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Pharmacology & Therapeutics 235 (2022) 108120

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Indirect mediators of systemic health outcomes following nanoparticle inhalation exposure

Ekaterina Mostovenko [a], Christopher G. Canal [a], MiJin Cho [a], Kirti Sharma [a], Aaron Erdely [b], Matthew J. Campen [c], Andrew K. Ottens [a,*]

[a] Department of Anatomy and Neurobiology, Virginia Commonwealth University, PO Box 980709, Richmond, VA 23298, USA
[b] Health Effects Laboratory Division, National Institute for Occupational Safety and Health, 1095 Willowdale Road, MS-2015, Morgantown, WV 26505, USA
[c] Department of Pharmaceutical Sciences, University of New Mexico, MSC09 53601, Albuquerque, NM 87131, USA

ARTICLE INFO

Available online 24 January 2022

Editor: S.J. Enna

Keywords:
Nanoparticles
Nanotubes
Nanomaterials
Inhalation toxicology
Neurotoxicology
Peptidomics

ABSTRACT

The growing field of nanoscience has shed light on the wide diversity of natural and anthropogenic sources of nano-scale particulates, raising concern as to their impacts on human health. Inhalation is the most robust route of entry, with nanoparticles (NPs) evading mucociliary clearance and depositing deep into the alveolar region. Yet, impacts from inhaled NPs are evident far outside the lung, particularly on the cardiovascular system and highly vascularized organs like the brain. Peripheral effects are partly explained by the translocation of some NPs from the lung into the circulation; however, other NPs largely confined to the lung are still accompanied by systemic outcomes. Omic research has only just begun to inform on the complex myriad of molecules released from the lung to the blood as byproducts of pulmonary pathology. These indirect mediators are diverse in their molecular make-up and activity in the periphery. The present review examines systemic outcomes attributed to pulmonary NP exposure and what is known about indirect pathological mediators released from the lung into the circulation. Further focus was directed to outcomes in the brain, a highly vascularized region susceptible to acute and longer-term outcomes. Findings here support the need for big-data toxicological studies to understand what drives these health outcomes and better predict, circumvent, and treat the potential health impacts arising from NP exposure scenarios.

Contents

Abbreviations: AT1, angiotensin II receptor type 1; ASD, autism spectrum disorders; CB, carbon black; CNT, carbon nanotubes; CAPs, concentrated ambient ultrafine particulates; eNOS, endothelial nitric oxide synthase; ENP, engineered nanoparticles; EVs, extracellular vesicles; IL, Interleukin; LOX-1, oxidized low-density lipoprotein receptor-1; MIP-1, macrophage inflammatory protein 1; MMP, matrix metalloproteinase; MeNPs, metal-based nanoparticles; MWCNT, multi-walled carbon nanotubes; NF-κB, nuclear factor kappa B; NP, nanoparticles; ox-LDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; SWCNT, single-walled carbon nanotubes; TNF, tumor necrosis factor; TSP, thrombospondin; UFP, ultrafine particulates..

* Corresponding author.
E-mail address: akottens@vcu.edu (A.K. Ottens).

https://doi.org/10.1016/j.pharmthera.2022.108120
0163-7258/

1. Introduction

Nano-sized particles, with at least one dimension under 100 nm, are persistent within our environment. These nanoparticles (NP) are endemic to our atmosphere, water sources, the soil and are carried by microorganisms (Hochella, Spencer, & Jones, 2015). Similarly termed ultrafine particulates (UFP) for non-manufactured sources, NPs are produced by natural events such as photochemical reactions, forest fires, dust storms or volcanic eruptions, but are also common byproducts of industrial processes such as welding, wood/charcoal burning, and vehicle exhaust. Lastly, nano-sized particles are engineered (ENP) for a wide variety of manufacturing demands. ENPs are commonly used for industrial purposes in water/sewage treatment, energy, auto and airspace engineering, as well as construction, agriculture, electronics, optics, sporting equipment, textile, cosmetics, and food safety. Moreover, there is a growing biomedical demand for ENPs for clinical diagnosis and therapy (Cheng, Morshed, Auffinger, Tobias, & Lesniak, 2014; Jain, Hirst, & O'Sullivan, 2012; Meyers, Doane, Burda, & Basilion, 2013), biotechnology (Sönnichsen, Reinhard, Liphardt, & Alivisatos, 2005), and bio sensing (Kwon & Bard, 2012; Wang, Xu, Kawde, & Polsky, 2001). Most commonly, ENPs are comprised of carbon (e.g., single and multi-walled carbon nanotubes (MWCNT) or nanofibers), noble metals (e.g., silver, gold) and metal oxides (e.g., ZnO, TiO_2). Diversity in origin and use translates to a wide variety of physicochemical properties with composition, size, shape and other aspects influencing the toxicological profile of NPs (Fenoglio et al., 2012; Nagai et al., 2011; Poland et al., 2008). NPs tend to inflict greater health deficits than larger particulates (Braakhuis et al., 2014; Breitner et al., 2011; Du et al., 2013; Franck, Odeh, Wiedensohler, Wehner, & Herbarth, 2011), entering the body more efficiently and presenting generally greater bioactivity with a larger surface area per mass (Oberdörster, Oberdörster, & Oberdörster, 2005). For example, pulmonary inflammation was enhanced with NPs over larger particles of the same material (Warheit, 2004). The impact of an NPs larger surface area is particularly pertinent for low solubility NPs like carbon black (Sager & Castranova, 2009). Overall, the health hazards of NPs remain of paramount concern with much to be explored.

