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Material particulado y resistencia a la insulina: el papel de la inflamación y el estrés oxidante

TESIS QUE
P R E S E N T A

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Este trabajo se realizó en el Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (CINVESTAV-IPN) bajo la tutoría de la Dra. Andrea De Vizcaya Ruiz. Debido a la situación de pandemia de Covid 19 que inició en Marzo de 2020 y transcurrió hasta Agosto 2021 no fue posible llevar a cabo actividades presenciales en el CINVESTAV-IPN, por lo que esta tesis consiste en una revisión bibliográfica del tema original, y se enviará a la revista "Environmental Toxicology and Pharmacology (ETAP)" para su publicación. Esta tesis fue apoyada por el proyecto del Consejo Nacional de Ciencia y Tecnología (CONACyT) CB-2016 286739. El C. Joab Eliu Sánchez Gasca recibió la beca 1008875 del CONACyT para la realización de sus estudios de maestría.

RESUMEN

La contaminación atmosférica por material particulado (PM) suspendido en el aire en ambientes urbanos es un problema ambiental y de salud pública a nivel nacional y global. Dado que el PM está presente inherentemente en el aire y su origen proviene de fuentes naturales como la actividad volcánica e incendios forestales no intencionales y actividades antropogénicas como procesos industriales relacionados a la quema de combustibles fósiles o procesos de transformación y la emisión de vehículos, la población se encuentra expuesta de manera involuntaria a este contaminante. Además, la presencia del PM en el aire en ciudades se ha relacionado con el incremento de enfermedades cardiopulmonares, y, recientemente, se ha asociado también con afecciones metabólicas como la diabetes mellitus tipo 2 y el síndrome metabólico que cursan con el desarrollo de un estado de resistencia a la insulina. Dada su reactividad, se plantea la hipótesis de que derivado del daño pulmonar causado por la exposición a PM se podría inducir una toxicidad sistémica, así como un estado de resistencia a la insulina al ejercer efectos metabólicos negativos (como la desregulación de adipocinas, citocinas y disfunción de la vía de la insulina) en órganos distales causada por mecanismos continuos o sostenidos de inflamación y estrés oxidante. Con base en lo anterior, el presente trabajo pretende proporcionar una revisión actualizada de la evidencia científica de la posible relación entre la exposición a PM y el desarrollo de resistencia a la insulina a través de los mecanismos de inflamación y estrés oxidante.

ABSTRACT

Air pollution by PM is a national and global environmental and public health issue. Since PM is inherently present in the air emitted from natural sources as volcanic activity and unintentional forest fires and anthropogenic activities such as industrial processes related to the burning of fossil fuels or transformation processes and vehicle traffic exhaust, the population is exposed inadvertently to this contaminant. Furthermore, the presence of PM in cities and megacities has been related to an increase in cardiopulmonary diseases; and, recently, it has also been associated with metabolic conditions such as type 2 diabetes mellitus and metabolic syndrome through the development of a state of insulin resistance. Given its reactivity, it is hypothesized that induced-lung injury from the exposure to PM may be involved in the development of a state of insulin resistance by exerting negative metabolic effects (such as dysregulation of adipokines, cytokines and dysfunction of the insulin pathway) in distal organs caused by continuous or sustained mechanisms of inflammation and oxidative stress. Based on the above, the present work aims to provide an updated review of the scientific evidence on how exposure to PM promotes the development of insulin resistance through the mechanisms of inflammation and oxidative stress.

Con el amor y gratitud que nunca dejarán de ser…

"Ruégote que las dos partes de tu espíritu sean sobre mí…"
- 2da de Reyes 2:9 (Reina – Valera 1909) -

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ACRÓNIMOS Y ABREVIATURAS

ACE: Enzima convertidora de angiotensina 1

ANG: Angiotensinogeno

Ang-1: Angiotensina tipo 1

Ang-2: Angiotensina tipo 2

AP-1: Proteína activadora tipo 1

ATP: Adenosín trifosfato

AT_1R: Receptor de angiotensina tipo 1

CAT: Catalasa

COPD: Enfermedad pulmonar obstructiva crónica

COX2: Ciclo-oxigenasa tipo 2

CP: Partículas gruesas

CRP: Proteína C reactiva

CVD: Enfermedades cardiovasculares

FP: Partículas finas

F6P: Fructosa 6 fosfato

GLUT: Transportador de glucosa

GPx: Glutatión peroxidasa

G6P: Glucosa 6 fosfato

G-CSF: Factor estimulante de colonias de granulocitos

HDL: Lipoproteínas de alta densidad

HOMA-IR: Modelo homeostático de evaluación de la resistencia a la insulina

ICAM1: Molécula de adhesión intracelular 1

IFNγ: Interferon gamma

IHME: Instituto de Métricas y Evaluación de la Salud

IL: Interleucina

InsR: Receptor de insulina

IR: Resistencia a la insulina

IRS: Sustrato del receptor a la insulina

JNK: Cinasa Jun N-Terminal

LDL: Lipoproteínas de baja densidad

MAPK: Proteín cinasas activadas por mitógeno

MCP-1: Proteína quimiotáctica de monocitos tipo 1

MD: Enfermedades metabólicas

MDA: Malonaldehído

MetS: Síndrome metabólico

MIP-3a: Proteína inflamatoria de macrófagos tipo 3

NAFLD: Enfermedad del hígado graso no alcohólico

NASH: Esteatohepátitis no alcohólica

NFκB: Factor nuclear kappa B

NLRP3: Dominio de unión a nucleótidos y proteína repetida rica en leucina 3

NO: Óxido nítrico

OMS: Organización Mundial de la Salud

OxS: Estrés oxidante

PAH: Hidrocarburos aromáticos policíclicos

PAMP: Patrones moleculares asociados a patógenos

PM: Material particulado

RAS: Sistema renina angiotensina

ROS: Especies reactivas de oxígeno

SOD: Superóxido dismutasa

TLR: Receptor tipo Toll

TNFα: Factor de necrosis tumoral alfa

Tyr: Tirosina

T1DM: Diabetes mellitus tipo 1

T2DM: Diabetes mellitus tipo 2

UFP: Partículas ultrafinas

VCAM1: Proteína de adhesion vascular cellular tipo 1

VLDL: Lipoproteínas de muy baja densidad

I. Introducción

La organización mundial de la salud (OMS) considera que la contaminación atmosférica representa una amenaza a nivel global, estimando que el 90% de la población mundial respira aire contaminado y que 7 millones de personas mueren anualmente a causa de esto. Asimismo, es importante hacer notar que es practicamente imposible evitar la exposición a este tipo de contaminantes en interiores y exteriores (ej. PM, ozono, dióxido de azufre, etc.) (WHO, 2018).

