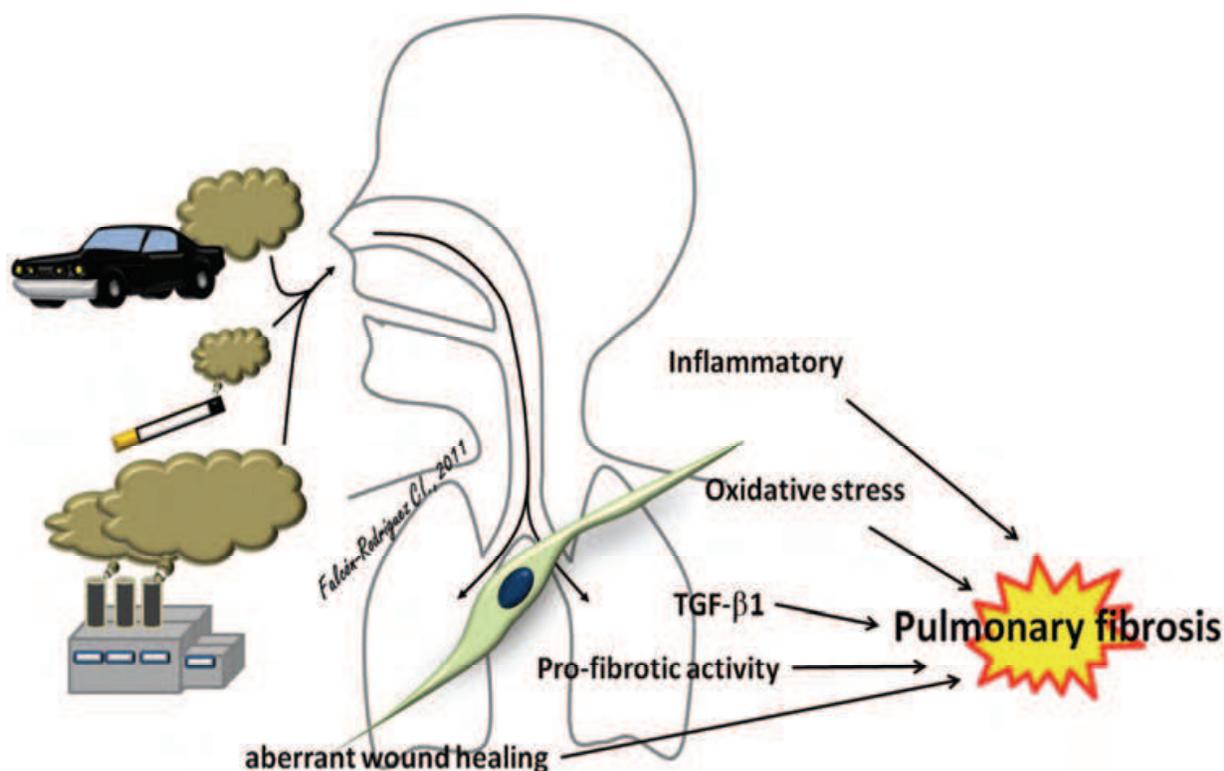


Fig. 8. Environmental pollution from various sources, such as transition metals, particle exposure, noxious drugs, cigarette smoke, induces repetitive cellular injury and inflammation. This leaves the tissue susceptible to increased TGF- β 1, inflammation, profibrotic signals and aberrant wound healing, all of which may contribute to the progression of pulmonary fibrosis.

contribute to activate TGF- β 1 (Westergren-Thorsson, et al., 2010). On the other hand, TGF- β 1 induces transdifferentiation of fibroblasts to myofibroblasts and perpetuates the fibrogenic process, also providing a protective effect against myofibroblasts apoptosis, which are not removed once the lung lesions healed (Song et al., 2011).