The ubiquitous NP environmental presence predisposes exposure via dermal, oral, and even intravenous/subcutaneous routes. However, inhalation is the most prevalent and robust mode of exposure, with a higher rate of uptake, large alveolar surface area, and a surfactant-enabled capture interface (Hoet, Bruske-Hohlfeld, & Salata, 2004) that can circumvent mucociliary clearance (Chalupa, Morrow, Oberdorster, Utell, & Frampton, 2004; Daigle et al., 2003). Yet NP inhalation not only can produce local pulmonary effects (Oberdörster et al., 2005), but cardiovascular dysfunction (Brook, Rajagopalan 3rd, et al., 2010; Peters, Dockery, Muller, & Mittleman, 2001; Shah et al., 2015), extensive inflammation in peripheral organs, and cognitive and neurodevelopmental deficits (Cipriani, Danti, Carlesi, & Borin, 2018; Dimakakou, Johnston, Streftaris, & Cherrie, 2018), as well. Traditionally, NP systemic outcomes have been attributed to particle translocation from the lung (Deng et al., 2007; Nemmar et al., 2001; Nemmar et al., 2002; Reddy, Krishna, Reddy, & Himabindu, 2010). Yet studying the natural fate of NPs in the periphery is challenging due to their small size, low mass deposition/translocation and limited methods for detection. Studies in humans have provided conflicting results, with several reporting the absence of translocation for some classes of NPs (Brown, Zeman, & Bennett, 2002). Even sensitive radio-labeling studies have been challenged to demonstrate significant translocation of NPs from the lung, in part due to radiolabel leaching (Möller et al., 2008; Nemmar et al., 2002). In a detailed electron microscopy assessment of oropharyngeal aspirated multi-walled carbon nanotubes (MWCNT), Mercer et al. estimated that only 1.1% of the mass translocated to the lymphatics and less than 0.01% to any other organ in the first 24 h post-exposure (Mercer et al., 2013). Follow-up nearly a year later showed that only 7.3% of the mass was cleared to the lymphatics, and just 0.04% of the MWCNT mass could be detected in other organs. Other metal/metal oxide NPs are more mobile, if not soluble, yet the pervasive extrapulmonary effects of confined NPs, like MWCNT, has substantiated indirect molecular mediator involvement.

A variety of indirect mechanisms have been proposed. Inhaled carbon nanotubes (CNT) provoke a system-wide immune response, which is partly due to spleen cyclooxygenase activation (Mitchell, Lauer, Burchiel, & McDonald, 2009). More broadly, NPs induce oxidative stress and inflammation in the lung that is believed to cause release of bioactive mediators into the circulation (Brook et al., 2010; Donaldson et al., 2005; Miller, Shaw, & Langrish, 2012). Yet there are reports of extensive cellular damage without any signs of oxidative stress or apoptosis (Tabet et al., 2009). Additionally, cardiovascular deficits following CNT exposure have been observed without pulmonary inflammation (Khandoga et al., 2010; Upadhyay et al., 2008). Thus, indirect mediators of extrapulmonary NP outcomes may be more varied and dynamic than expected (Erdely et al., 2009; Mitchell et al., 2009). Accordingly, this review describes the state-of-knowledge on systemic outcomes caused by NP lung exposures (Fig. 1) and the involvement of indirect molecular mediators in extra-pulmonary pathobiological responses. Where appropriate, studies of UFP and fine particulate matter are discussed in comparison to help illustrate outcomes and mechanisms.