Actualmente, el impacto de la contaminación atmosférica se ha centrado en el estudio del material particulado (PM). Con base en ello, la *"Global Burden of Disease"* en 2017 publicó que las partículas finas (FP) son la causa del 7.6% del total de muertes a nivel mundial (Schraufnagel et al., 2019). Además, existe evidencia creciente sobre la relación entre la exposición al PM con múltiples enfermedades, las cuales no se encuentran limitadas a las vinculadas con el daño pulmonar. En 2019 el "Comité Ambiental del Foro Internacional de Sociedades Respiratorias" publicó que la exposición a PM y otros contaminantes atmosféricos se asocia positivamente con el incremento de enfermedades metabólicas (MD) como la diabetes mellitus tipo I y II (T1DM y T2DM), síndrome metabólico (MetS), hipertensión idiopática, enfermedad del hígado graso no alcohólico (NAFLD), obesidad (Dang et al., 2018; Schraufnagel et al., 2019) y desnutrición (relacionada con retraso en el crecimiento) (Kannan et al., 2006; Peter et al., 2015; Sinharoy et al., 2020; Spears et al., 2019), entre otros.

Durante la última década, evidencia epidemiológica ha relacionado la exposición a niveles altos de PM en zonas urbanas y la presencia frecuente de padecimientos como la T2DM y MetS. Por ejemplo, Bowe et al. (2018) demostró que la exposición a FP se asocia con el incremento en el riesgo de desarrollar T2DM. Se estima que aumentos de 10 $\mu g/m^3$ en la concentración ambiental de FP incrementan el riesgo de desarrollar DMT2 entre 5-27% y de 1-15% para partículas gruesas (CP) (Wolf et al., 2016). De igual forma, Lee et. al. (2019) observó que la exposición a concentraciones promedio de 26 $\mu g/m^3$ de FP se asocia con un riesgo mayor (HR: 1.070, 95% IC: 1.032-1.110) de desarrollar MetS. Además, en el mismo estudio, se encontraron asociaciones positivas con obesidad (HR: 1.510, IC 95%: 1.422-1.601), hipertensión (HR: 1.499, IC 95%: 1.441-1.559), hipertrigliricidemia (HR: 1.468, CI 95%: 1.424-1.513), HDL (HR: 1.627, CI 95%: 1.564-1.693) e hiperglucemia (HR: 1.380, CI

95%: 1.338-1.423). No obstante, existe un estrecho vínculo en el desarrollo de T2DM y el MetS. Ambas enfermedades, así como los padecimientos metabólicos previamente mencionados, se caracterizan por la presencia de un estado de resistencia a la insulina (IR) (Yaribeygi et al., 2018).

Actualmente, aunque no se conoce el mecanismo exacto por el cual la exposición a PM promueve el desarrollo de MD, múltiples autores sostienen que esto puede ser consecuencia de las diferentes características del PM, entre las que se encuentran el tamaño y la composición, además de la concentración ambiental de exposición. En este sentido, existe un vínculo estrecho en el que la exposición a contaminantes atmosféricos, como el PM, se presentan como factor de riesgo al promover el estado de IR, el cual, podría ser posiblemente potenciado por mecanismos de inflamación y estrés oxidante (OxS) (Cuiquing et al., 2013; Gomes-Heck et al., 2017; Kodavanti, 2015; Wolf et al., 2016). Por ello, el objetivo del presente escrito fue revisar y organizar la información para proporcionar una visión actualizada de la evidencia toxicológica sobre cómo la exposición a PM promueve el desarrollo de la IR a través de los mecanismos de inflamación y estrés oxidante.

II. Revisión bibliográfica

Airborne particulate matter and insulin resistance: the role of inflammation and oxidative stress

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Highlights

- Lung injury caused by exposure to particulate matter releases systemic mediators of inflammation and oxidative stress that can reach distal organs.
- Inflammation and oxidative stress of pulmonary origin can promote insulin resistance due to adverse metabolic effects in distal organs via the dysregulation of biologically important molecules (such as adipokines and cytokines) and the insulin pathway dysfunction.
- An increase in the atmospheric concentration of particulate matter is linked with the prevalence of insulin resistance-related diseases.

Abstract

Particulate matter (PM) air pollution is a global environmental and public health concern. Recent reports have identified associations between urban PM concentration and increments in non-communicable diseases such as type 2 diabetes mellitus and metabolic syndrome. The link between both conditions involves insulin resistance (IR) development. PM-induced lung injury alters the metabolic state (e.g. dysregulation of adipokines, cytokines and, dysfunction of the insulin pathway) of distal organs. These alterations result from sustained inflammation and oxidative stress, leading to IR. The present narrative review provides an updated revision of the toxicological evidence supporting that PM exposure promotes IR through inflammation and oxidative stress.

Keywords: Particulate matter, insulin resistance, inflammation, oxidative stress.

1. Introduction

Exposure to airborne particulate matter (PM) is positively associated with the increase in metabolic diseases (MD) such as type II diabetes mellitus (T2DM) and metabolic syndrome (MetS) (Dang et al., 2018; Schraufnagel et al., 2019). There is a close link in the development of T2DM and MetS; both conditions are characterized by insulin resistance (IR) (Freeman & Pennings, 2020; Yaribeygi et al., 2018). Currently, the exact mechanism by which PM promotes T2DM and MetS is unknown. Some authors propose that exposure to PM promotes IR development, triggered or enhanced by mechanisms of inflammation and oxidative stress (OxS) (Gomes-Heck et al., 2017; Kodavanti, 2015; Wolf et al., 2016). Hence, this narrative review aims to synthetize the scientific evidence that supports the notion that PM exposure can impact systemic health and in particular its relationship with inflammation and OxS in an IR condition.