Asbestos can induce lung fibrosis in occupational and experimental exposures, (Ross and Murray, 2004; Dai & Churg, 2001). Mineral dusts can directly induce fibrosis in the airway wall, and this has been studied *in vivo*. Coexposures to cigarette smoke or ozone increase the fibrogenic effect of mineral dusts (Churg & Wright, 2002; Churg et al., 1996). Asbestosis and mineral dusts exposure increase the gene expression of profibrotic factors: TGF- β 1 and platelet derived growth factor (PDGF) that also increases procollagen. These changes may explain fibrosis progression (Churg and Wright, 2002; Churg et al., 1999). There is also human evidence of small airway remodeling in chronic exposure to high levels of particulate air pollution (Churg et al., 2003).

Oxidative stress, as a consequence of an inflammatory stimulus such as air pollution, plays a critical role in the pathogenesis of IPF (Park et al., 2009). Fibrotic stimuli of unknown origin are thought to create an imbalance between oxidant production and antioxidant protection, resulting in the accumulation of reactive oxygen species (ROS) (Rahman et al., 1999). The precise pathways leading from injury to fibrosis are not well established, but oxidants may contribute to the production of profibrotic factors such as TGF β , and oxidized proteins have been reported in human subjects with IPF. In addition, some studies have reported

that various antioxidant enzyme systems protect against lung fibrosis (Gao et al., 2008; Khang et al., 2003).

5.6 Chronic obstructive pulmonary disease (COPD)

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive condition characterized by airflow limitation which is usually reversible (MacNee, 2007). Although smoking habit is the main factor associated with COPD, air pollution has been implicated in its pathogenesis, and there is enough evidence to support the association between air pollution and COPD exacerbations and worsening of those with pre-existing COPD. Particulate Matter (PM), Nitrogen Oxides (NO_x) are associated with its development (Salvi & Barnes, 2009).

Some of the observed changes are the increase in the presence of goblet cells (mucous metaplasia) as well as submucose glands hyperplasia. This increase in mucus production will result in reduced mucociliary clearance. Emphysema, the enlargement and destruction of the alveolar spaces, is also part of this entity, because the decrease in the elastic recoil of the lung the air is trapped in the alveoli. Small airways are very important components in this entity. The changes, such as inflammation and fibrosis modify the prognosis: the greater the damage the poorer the prognosis.

The main participant in the progression of the bronchial damage is the inflammatory response. The epithelial cells generate this response when they are exposed to air pollutants or other irritants such as cigarette smoke, then a variety of pro-inflammatory, pro-fibrotic and mitotic factors are liberated. These factors increase endothelial permeability; activate macrophages, CD8⁺ Lymphocytes, and neutrophils. These cells produce more inflammatory factors, which, in chronic exposure inflammation leads to airway remodeling. (Figure 9) (Roth, 2008).