2. Common inhaled nanoparticles and exposure sources

NPs can be classified into three groups based on their origin: naturally occurring (found in plants, insects, *etc.* or generated from skin and hair shedding), process-derived (industrial and combustion byproducts), and engineered (manufactured by humans to fulfill specific physicochemical requirements). Natural NPs are formed by bio/photochemical, mechanical, and thermal processes (Sharma, Filip, Zboril, & Varma, 2015). Alternatively, they can also form in outer space and later get introduced to Earth's atmosphere (Hochella et al., 2015). For example, large carbon structures such as fullerenes, commonly found in soot (Krätschmer, Lamb, Fostiropoulos, & Huffman, 1990), have also been detected in deep space (Ehrenfreund & Foing, 2010). Natural NPs are commonly formed by wind erosion, evaporation of sea spray, and overall weathering of rocks and minerals. Natural NPs also form through thermal processes such as the combustion of biomass or volcanic activity. Natural NPs are also produced by biomineralization, a form of biologically induced, controlled mineralization (Sharma et al., 2015) that results in inorganic nanominerals containing iron and silica, calcium carbonate, and calcium phosphate (Te et al., 2012). Other NNP sources include wastewater from ore and other mines, cold CO_2 seeps, and hydrothermal vent emissions, which can contain a wide variety of heavy metals (Ag, Au, Fe, Mn, Cr, Cu, Ba, Pb) and their sulfides (FeS_2, Ag_2S, CuS, CdS, and ZnS) (Sharma et al., 2015). Overall Natural NPs represent a diverse group of particles with varied chemical composition that can enter the atmosphere and pose an inhalation exposure concern. While the toxic potential of Natural NPs is generally regarding as limited, it is important to consider that their overall environment abundance is several orders in magnitude greater than ENPs, and not always lower in concentration, depending on proximity to sources such as wildfires or volcanism (Hochella et al., 2015).

Human-generated NPs constitute ~10% of all atmospheric NPs (Taylor, 2002) with combustion byproducts of fuel oil and coal burning (Linak, Miller, & Wendt, 2000), airplane engines (Kelly, Wagner, Lighty, & Sarofim, 2005), and vehicle exhaust (Kagawa, 2002) being the main contributors particularly in metropolitan areas (Singh, Phuleria, Bowers, & Sioutas, 2006). Even with the enforcement of stricter vehicle emission standards in the U.S., mean daily occupational exposures to diesel exhaust particulate remains high between 0.7 and 4 $\mu g/m^3$ (Debia, Neesham-Grenon, Mudaheranwa, & Ragettli, 2016), and over 90% of atmospheric carbon-based NPs coming from diesel combustion (Kittelson, 2001). Yet, vehicle emissions are a complex mixture of hydrophobic soot aggregates (41%), hydrophilic (9%), and hygroscopic

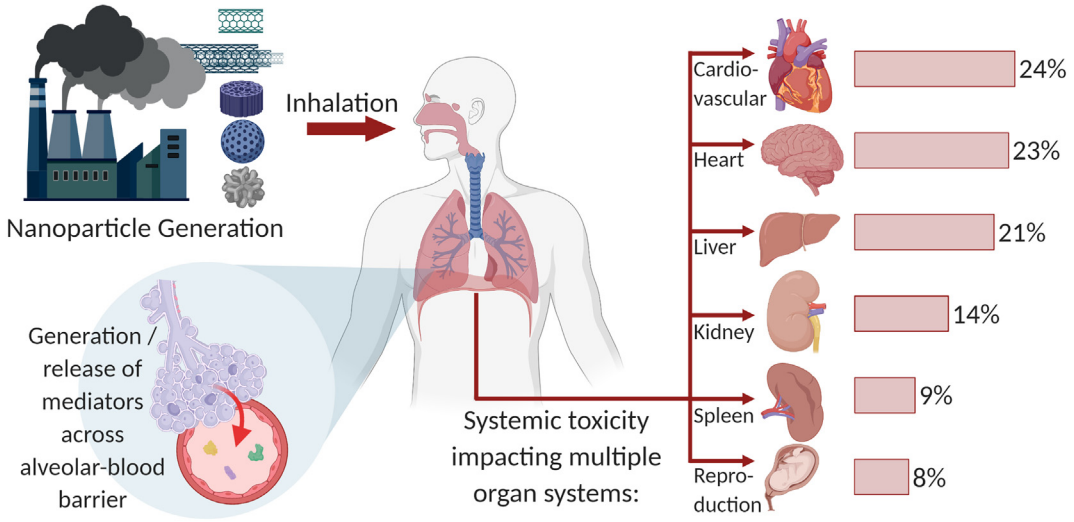

Fig. 1. Diverse organ targets of inhaled nanoparticle (NP) exposure. A growing body of literature reports on the extrapulmonary burden of inhaled NPs, most prominently on cardiovascular and neurological systems, which are the most cited in this review. Shown is the percentage of PubMed entries (809 in total) on "nanoparticle(s)" and "inhalation" citing the listed extrapulmonary organ targets.