2. Airborne particulate matter

Airborne particulate matter (PM) is a heterogeneous mixture of liquid and solid particles of organic and inorganic components, which exist as a polydisperse suspension in the air. Although the origin of PM varies, many of it is essentially composed of an elemental carbon nucleus to which different chemical constituents are adhered to it, such as polycyclic aromatic hydrocarbons (PAH), sulphates, nitrates, metals and metalloids (e.g., V, Cu, Fe, Cd, Hg, Pb, As, Ba, Cr, Zn, etc), and also contain biologicals such as pollen or toxins of bacterial and fungal origin (Mukherjee & Agrawa, 2017). Moreover, the type and concentration of PM constituents directly depend on spatiotemporal related variables, among them are atmospheric conditions and anthropogenic emission sources of specific locations (Cheng et al., 2016; Manzano-León et al., 2016), ie. temperature, humidity, agricultural and industrial

activities, vehicle traffic, fuel characteristics, soil erosion, volcanic activity and forest fires (Kampa & Castanas, 2008). Based on its aerodynamic diameter, PM can be classified into total suspended particles (TSP) (>10 μm), particles of ≤10 μm of aerodynamic diameter or PM_{10}, coarse particles (CP) (<10 – 2.5 μm), fine particles or $PM_{2.5}$ (FP) (≤2.5 μm) and ultrafine particles (UFP) (≤0.1 μm). PM size is critical for its toxicity via the inhalation route of exposure in humans since smaller PM size allows it to penetrate deeper into the respiratory airways inducing local tissue injury, additionally PM can translocate or dissolve in different biological fluids such as lung surfactant fluid, lymph, and blood. Thus, PM can exert its toxic action directly in the lung and in distant organs or tissues beyond the port of entry, the respiratory tract (Kampa & Castanas, 2008; WHO, 2018).

3. Toxicity of PM exposure: inflammatory and oxidative damage and their link with the metabolic effects

After contact with a biological target, mainly via the respiratory system, PM exerts its toxicity through two closely related cellular processes, the inflammatory response and OxS (Ovrevik et al., 2015; Schraufnagel et al., 2019; Thompson, 2018). Following PM exposure, these mechanisms impact the respiratory system and induce bronchoconstriction, epithelial irritation, edema and fibrosis, and respiratory diseases such as asthma, emphysema, chronic obstructive pulmonary disease (COPD) and have been linked with lung cancer (Yang et al., 2020). Furthermore, evidence indicates the manifestation of adverse effects on the cardiovascular system beyond the pulmonary events that are directly related to the exposure to PM, converting the cardiovascular system a target of PM toxicity. Moreover, several authors report central compartment effects and consequences due to direct translocation of PM into the circulation or via biological mediators. In the cardiovascular system is directly

related to cardiovascular diseases (CVD), involving atherosclerosis, stroke, myocardial infarction, heart failure and even deep vein thrombosis. Exposure to PM increases in the blood concentration of intracellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1) and fibrinogen. These four molecules are essential indicators of alteration in the vascular endothelium´s homeostatic state (Bourdrel et al., 2017; Weidong et al., 2018). Exposure to environmental pollutants can generate OxS in the vascular endothelium, decreasing nitric oxide (NO) availability, which would lead to vasodilation and damage to the endothelium. Vascular endothelial dysfunction is directly related to the promotion of atherosclerosis. Some authors have shown that PM exposure can decrease blood flow due to increased vascular resistance. However, OxS can also alter the functional structure of circulating lipids. In this sense, PM favors the structural oxidation of lipids, promoting an increase in the concentration of oxidized lipids, known pro-atherogenic molecules, which can diffuse to the subendothelial space and stimulate the release of vasoactive substances and pro-inflammatory molecules such as ICAM-1, VCAM-1 and monocyte chemotactic protein type 1 (MCP-1) which recruit monocytes and macrophages to the endothelium. Furthermore, exposure to PM also promotes vascular inflammation, lipid oxidation, foam cell formation and endothelial plaque progression events that are closely related to CVD and MD (Bourdrel et al., 2017; Manzano-León et al., 2013).

Interestingly, other studies as that reported by Aztatzi-Aguilar et al. (2015) introduce a new perspective evidencing the relationship between PM exposure, cardiovascular damage and the renin-angiotensin system (RAS) via the modulation of angiotensin-1 receptor (AT_1R), this study focused on assessing the cardiopulmonary toxicity in rats sub-chronically exposed to PM by inhalation. In addition, the activation of Acta1a and Col3a1 in the heart as biomarkers of a reprogramming response due to the inflammation and OxS by PM exposure

were observed. In this study, an increased in the secretion of IL-6 and in the transcript and protein levels for AT_1R in the lungs and heart were also reported. These responses occurred concomitant with an increase of the angiotensin-converting enzyme type 1 (ACE) in the lungs. This finding is relevant because angiotensinogen (ANG) generates type 1 angiotensin (Ang-1), which is a substrate for the ACE, producing type 2 angiotensin (Ang-2) the end-ligand for the AT_1R. Systemic inflammation caused by PM exposure can intensify this event, since increments of TNFα and IL-1β are inducers of ANG production, and IL-6 for AT_1R. Hence, these studies have opened the door to new research perspectives, such as to suggest that a factor that contributes to the development of IR is RAS hyperactivity (Olivares-Reyes et al., 2009), which in this scenario is activated by PM exposure. One of the current research perspectives focuses on the cross-linking of the RhoA / Rho-kinases pathway, activated by the AT_1R and the insulin pathway. Likewise, some authors suggest that this could be due to erroneous phosphorylation or inhibition at the level of the insulin receptor substrate (IRS) (Aztatzi-Aguilar et al., 2015; Forrester et al., 2018).

These processes suggest that the interaction or crosstalk in these molecular pathways may contribute in the development of IR, metabolic effects in distal tissues (beyond the lung) and, consequently, in some cases, the promotion of T2DM and MetS.

3.1. The hypothesis of lung injury and the link with metabolic effects

The scientific evidence demonstrates that PM inhalation effects are not limited to the pulmonary level, but it reach other organs beyond the respiratory tissue and alter their morphophysiology, either due to the particle's presence, one of its components or via biological mediators (Aztatzi-Aguilar et al., 2015; Dang et al., 2018; Gomes-Heck et al., 2017; Kodavanti, 2015). Based on this notion, inflammation and OxS mechanisms of PM

toxicity, some authors hypothesize that the initial lung injury caused by PM exposure produces a state of systemic inflammation. This systemic inflammation promoted by involuntary exposure to PM is also known as low-grade systemic inflammation (León-Pedroza et al., 2015; Wolf et al., 2016). The consequent release of biological mediators such as cytokines, chemokines and growth factors (TNFα, IL-1β, IL-6, IL-8, MCP-1 and G-CSF), vasoactive molecules (VCAM1, ICAM1, CRP and fibrinogen) and, oxidated proteins and lipids can produce a negative metabolic response involving peripheral tissues, such as liver, adipose tissue and skeletal muscle, that are participants in metabolic alterations such as IR condition **(Figure 1)** (Bass et al., 2013; Sun et al., 2013). Reyes-Caballero et al. (2019) evaluated the metabolic alteration after subchronic exposure to FP in C57BL7/6 mice with a normal diet. They observed a decrease in glucose-6-phosphate (G6P), fructose-6-phosphate (F6P) and glycogen in the liver, thus evidencing an alteration in glucose metabolism. Also, they observed the depletion of hepatic ATP (possibly due to changes in the mitochondria oxidative phosphorilation) that combined with the decreased G6P levels as a substrate, reduced glycolysis and the Krebs cycle. Increased total NAPDH and decreased glutathione capture promoting OxS and the decreased of antioxidant mechanisms.