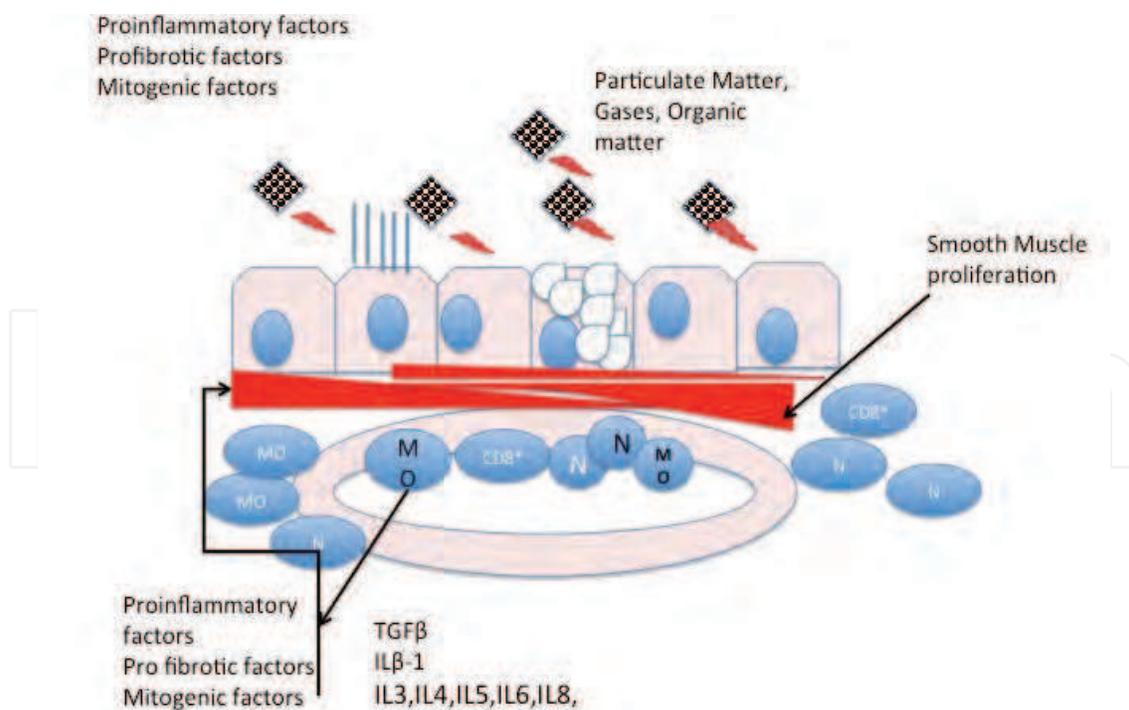


Fig. 9. The respiratory epithelium produces proinflammatory factors that will activate macrophages (MO), will increase neutrophil (N) and CD8⁺ lymphocytes migration (CD8⁺). Also, smooth muscle proliferation is observed, as well as an alteration of the extracellular matrix.

Remodeling includes smooth muscle and fibroblast proliferation, synthesis of extracellular matrix (MMPs), decrease in proteases synthesis and increase in gelatinases. The sum of all these events will maintain the obstruction observed in these patients.

6. Conclusion

Further studies are needed to assess the impact of atmospheric pollution in the development of respiratory diseases, and to explore new therapeutic approaches to reverse the progression of the chronic changes that currently are observed in asthma, COPD, fibrosis and cancer.

7. Perspectives

More information about the differences in the response to air pollutants is needed, as well as the possible treatments, if any of the biomarkers is found. This drives us to the need for more specific biomarkers to identify the severity of the inflammation, or the type of inflammation. Because air pollution is a complex mixture of organic and inorganic elements, more detailed information about specific characteristics of each pollutant response would be very helpful.

The lung has its own responses and support for more research in this field of interest, must be encouraged.

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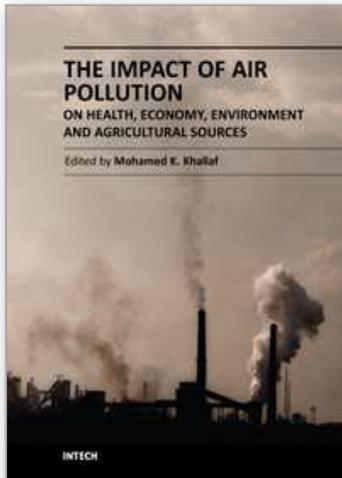
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This book aims to strengthen the knowledge base dealing with Air Pollution. The book consists of 21 chapters dealing with Air Pollution and its effects in the fields of Health, Environment, Economy and Agricultural Sources. It is divided into four sections. The first one deals with effect of air pollution on health and human body organs. The second section includes the Impact of air pollution on plants and agricultural sources and methods of resistance. The third section includes environmental changes, geographic and climatic conditions due to air pollution. The fourth section includes case studies concerning of the impact of air pollution in the economy and development goals, such as, indoor air pollution in México, indoor air pollution and millennium development goals in Bangladesh, epidemiologic and economic impact of natural gas on indoor air pollution in Colombia and economic growth and air pollution in Iran during development programs. In this book the authors explain the definition of air pollution, the most important pollutants and their different sources and effects on humans and various fields of life. The authors offer different solutions to the problems resulting from air pollution.

How to reference

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