particles (45%) (Kireeva, Popovicheva, Persiantseva, Timofeyev, & Shonija, 2009), which divides into solid, condensed (or liquid), and gaseous fractions (Chan et al., 2007; Jayaram, Agrawal, Welch, Miller, & Cocker, 2011; Westerholm & Egeback, 1994). The solid fraction is primarily elemental carbon with NPs between 10 and 30 nm in diameter (Liati & Dimopoulos, 2010; Zhu, Lee, Yozgatligil, & Choi, 2005) that can agglomerate into larger soot 60–100 nm NP aggregates (Burtscher, 2005), all of which can deposit deep into the alveolar and bronchial space (Dockery, 2009). Yet as exhaust plumes mix with ambient air, NPs rapidly evolve into new particles through nucleation and ablative process to change in size and mass (Zhang & Wexler, 2004; Zhang, Wexler, Zhu, Hinds, & Sioutas, 2004). Influencing these processes are the dilution ratio and temperature, which play a pivotal role in transforming vehicle exhaust NPs (Morawska, Ristovski, Jayaratne, Keogh, & Ling, 2008; Zhang et al., 2005). For example, temperature and compression differences between engine types results in a 20–200 nm diesel NP fraction range (Lidia Morawska, Bofinger, Ladislav Kocis, & Nwankwoala, 2009) that is wider than the 30–60 nm range for gasoline (Ristovski, Morawska, Bofinger, & Hitchins, 1998). While principally carbonaceous, exhaust NPs are also impregnated with various sulfates, metals and metal oxides originating from lubricants and fuel additives (Burtscher, 2005; Matti, 2007). In all, combustion-derived NPs pose an urgent health concern with variability in size and chemical composition affecting their toxic potential.

NP toxicity is influenced by concentration, duration of dose, surface area to volume ratio, chemistry, magnetism, crystallinity, electronic configuration, aggregation behavior, and ion leaching characteristics (Nel et al., 2009; Schrand et al., 2010). These properties are particularly characteristic of engineered metal-based NPs (MeNP). Occupational exposure to metals such as Al, Mn, Pt, Cr, Co, Ni, Be, and Hg is common in industrial plants, mines and with welding, all of which produces pulmonary pathology in humans (Nordberg, Fowler, Nordberg, & Friberg, 2007). Upon interaction with immune cells, inhaled MeNPs promote reactive oxygen species (ROS) formation and the accumulation (Young et al., 2021) of cytotoxic oxidized glutathione (Nel, Xia, Mädler, & Li, 2006). While most MeNPs are limited to industrial sites, silver and TiO_2 NPs are broadly utilized in variety of household items such as sporting goods, air sanitizer sprays, wet wipes, food storage containers, shampoos, toothpastes, cosmetic creams and sunscreens (Donaldson, Stone, Tran, Kreyling, & Borm, 2004; Vance et al., 2015; Weir, Westerhoff, Fabricius, Hristovski, & Von Goetz, 2012). Another synthetic metal oxide NP commonly found in household goods is ZnO, used for UV shielding (Becheri, Dürr, Lo Nostro, & Baglioni, 2008; Osmond & McCall, 2010) and wood sealing agents (Cooper et al., 2017). Welding fumes from galvanized steel are yet another airborne source of ZnO NPs (Fine et al., 2000; Wesselkamper, Chen, & Gordon, 2001). Thus, MeNPs pose both industrial production and post-production toxicity concerns for workers and consumers alike (Osmond & McCall, 2010).

Silica (silicon dioxide, SiO_2) is yet another widely utilized nanomaterial. In 2018, the global silica market was estimated at $5.22 billion and expected to grow at an annual 8.6% out to 2026 (Grand View Research, 2019a). While, silica naturally exists on Earth in crystalline (quartz, cristobalite, tridymite, coesite, and stishovite) and amorphous forms (diatomaceous earth) (Napierska, Thomassen, Lison, Martens, & Hoet, 2010), amorphous silica could also be synthesized to form micron- or nano-sized silica in gel, precipitate, pyrogenic, mesoporous and colloidal silica forms (Fruijtier-Pölloth, 2012). Precise control over particle size, shape and other physical properties makes synthetic silica NPS attractive in various industrial process (Pisani et al., 2015). For instance, nanosilica is universally applied in biomedical and biotechnological fields for biosensors, biomarkers, cancer therapy, gene transfection, drug delivery, and enzyme immobilization tools (Barik, Sahu, & Swain, 2008; Cheng et al., 2010; Tsai, Chen, Hung, Chang, & Mou, 2009; Wang et al., 2015). Pyrogenic (fumed) silica is used extensively as a strengthening filler or thickening agent in polyester, silicone, paints, printing inks, coatings, and adhesives as well as a desiccant in cosmetics and toothpastes. Pyrogenic silica NPs are used in electronics and optical fiber industries. Natural silica sources also pose an NP threat, mainly from quartz quarries and downstream applications (e.g., cutting countertops), ceramics production and as a primary component of volcanic ash [nearly 9% of world's population lives in the vicinity of an active volcano (Small & Naumann, 2001)]. However, naturally sourced silica is generally larger in scale, from 0.5 to 10 μm (Napierska et al., 2010), so more uniform industrial nanosilica poses significantly greater pulmonary health risk. Industrial nanosilica has high surface-to-volume ratio and surface reactivity qualities that are useful in manufacturing. However, these properties also enhance their ability to induce oxidative stress (Wang et al., 2009; Ye et al., 2010; Ye, Liu, Chen, Sun, & Lan, 2010), cross the alveolar capillary barrier, and penetrate into the systemic circulation (Nemmar et al., 2001; Nemmar et al., 2002; Oberdörster et al., 2002).