These mechanisms would explain the relationship between PM exposure and IR development. Additionally, the pathophysiology afore mentioned sets the basis for an IR condition (Dang et al., 2018; Gomes-Heck et al., 2017; Kodavanti, 2015; Schraufnagel et al., 2019).

4. Insulin resistance

IR is defined as a state or condition in which insulin exhibits a decrease in responsiveness at a cellular level in peripheral tissues; it mainly affects the liver, adipose tissue and skeletal

muscle; as result, blood glucose levels do not drop. This disorder is favored by a systemic oxidant and inflammatory environment accompanied by an increase in insulin secretion that tries to compensate for the cellular defect to maintain blood glycemic balance (Petersen & Shulman, 2018; Yaribeygi et al., 2018). IR is the main factor among a group of metabolic events that compose MetS, considered a stage that precedes T2DM. IR is related to dyslipidemia, elevated blood pressure, and accumulation of abdominal fat or obesity, risk factors that also contribute too for MD, such as MetS (Petersen & Shulman, 2018). These parameters also belong to the leading group of the "Global of Burden of Diseases" leading group that have defined the list of global risk factors for deaths and disability-adjusted life-years. Among these are metabolic and environmental factors of importance for the development of IR, such as increased blood pressure, high fasting plasma glucose, high total cholesterol, high body-mass index, childhood undernutrition and low physical activity; additionally, PM pollution and household air pollution from solid fuels are also on the list, within the first ten positions (Cohen et al., 2017). These parameters are strongly related to a sedentary lifestyle and a high-caloric diet, factors that come together in the concept of an obesogenic environment, defined as the set of environmental and social factors to which an individual is exposed that allows them to gain bodyweight until they exceed the limit that guarantees good health (Lind et al., 2016).

Based on all the above, it is common for individuals with IR to initially present metabolic alterations such as hyperinsulinemia and hyperleptinemia and sustained hyperglycemia levels. Subsequently or concomitantly, they may also present hypertension, elevated triglyceride levels, dysregulation (and in many cases increased) of low-density lipoproteins (LDL) and very-low-density proteins (VLDL), elevated inflammatory markers (such as TNFα, IL-1β, IL-6 and leptin), endothelial dysfunction, and a prothrombic state. Likewise,

obesity is a promoting factor for the presence of the criteria afore mentioned (Freeman & Pennings, 2020; Petersen & Shulman, 2018; Yaribeygi et al., 2018). However, it is essential to mention that the clinical existence of IR varies depending on the standards considered, in humans, the homeostasis model assessment of insulin resistance (HOMA-IR), which is the quotient between fasting glucose and insulin concentration, is commonly used to establish it (Freeman & Pennings, 2020; Petersen & Shulman, 2018).

IR is a multifactorial condition strongly associated with risk factors such as genetic susceptibility, dietary/hygiene habits, body composition and environmental pollution; more specifically, there is a solid association with atmospheric pollutants exposure such as PM (Freeman & Pennings, 2020; Kodavanti, 2015). Lind et al. (2016) report that genetics, DNA mutations, sedentary lifestyle, and imbalance of calories consumed in obesogenic environments do not fully explain the obesity epidemic, which is also a fundamental factor in IR development. Thus, other factors as environmental pollutants can play a fundamental role in this process, and, notably, the inflammatory response and OxS, induced by PM exposure, are essential players, thus constituting as underlying factors of to the exposure to environmental pollutants associated with IR development.

The molecular mechanisms involved in IR essentially focus on the signal transduction by insulin. This signaling pathway is complex and involves a variety of regulatory proteins. Any alteration in the expression, function, or modulation of the constituents in the signaling pathway can result in IR. Briefly, insulin binding to the membrane receptor (InsR) causes conformational changes in the membrane by inducing phosphorylation in tyrosine (Tyr) residues. The Tyr residues are then recognized by the IRS. This set promotes activating two pathways that mediate additional insulin responses: mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/ protein kinase B (PKB), also as known Akt

(PI_3K/Akt). It is essential to highlight that the PI_3K/Akt pathway is responsible for translocating glucose transporters (GLUT) to the cell membrane to absorb glucose; this mechanism is favored by inactivating AS160 and the RabGTP-GDP energy exchange. Thus, post-translational modifications, mutations or decrease in the number of insulin receptors (InsR), alteration in the structure of insulin and reduction and inhibition of GLUT and IRS are just some of the molecular targets or classic elements for promoting an IR condition (Petersen & Shulman, 2018; Yaribeygi et al., 2018). It should be noted that many of these molecular targets also relate to exposure to PM, as we will discuss in the following section.

5. Experimental and epidemiological evidence of the relationship between PM toxicity mechanisms and IR

According to the lung injury hypothesis, the damage from PM exposure initiates in the lungs through inflammation and OxS processes. Both constitute mechanisms that play a critical role in the development of IR by a promotion of metabolic alterations that end up in the dysfunction of other organs beyond the lung. The inflammation and OxS are conditions constantly activated by the exposure to PM that alter the normal state of the organism. Several authors report the deregulating of adipokines (adiponectin, leptin and resistin, proteins related to insulin sensivity and glucose metabolism), increasing the concentration of fatty acids and their metabolites (triglycerides and LDL) and the increase in the circulating or tissue-specific concentration of cytokines (TNFα, IL-1β, IL-6 and IL-8) after PM exposure. Also, an increase in markers of oxidative damage such as malondialdehyde (MDA), oxidized proteins, and hydroperoxides are present in the blood and peripheral tissues, thus the oxidative cell injury of this tissues contribute to a sustained inflammatory state (Dang et al., 2018; Gomes-Heck et al., 2017; Kodavanti, 2015; Petersen & Shulman, 2018; Yaribeygi et

al., 2018). Inflammation and OxS mediate the toxicity of PM in the developments of IR and, consequently, MD, such as T2DM, MetS, arterial hypertension, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD) and obesity, and these pathogenic processes mainly affect the liver, adipose tissue and skeletal muscle (Gomes-Heck et al., 2017; Kodavanti, 2015; Ovrevik et al., 2015; Petersen & Shulman, 2018; Schraufnagel et al., 2019; Thompson, 2018; Yaribeygi et al., 2018).

5.1. Inflammation by PM exposure in the IR development

It is known that PM induces pulmonary inflammation depending on its size, concentration, and chemical composition. The inflammatory response relates to regulating of genes and the expression of pro-inflammatory factors such as interferons, interleukins and chemokines. Other molecules also associated with the pro-inflammatory profile generated by exposure to PM are TNFα, interferon-gamma (IFNγ), cyclooxygenase 2 (COX-2), IL- 1, IL-6, IL-8, IL-18 and IL-32, granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein 3a (MIP-3a) and MCP-1, some also characteristic of cytokine profile related to IR development (Castañeda et al., 2018; Dang et al., 2018; Gomes-Heck et al., 2017; Kodavanti, 2015; León-Pedroza et al., 2015; Ovrevik et al., 2015; Thompson, 2018; Weidong et al., 2018; Yaribeygi et al., 2018). These mediators recruit mainly macrophages, monocytes, neutrophils and eosinophils, promoting local damage that may spill over other systems. These molecules can also induce a regulation imbalance among T-helper cells Th1, Th2 and Th17, reinforcing the lungs' inflammatory response and a delayed-type hypersensitivity. Another mechanism involved in the proinflammatory effects of PM, specifically CP, is the activation of the nucleotide-binding domain and leucine-rich repeat protein 3 (NLRP3) inflammasome. This pathway involves endotoxin and PAH content of the particles, increasing pro-oxidant

species, the activation of toll-like receptors (TLR), increased levels of TNFα and IL-1β, pore-forming toxins and decrease of ATP levels, resulting in damage to cell structures, such as lysosomes, the endoplasmic reticulum, and the mitochondria. NLRP3 participates in the proteolytic maturation of IL-1β and IL-18, perpetuating the pro-inflammatory cycle (Duan et al., 2019). Alternative route of PM activating inflammatory pathways is recognizing via the pathogen-associated molecular patterns (PAMP) related to aerobiological components present in PM (e.g. endotoxin, pollen, etc.) that bind to TLR2 and TLR4. Activation of this type of receptor promotes the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), which regulates the expression of TNFα, IL-1β, IL-6 and IL-8. Furthermore, these same molecules are potent activators of the NFκB cascade, again feeding back the inflammatory cycle in a paracrine and autocrine mode (Weidong et al., 2018).

The role of inflammation caused by PM could be one of the most critical mechanisms in IR, because the peripheral tissues may present an increased secretion of inflammatory factors and infiltration of immune cells during the stage of systemic inflammation. Such is the case of adipose tissue. Adipocytes begin to accumulate an excess of intracellular fatty acids, which leads the tissue to hypertrophy and hyperplasia and to the promotion of OxS by lipid peroxidation reactions. Furthermore, this can generate a cellular burst that reinforces the local inflammatory process characterized by increased levels of TNFα, IL-1β, IL-6, leptin and resistin and a decrease in adiponectin. The resulting hyperleptinemic condition decreases insulin sensitivity in peripheral tissues. Finally, this pathogenic process also affects the liver and skeletal muscle, perpetuating the inflammatory state. Likewise, dyslipidemia and hyperglycemia after PM exposure reinforce the inflammatory process by activating TLR by free fatty acids and products of lipid oxidation and advanced glycation. Furthermore, it is

also known that TNFα can inhibit the PI_3K/Akt pathway, preventing the translocation of GLUT (León-Pedroza et al., 2015; Petersen & Shulman, 2018).

5.2. OxS by PM exposure in the IR development

On the other hand, respiratory tract injury due to oxidative processes after PM exposure (Weidong et al., 2018), an essential factor is the PM surface area, which closely relates to particle size. UFP have a larger contact surface area than FP and CP. The larger surface area makes PM more reactive and capable of generating a more intense injury. Additionally, among the PM components mentioned before, transition metals, PAHs, nitrates, sulphates, and, also biological compounds are disruptors of the cellular redox balance, contributing to the increase in the concentration of oxidizing species and promoting OxS (Thompson, 2018; Van Berlo et al., 2012). Transition metals can induce Fenton and Haber-Weiss reactions promoting an oxidative microenvironment by ROS and reactive nitrogen species (RNS). The hydroxyl radical (•OH) is the main oxidizing species generated and highly toxic due to its potential to reduce and its high capacity to interact with organic structures to form secondary radicals (Thompson, 2018; Tuet et al., 2016). Other radicals involved in the generating of ROS include the radical alkoxy (RO), superoxide anion ($\bullet O_2^-$), alkyl peroxy (ROO) and hydrogen peroxide (H_2O_2) (Van Berlo et al., 2012).

The damage caused by PM-induced ROS overproduction stimulates the release of pro-inflammatory cytokines through the activation of the NLRP3 inflammasome, NFκB, AP-1 and MAPK (Van Berlo et al., 2012; Weidong et al., 2018). Also, this response can be reinforced by the activation of macrophages and neutrophils, and the increase of ROS production after phagocytosis of PM (Haberzettl et al., 2014). Furthermore, ROS can oxidize essential molecules, that are necessary in maintenance of proper cell functioning such as

lipids, nucleic acids, and proteins, resulting in cellular damage (Haberzettl et al., 2014; Tuet et al., 2016). Finally, although the cells of the pulmonary epithelium secrete antioxidants like glutathione, superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), glutathione reductase (GR) and glutathione S- transferase (GST) to protect from oxidative damage, the impairment of this defense system as a result of PM exposure has been frequently reported. The impairment relates to decrements of antioxidant protein levels, as exemplified by a consistent increment of lipid peroxide concentration (Haberzettl et al., 2014; Thompson, 2018).