Carbon black (CB) is often used as a substitute for silica in industry (Grand View Research, 2019b). For example, CB is a filler in automobile tires that increases its elasticity along with its ability to absorb microwave energy to prolong tire life (Scuracchio, Waki, & Da Silva, 2007). It is also extensively used in the production of films, conductive packaging, moldings, fibers, semi-conductive cable compounds and pipes (Grand View Research, 2019a). In 2018 the global CB market size was estimated at $17.22 billion, with an expected annual growth rate of 6.0% through 2024. Production of CB takes place via either thermal decomposition or partial combustion reactions raising the risk of occupational exposure. Raw CB is 95% elemental carbon, with small amounts of inorganic and organic materials, and is arguably minimally toxic (not be confused with black carbon soot) (Long, Nascarella, & Valberg, 2013; Watson & Valberg, 2001). However, polycyclic aromatic hydrocarbons and other toxic substances can also be adsorbed during synthesis to alter CB toxicity (Boström et al., 2002). The toxic profile of CB thus varies mainly by its surface area and surface-bound toxins (Lindner et al., 2017). CB nanoparticles can deposit deep in the lung and induce severe pulmonary pathological effects, to include lung cancer (Parent, Siemiatycki, & Renaud, 1996; Rosmanith, Kandus, & Holuša, 1969). Chronic CB inhalation exposure has also been suggested to also impact other organs such as thymus and spleen (Chu et al., 2019), raising broader concerns over its toxicity. Circulating inflammatory potential, as described further below, is elevated in workers exposed to high levels of CB (Tang et al., 2020) and indices of genomic instability have been observed in sputum (Cheng et al., 2020).

Yet the most diverse class of ENPs are the CNTs, which can be engineered to possess an extraordinary variety of useful electrical, mechanical, optical, thermal, and chemical properties. Discovered by Sumio Iijima in 1991, CNTs are cylindrical carbon structures of wrapped graphene, either as single-walled or multi-walled tubes (Dai, 2002; Iijima, 1991). CNTs are strong and lightweight materials (Dresselhaus, Dresselhaus, & Eklund, 1996) favorable for conductive, high-strength composites, sensors, field emission displays and radiation sources, nanometer-sized semiconductor devices, and probes (Dresselhaus, Dresselhaus, Charlier, & Hernández, 2004). They are also used as biosensors, in tissue engineering, and as drug delivery systems (Simon, Flahaut, & Golzio, 2019) due to their ability to interact with macromolecules like proteins and DNA (Foldvari & Bagonluri, 2008; Zeinabad, Zarrabian, Saboury, Alizadeh, & Falahati, 2016). However, they also act as sorbents for organic pollutants, metals, fluoride, polycyclic aromatic hydrocarbons and radionuclides (Fiorito, Serafino, Andreola, & Bernier, 2006; Jia et al., 2005; Yang, Zhu, & Xing, 2006), which vastly affects their toxic potential. Exposure to CNTs can occur during six stages of manufacturing with various degrees of impact (Ono-Ogasawara, Takaya, & Yamada, 2015; Schlagenhauf, Nüesch, & Wang, 2014). First, CNT synthesis involves considerable manual handling of the raw material when extracting from the furnace growth tubes. Secondary manufacturing of interim products such as master batches and dispersed solutions involves agitation and mechanical abrasion that can cause release into the air. For example, Maynard et al. reported up to 53 μg/m^3 of single-walled CNT (SWCNT) dispersed into the air with agitation, which varied greatly with the process of manipulating the material (Maynard et al., 2004). Fonseca et al. showed that airborne CNT concentration during secondary manufacturing depended greatly on ventilation with as little as 1.7×10^{-3} fibers/cm^3 with high-flow ventilation to as much as 5.6 fibers/cm^3 without local exhaust (Fonseca et al., 2014). CNT nanoparticles often clump, however, forming rope-like structures that can be straight, bend, curled and flexible, with diameters ranging from 20 to 200 nm and lengths between 10^3 and 10^6 nm (Donaldson et al., 2006). CNT also sediments easily and adheres to surfaces (e.g., safety gloves can have between 0.2 and 6 mg per hand), which may re-aerosolized (Maynard et al., 2004). Stage three involves composite formation where NPs can be released during drying/curing. Stage four involves mechanical manipulation and testing of the final product, where NPs are released by tooling, cutting, or sanding of products into their final form. Stages five and six involve the handling of the final product by the consumer and its eventual disposal; however, CNT release is considered relatively minimal during these last two stages of the life cycle (Kingston et al., 2014). Yet the overlap between CNT and asbestos life-cycles in terms of airborne exposure risk are similar enough to raise health concerns in workers and consumers alike (Nowack et al., 2013). Moreover, health outcome studies with CNT exposure have supported its initiation of systemic pathological responses (Table 1), to include extra-pulmonary inflammation (Erdely et al., 2011), cardiovascular dysfunction (Nurkiewicz et al., 2006), atherosclerosis (Niwa, Hiura, Murayama, Yokode, & Iwai, 2007), and neurological deficits (Liao et al., 2014).