The first aspect investigated about OxS and IR development was that of the regulation of redox switches resulting from cross-communication between the generation of OxS in the mitochondria during the cellular respiration process and the activation of oxidases, considered redox switches. Although this has not been ultimately confirmed, it is hypothesized that these enzymes activation can lead to a vicious cycle of redox stimulation that becomes harmful to cells, predominantly in peripheral tissues (Hurrle & Hsu, 2017).

A well-documented pathway that OxS blocks is PI_3K/Akt cellular pathway, whose activity is diminished due to an erroneous phosphorylation, intervening directly in the insulin pathway and promoting IR condition (Hurrle & Hsu, 2017). This type of case is discussed in the next section.

5.3. Epidemiologic, *in vivo* and *in vitro* studies

Brook et. al. (2013) initiated the epidemiological evaluation of the associations between PM exposures and IR. They studied the impact of subacute exposures to FP (5 h/day, 5 days) in 25 healthy adults living in an urban area of Michigan. The study found associations between increased HOMA-IR and FP (0.7, 95% Cl: 0.1-1.3 per 10 $\mu g/m^3$ increment). The increase in

the value of HOMA-IR would imply a modification in insulin sensitivity and, therefore, the promotion of IR. These results opened the door to subsequent epidemiological studies. Khafaie et al. (2018) studied associations between exposure to the ambient urban concentrations of PM_{10} and glucose metabolic parameters in 46-year-old patients in the city of Pune in India. The results indicated that a concentration of 43.83 $\mu g/m^3$ of PM_{10} in the air was significantly associated with an increase in the arithmetic mean of glycosylated hemoglobin (HbA1c) (2.25 mmol/mol), an increase in the plasma glucose 2h after a meal (0.38 mmol/l) and a 4.89% increase in the geometric mean of the HOMA-IR. The joint modification of these parameters suggests the possibility of a deficiency in glucose uptake by peripheral tissues, increasing the probability of developing insulin resistance. Finally, Tamayo-Ortiz et al. (2021) used adjusted logistic regression models (by surveys) to calculate the obesity probability ratios for each 10 mg/m^3 increase in FP in different strata (children, adolescents, and adults) of the Mexico City population. The study demonstrated the related overall positive association between FP exposure and obesity of 1.96 value (95% CI: 1.21-3.18). In addition, it was observed that in adolescents, an increase in the environmental concentration to FP (10 mg/m^3) was associated with an increase in the presence of obesity in individuals for different years (OR: 3.53, 95% CI: 1.45 -8.58 in 2006; OR: 3.79, 95% CI: 1.40-10.24 in 2012). Regarding this, this condition is important because, as previously as mentioned, obesity is a condition closely related to IR.

On the other hand, *in vivo* experimental studies also relate exposure to PM and development of IR. Exposure in animal models has made it possible to observe pathophysiological responses related to the inflammatory response. For example, Xu et al. (2011) evaluated the role of inhaled FP exposure on IR and inflammation-related parameters in a 3-week-old C57BL/6 mouse model. This study demonstrated that after subchronic inhalation exposures

(6 h/day, 5 days/week, for 10 months), HOMA-IR, plasma TNFα, macrophage infiltration in the liver and adipose tissue increased in the exposed mice. Also, it was indirectly shown by evaluating at the levels of phosphorylated Akt protein that peripheral tissues (skeletal muscle, liver and adipose tissue) were differentially affected, especially skeletal muscle. These results demonstrate that PM exposure is directly involved in peripheral tissue dysfunction and decreased insulin pathway response. Sun et al. (2013) evaluated the effect of inhalational co-exposure to concentrated air particles (CAP) FP and ozone in male Sprague-Dawley (SD) rats on a high fructose diet for 8 weeks; the exposure schedule was 8 hours/day, 5 days/week, in 2 weeks. The results showed a macrophage infiltration in the epicardial and perirenal adipose tissue was observed. Also, observed an increase in the mRNA levels of pro-inflammatory genes such as TNFα, MCP-1 and leptin, concomitant with a decrease of anti-inflammatory genes such as IL-10 and adiponectin in the adipose tissue. The experimental design of this study allowed to observe the promotion of the inflammatory response of adipose tissue. Furthermore, the increase in the expression of the leptin gene and the decrease in the expression of the adiponectin gene are related to the promotion of IR. Zheng et al. (2013) evaluated the effect of FP exposure on IR generation and its relationship with a NASH-like phenotype in a C57BL/6 murine model exposed by inhalation to FP. This study showed an increase in the HOMA-IR and in serum TNFα and, plasma triglycerides, LDL and VLDL. Likewise, increased transcript levels of IL-1β, IL-6, TLR2 and TLR4 in the liver, TLR's being potential activators of factor NFκB transcription factor. Additionally, in the same study it was demonstrated that the JNK/AP-1 pathway was activated in the RAW264.7 cell line of macrophages and NFκB in liver tissue, suggesting that these are the cellular pathways that could be responsible for the inflammatory process after exposure to the particles. The most important finding was the decrease in the protein level of IRS1 in the

liver because this explains the presence of IR in the experimental model. Finally, it was identified that mice exposed to FP developed moderate NASH, decreased liver glycogen levels, and increased activation of lung and liver macrophages. Moreover, Yi et al. (2017) conducted a study to evaluate FP's instillation in a model of gestational diabetes in SD rats at two doses of 15 mg/kg (cumulative dose of 30 mg/kg). They observed significant increases in postprandial glucose and IL-6 levels in blood samples and methane dicarboxylic aldehyde in to FP exposed animals' pancreas. This is consistent with the significant decrease in pancreatic levels of GPx and GLUT2. Likewise, they observed periductal inflammation damage in the pancreas of the exposed group. This evidence strongly supports the hypothesis of lung injury and its adverse metabolic effects on organs and tissues beyond the lungs, suggesting that this response can also be observed in the pancreas. Additionally, plasma glucose, plasma insulin and HOMA-IR levels were measured. Increases were observed, although without statistical significance, in all three parameters, which are directly related to the presence of IR.

There is little *in vitro* evidence related to the development of IR. For example, Li et al. (2016) used a combined *in vitro* PM exposure study where mouse macrophage Ana-1 cell lines were exposed to FP. The resulting conditioned medium was used to stimulate cultured NCTC clone 1469 mouse hepatocytes. The results showed that the hepatocytes increased the phosphorylation of Ser307 for IRS1 and a decrease in Ser473 of Akt, as well as an increase in the protein expression of phosphorylated forms of JNK; JNK1 and JNK2. The study concludes that the particles can induce IR in mouse hepatocytes and contribute to the understanding PM's systemic toxicity and its role in diseases such as MetS and T2DM.