Direct passage from the lung into the circulation has been observed for certain types of NPs, others are phagocytosed effectively by macrophages and transferred through the lymphatics, while high-aspect ratio particles are more lasting within the lung. It is principally the smaller, compact particles like the MeNPs that readily translate from the lung, particularly those that have less than a 35 nm hydrodynamic diameter and a non-cationic surface charge (Choi et al., 2010; Takenaka et al., 2001). Other NPs made from CB or polymers get readily taken up by lung macrophages, which have been shown via particle labeling to translocate out of lung into the lymphatics and beyond into the circulation, liver and heart (Furuyama, Kanno, Kobayashi, & Hirano, 2009; Shwe, Yamamoto, Kakeyama, Kobayashi, & Fujimaki, 2005). Yet NPs with tube- and fiber-like profiles do not readily enter the circulation or get cleared to the lymphatics, remaining longer-term within the lung while still inducing tangible systemic effects (Chen et al., 2006; Mercer et al., 2013; Wiebert et al., 2006), pointing to involvement of relevant indirect mediators. Additionally, limited evidence mechanistically confirms that systemic toxicity of particles arises from their direct action at the site of injury (e.g., in the aorta or the brain). Findings of systemic toxicity from ozone inhalation – which fails to penetrate beyond the epithelial lining fluid of the lung (Postlethwait, Cueto, Velsor, & Pryor, 1998; Pryor, Squadrito, & Friedman, 1995) – strongly argue for pulmonary responses to inhaled toxicants as an essential driver of systemic health outcomes (Garcia et al., 2021; Mumaw et al., 2016; Tyler et al., 2018).

3. Systemic health outcomes of nanoparticle exposure

3.1. Systemic inflammation

Inhalation of various NPs has been found to induce peripheral inflammation. For example, inhalation of ultrafine CB for seven hours increased circulating blood leukocytes and stimulated the release of polymorphonuclear leukocytes from the bone marrow within 48 h (Gilmour et al., 2004). Moreover, human occupational exposure to CB significantly stimulated secretion of pro-inflammatory cytokines interleukin (IL)-1, IL-6, IL-8, macrophage inflammatory protein (MIP)-1β, and tumor necrosis factor (TNF)-α into the circulation (Zhang et al., 2014). NP inhalation can also produce inflammation in other organ systems. In a mouse model of subacute (4-week) NP inhalation of diesel exhaust enriched with cerium oxide, IL-1β and TNF-α levels were both significantly increased in the brain (Cassee et al., 2012). Interestingly, these studies suggested greater susceptibility in the brain, as there were no measured cytokine changes in spleen or liver tissues of the same animals. In a whole-body inhalation chamber, animals exposed to nickel hydroxide NPs for either 1 week or 5 months (0 or 79 μg/m^3, 5 h/d, 5 d/wk) showed serum amyloid P mRNA levels significantly increased over control, a marker of liver inflammation and injury. Additionally, animals with the 5 month exposure exhibited significant increases in spleen CCL-2, IL-6, and TNF-α mRNA as well as increases in Ccl-2 and Il-6 within the heart (Kang et al., 2011). Interestingly, serum cytokines showed no significant differences in either nickel hydroxide exposure cohort, suggesting that extra-pulmonary organ inflammation can be mediated by other circulating factors, and that this

Table 1
Overview of different types of nanoparticles and their systemic effects following inhalation exposure.