6. Conclusions

The evidence presented in this review suggest a close link between PM exposure and the development of IR. It is pertinent to remember that PM alone can stimulate pro-inflammatory and pro-oxidant cellular microenvironments, and both are decisive risk factors in the development of IR condition. In summary, the inflammation and OxS mediated pulmonary alterations caused by PM exposure have further repercussions that could affect the health of exposed individuals, especially those populations at risk or predisposed to MD. The resulting biological mediators impact the central compartment and end up modifying the metabolism of the other organs and tissues, such as the heart, liver, adipose tissue, and skeletal muscle, among others.

We presented review support that exposure to PM act as a promoting factor in the development of IR. Also, it is pertinent to remember that PM is a heterogeneous mixture of different substances. Therefore, it is not documented if there are one or more critical PM components associated with IR development. Thus, to clarify this, future studies will require, in addition to PM's speciation and chemical characterization, co-exposures with standards of the different PM's components. Other aspects to consider in future studies related to the elucidation of extrapulmonary damage result from the direct effect on translocated particles or metabolic mediators and a better understanding of the biomarkers used to identify adverse outcomes. However, although the studies are conclusive in demonstrating the relationship between exposure to PM and the modification in metabolic parameters, which results in the promotion of IR, much work remains to be done. It is necessary to improve the experimental designs to be able to give uniformity to the data and to reduce uncertainty. In this sense, it would be essential, for example, to highlight the importance of always evaluating HOMA-IR and glucose levels in epidemiological and animal models, as well as exploring the

different molecular events in cellular models that result in dysfunction of the insulin pathway, an aspect that is still under development today; this, of course without forgetting to continue the study of related inflammatory and oxidative events. It is also essential to evaluate standard parameters (e. g. measurement of blood pressure, triglyceride levels, HDL, LDL, VLDL, and anthropogenic or body measurements) clearly related to the IR status.

In this sense, the lung injury, and its link with the harmful metabolic effects in distal organs and tissues through the pro-inflammatory and pro-oxidant environment are the link between the PM exposures and IR development, thus their evaluation as associated events should be included.

Based on the experimental and epidemiological literature reviewed, inflammation and OxS are the main underlying mechanisms of toxicity related to IR development. The development of IR or at least its promotion through the hypothesis of lung injury and its adverse metabolic effects in distal organs and tissues beyond the lungs, occurs through biological mediators by inflammation and OxS. The current hypothesis postulates that exposure to PM is related to the development of IR through inflammation and OxS that originated in the first contact with the lungs, triggering systemic damage due to metabolic alteration.

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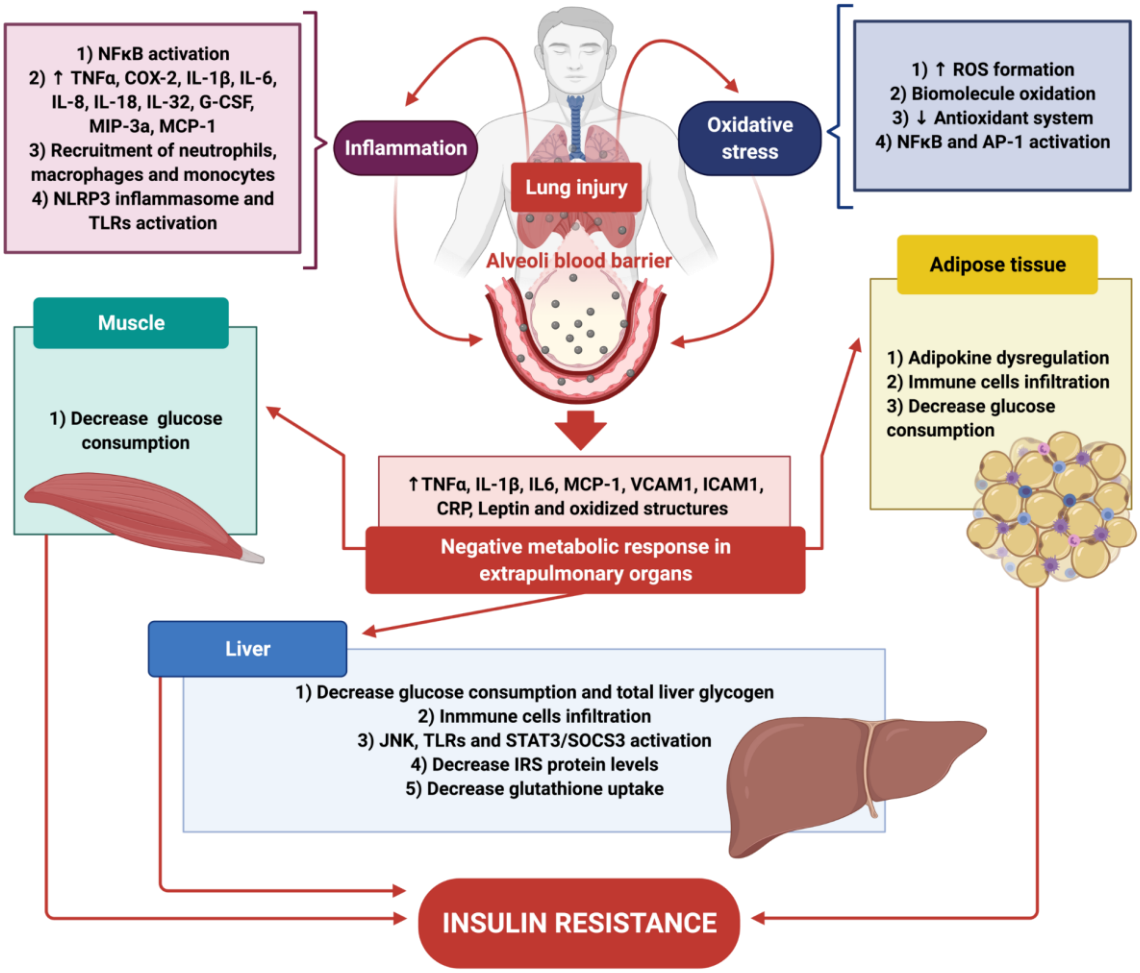

Figure 1. Hypothesis of PM lung injury and adverse metabolic effects beyond the lungs. Lung injury from exposure to air pollutants refers to the generation of a state of inflammation and oxidative stress in the lungs. Given the reactivity of PM, the particle, its constituents or the biological mediators produced in the lungs can cross the alveolar-capillary barrier and be transported by the bloodstream, promoting a state of systemic inflammation due to the release of mediators such as cytokines and vasoactive substances that can provoke a negative metabolic response in organs beyond the lungs, such as peripheral organs such as the liver, adipose tissue and skeletal muscle, and promote the IR condition.

III. Discusión y conclusiones

Con base en la evidencia presentada a lo largo del trabajo, esta revisión proporciona información del estrecho vínculo entre la exposición a PM y el desarrollo de RI. Es pertinente recordar que el PM por sí solo puede estimular microambientes celulares proinflamatorios y prooxidantes, y ambos son factores de riesgo decisivos en el desarrollo de la condición de RI. Aunque desde la perspectiva toxicológica es claro, dado que, se observó en diversos estudios que la exposición a PM puede inducir más de un criterio patológico, manifestándose diferentes signos y síntomas relacionados con la RI. No obstante, la toxicología como rama de la ciencia todavía tiene el reto de esclarecer aún más la relación entre la exposición al PM y la presencia de la IR, pues es necesario aclarar que múltiples autores realizan sus ensayos en modelos experimentales con predisposición a MD como la T2DM y MetS. El desarrollo de la RI o al menos su promoción a través de la hipótesis de la lesión pulmonar y sus efectos metabólicos adversos en órganos y tejidos distales más allá de los pulmones, se produce por mediadores biológicos mediante la inflamación y el OxS tras la exposición al PM.

En este sentido el planteamiento de nuevos diseños experimentales *in vivo* con controles sanos y sin predisposición esclarecerían si el PM es un factor promotor relevante en el desarrollo de la IR. Estudios como el de Brook et. al. (2013) apoyan la noción de que el PM es un factor de importante de riesgo ya a que los resultados sugieren que aún en exposiciones de periodos cortos de tiempo en población humana sana puede existir una reducción de la sensibilidad a la insulina y, por tanto, posiblemente la promoción de la RI. Sin embargo, esto no es una hipótesis clara y aún se encuentra poco fundamentada, dado que existen muchas variables que posiblemente no fueron controladas en el estudio previamente mencionado. Además, es pertinente recordar que el PM es una mezcla heterogénea de diferentes sustancias. Por lo tanto, no está documentado si hay uno o más componentes de PM críticos asociados con el desarrollo de IR. Para aclarar esto, los estudios futuros requerirán, además de la especiación y caracterización química del PM, co-exposiciones con estándares de los diferentes componentes de PM. Aunque a lo largo del artículo presentado no se ahondó en demasía este punto específico, es importante mencionar que estudios como el de Li et al., (2016) y Xu et al., (2018) confirman que la presencia diferencial en la concentración de la mezcla presente de compuestos en el PM podrían agudizar o empeorar la respuesta tóxica y,

por lo tanto, la relación con la RI. En consecuencia, esto ayudaría a definir si algún componente específico del PM promueve el desarrollo de la IR. Si retomamos la idea anterior, respecto a la heterogeneidad de las partículas, se promueve un ambiente proinflamatorio y alteraciones pulmonares mediadas por OxS tras la exposición a PM; teniendo repercusiones adicionales que podrían afectar la salud de las personas expuestas, especialmente aquellas poblaciones en riesgo o predispuestas a MD.

Los mediadores biológicos resultantes, adipocinas y citocinas, así como derivados del efecto del OxS (biomoléculas, como lípidos y proteínas oxidadas), impactan en el compartimento central y terminan modificando el metabolismo de otros órganos y tejidos, como el corazón, el hígado, el tejido adiposo y el músculo esquelético, entre otros. No obstante, aún con la evidencia presentada, únicamente Laing et al. (2010) consideró en su diseño experimental *in vivo* probar que el PM puede llegar a órganos y tejidos distales. Por ello, es imperativo comprobar que la partícula si puede llegar y dañar directamente al órgano en estudio.

Por otro lado, aunque los estudios son concluyentes al demostrar la relación entre la exposición a PM y la modificación de los parámetros metabólicos, que resulta en la promoción de la RI, aún es importante estudiar varios elementos. En este sentido, sería fundamental resaltar la importancia de evaluar siempre los niveles de los parámetros fisiológicos de las MD como el HOMA-IR y los niveles séricos de glucosa en modelos epidemiológicos y animales, así como los parámetros estándar (ej. medición de la presión arterial, niveles de triglicéridos, HDL, LDL, HLDL y mediciones antropogénicas o corporales) relacionados con el estado de RI. Del mismo modo, sería pertinente que se evaluaran nuevos biomarcadores que se vinculen a la RI para saber si se modifican por la exposición a PM; algunos de los cuales podrían ser otras adipocinas, como resistina (cuya acción central es disminuir la sensibilidad de la insulina) (León-Pedroza et al., 2015; Petersen & Shulman, 2018) y/o la incretina principal y responsable de casi todo el efecto incretina, el péptido similar al glucagón tipo 1 (GLP-1) (encargado de la secreción de insulina dependiente de glucosa y supresión posprandial del glucagón) (Gómez, 2016); además de marcadores de OxS, como el MDA, lipoperóxidos y otras estructuras oxidadas como moléculas confirmatorias de la pérdida del balance oxidante.

También, deseamos resaltar la ventana de oportunidad debido a la falta de información para explorar los diferentes eventos moleculares en modelos celulares, como la vía de las JNK, AT_1R en función de la vía de las RhoA-Rhocinasas y las diferentes isoformas de las PKC que resultan en disfunción de la vía de la insulina, aspecto que todavía se encuentra en desarrollo; esto, por supuesto, sin olvidar la relación con el estudio de los eventos inflamatorios y oxidantes relacionados a ello, como la desregulación de citocinas y adipocinas, el reclutamiento y la infiltración de células del sistema inmune en tejidos periféricos, la activación del inflamasoma, los TLR y factores de transcripción (NFκB y AP-1), así como los derivados oxidados de biomoléculas.

En conclusión, según la literatura experimental y epidemiológica revisada, la inflamación y OxS son los principales mecanismos subyacentes de toxicidad relacionados con el desarrollo de RI. La hipótesis actual postula que la exposición a PM está relacionada con el desarrollo de RI por inflamación y OxS que se originó en el primer contacto con los pulmones, desencadenando daño sistémico relacionado con alteraciones metabólicas.

IV. Referencias

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