Nanoparticle		Size Distribution	Systemic Health Outcome			
			Inflammation	Cardiovascular Dysfunction	Neurological Deficits	Cancer
Traffic related air pollution	Ultrafine Particulate Matter (UFP)	< 100 nm	–	(Ibald-Mulli et al., 2002; P Elder et al., 2004; Chuang et al., 2005; Delfino et al., 2005; Lanki et al., 2006; Upadhyay et al., 2008; Andersen et al., 2010; Khandoga et al., 2010; Sannolo et al., 2010; Strak et al., 2010; Miller et al., 2012)	(Allen, Liu, Pelkowski, Palmer, et al., 2014; Allen, Liu, Weston, Conrad, et al., 2014; Allen, Liu, Weston, Prince, et al., 2014; Babadjouni et al., 2018; Cory-Slechta et al., 2018; Guerra et al., 2013; Heusinkveld et al., 2016; Klocke et al., 2017; Klocke et al., 2018; Ljubimova et al., 2013; Sobolewski et al., 2018)	(Ljubimova et al., 2013)
	Diesel/mixed Engine Exhaust	< 200 nm	(Cassee et al., 2012)	(Kodavanti et al., 2011; Lund et al., 2011; Mills et al., 2011; Sack et al., 2016; Thompson et al., 2019)	(Bolton et al., 2012; Bolton et al., 2013; Bolton et al., 2014; Bolton et al., 2017; Cole et al., 2016; Ehsanifar et al., 2019; Fleegal-DeMotta, Doghu, & Banks, 2009; Hullmann et al., 2017; Levesque, Surace, et al., 2011; Levesque, Taetzsch, et al., 2011; Lucero et al., 2017; Lund et al., 2009; Morgan et al., 2011; Morris-Schaffer et al., 2019; Oppenheim et al., 2013; Suwannasual et al., 2018; Suwannasual et al., 2019; Woodward et al., 2017; Woodward et al., 2018)	–
	Carbon Black	30–300 nm	(Gilmour et al., 2004; Niwa et al., 2008; Zhang et al., 2014)	(Niwa et al., 2008)	(Onoda, Kawasaki, Tsukiyama, Takeda, & Umezawa, 2017; Onoda, Takeda, & Umezawa, 2017; Umezawa et al., 2018)	–
Metal containing	TiO_2	primary - 20 nm, agglomerates <200 nm	(Nurkiewicz et al., 2006; Park, Yoon, et al., 2009)	(Helfenstein et al.; Nurkiewicz et al., 2006; Leblanc et al., 2010; Halappanavar et al., 2011; Nichols et al., 2018; Kunovac et al., 2019)	(Bailey et al., 2018; Disdier et al., 2017; Hougaard et al., 2010)	–
	CeO_2	83 ± 1.8 nm	(Cassee et al., 2012)	(Gojova et al., 2009)	–	–
	CdO	~ 15 ± 2 nm	(Blum et al., 2014)	–	–	(Bertin & Averbeck, 2006)
	$Ni(OH)_2$	primary - 5 nm, agglomerates −40 nm	(Kang et al., 2011)	(Kang et al., 2011)	–	–
	ZnO	< 100 nm	–	(Wang et al., 2010)	–	–
	Mn	0.1–1 μm	–	–	(Al-Lozi et al., 2017; Bailey et al., 2018; Bowler et al., 2006; Bowler et al., 2011; Ijomone et al., 2019; Park, Bowler, & Roels, 2009; Roels et al., 2012; Tjalkens et al., 2017)	(Falcone et al., 2018)
	Fe	0.1–1 μm	–	–	–	(Falcone et al., 2018)
	Fe_2O_3	< 100 nm	–	(Wang et al., 2010)	–	–
	Cu	25 nm	(Adamcakova-Dodd, Monick, Powers, Gibson-Corley, & Thorne, 2015)	–	–	–
	Silver	45 nm	–	(Park et al., 2011; Rosas-Hernández et al., 2009)	–	–
Carbon nanotubes	Single wall	diameter 0.4–1.2 nm, length 1–3 μm	–	(Li et al., 2007)	–	(Kisin et al., 2007; Rodriguez-Yañez et al., 2013; Sanchez et al., 2009; Sargent et al., 2009; Senchukova, 2019)
	Multi-walled	diameter < 100 nm, length < 6 μm	–	(Aragon et al., 2016; Mandler et al., 2017; Mandler et al., 2018)	(Aragon et al., 2017)	(Fukushima et al., 2018; Kasai et al., 2016; Muller et al., 2008; Rodriguez-Yañez et al., 2013; Sanchez et al., 2009; Sargent et al., 2014; Senchukova, 2019)
Silica contain-ing	Silica	primary 12–200 nm	(Du et al., 2013)	–	–	(Chen et al., 2014; Gehrke et al., 2013; Shi et al., 1998)
	SiO_2	37.9 ± 3.3 nm	–	(Chen et al., 2008)	–	–

may be NP-dependent. Cadmium oxide NP exposure in mice for seven days, for example, led to increased pro-inflammatory markers IL-1β, interferon-γ, and TNF-α in the blood as well as in bronchiolar lavage fluid at both 1 and 7 days following the last exposure (Blum et al., 2014). Similarly, Park et al. demonstrated that after instillation of nano-TiO_2 (5 mg/kg, 20 mg/kg, and 50 mg/kg), pro-inflammatory cytokines IL-1, TNF-α, and IL-6 increased in the blood and bronchiolar lavage fluid at all concentrations acutely (1 day post) (Park, Yoon, Choi, Yi, & Park, 2009). Park et al. also tracked blood and bronchiolar lavage fluid cytokine concentration over the next two weeks to find a mixed response of decreasing pro-inflammatory IL-6 and anti-inflammatory IL-10 while pro-proliferative IL-2 and anti-inflammatory IL-4 were found to significantly increase, reaching their highest concentration at the end of the two-week period. Overall, peripheral cytokine induction varies with NP type and dose, yet there remains evidence for organ inflammation even with minimal alteration in circulating cytokines, suggesting other involved circulating mediators.

3.2. Cancer pathobiology

Metal nanomaterials, silica nanoparticulates, and combustion UFPs have all demonstrated carcinogenic properties after inhalation. For example, mice exposed (whole body inhalation) to a mean of 34.5 mg/m^3 iron-abundant gas metal arc welding fumes for 8-weeks induced lung carcinogenesis within 30 weeks of exposure (Falcone et al., 2018). Silica particulates showed similar effects in vivo, exhibiting signs of persistent oxidative stress, cell membrane damage, site-specific cleavage of double-stranded DNA, and other DNA damage, eventually leading to carcinogenesis in the lungs (Shi, Castranova, Halliwell, & Vallyathan, 1998). Biomolecular mechanisms under study for NP-induced pulmonary cancer include the nuclear translocation of nuclear factor kappa B (NF-κB) proteins that activate reactions leading to the displacement of inhibitor IκB and induction of activator protein-1, which promotes tumor growth (Gehrke et al., 2013; Shi et al., 1998).

The oncogenic potential of CNTs is particularly concerning given their physical similarity to asbestos fibers. Recent studies found that CNTs can induce malignant tumors (Fukushima et al., 2018; Senchukova, 2019). Kasai et al. showed that whole-body inhalation exposure to MWCNT (0.2 and 2 mg/m^3) for 104 weeks (5 days/week) promoted lung carcinoma formation in male more so than female rats (Kasai et al., 2016). They later reported that MWCNT-7 fibers in this 104 week model generated oxidants and cytokines leading to inflammation and fibrosis, which they surmise drove cycles of cell and DNA damage, forming the observed preneoplastic lesions with the potential to form tumors (Fukushima et al., 2018). MWCNT induces cytotoxicity and oxidative stress in human mesothelial cells, as affirmed in vitro, and can transform those cells much like asbestos does through chromosomal aberrations by interacting with the mitotic spindle (Nagai et al., 2011; Rodriguez-Yañez, Muñoz, & Albores, 2013; Sanchez, Pietruska, Miselis, Hurt, & Kane, 2009). Similar findings were also evident with SWCNTs. For example, Chinese hamster lung fibroblasts showed increased micronucleus formation when exposed to 0.23% SWCNTs in vitro (Kisin et al., 2007). Rat type II pneumocytes and a human epithelial cells (MCF-7) also exhibited induced clastogenic and aneugenic micronuclei formation, respectively, when exposed to SWCNT and MWCNT in vitro (Muller et al., 2008). Human airway epithelial cells also showed fragmented centrosomes, aneuploid chromosomes, and multiple mitotic spindle poles 24 h after exposure to SWCNTs in vitro (Sargent et al., 2009). Interestingly, Sargent et al. found that SWCNTs associated directly with cellular tubulin, indicating that with these nanotubes being of similar size to microtubules they can be incorporated into the mitotic spindle apparatus directly and, thus, cause errors in mitotic spindle activities. CNT size and geometry can also influence pro-inflammatory effects, with long and thin nanofibers resulted in higher toxicity and carcinogenic activity than short, thick fibers in vitro (Senchukova, 2019). Fraser et al. found genotoxicity, micronuclei formation and oxidative stress across at least six of seven types of CNT and two types of carbon nanofibers in vitro; however, severity was principally dependent on a larger size in both length and diameter (Fraser et al., 2020). Other physical attributes like specific surface area, dustiness, metal residue or surface charge showed no discernable toxicity pattern. Yet, the oncogenic potential of inhaled CNT appears limited to the lung. For example, mice exposed to high amounts of MWCNT-7 (5 mg/m^3, 5 h/d, 5 d/wk) for 15 days exhibited bronchiolo-alveolar adenoma and lung carcinoma development at 17 months post exposure without evidence of tumor formation in other organs (Sargent et al., 2014). Interestingly, inhaled NPs are being hailed as a promising means for targeted chemotherapy in lung cancer with improved internalization into cancer cells, warranting the need to balance nano-carcinogenicity with the biomedical promise of NPs (Ahmad et al., 2015).

3.3. Cardiovascular dysfunction

The most documented extrapulmonary effect of inhaled NP is upon the cardiovascular system as illustrated in Fig. 1 (Medina, Santos-Martinez, Radomski, Corrigan, & Radomski, 2007; Oberdörster et al., 2005). Adverse cardiovascular effects have included altered heart rate, hypertension, thrombosis, arrhythmias, increased myocardial infarction, and atherosclerosis. These effects have been similarly identified across ultrafine/nanoparticulate exposures in humans (Andersen et al., 2010; Chuang, Chan, Chen, Su, & Lin, 2005; Delfino, Sioutas, & Malik, 2005; Lanki et al., 2006) and animal models alike (Chen et al., 2008; Elder et al., 2004; Kang et al., 2011; Leblanc et al., 2010; Park, Choi, & Park, 2011; Wang, Wang, Ding, & Zhang, 2010), including epidemiological studies that demonstrate correlations between UFP exposure and increased cardiovascular pathological alterations (Ibald-Mulli, Wichmann, Kreyling, & Peters, 2002; Sannolo, Lamberti, & Pedata, 2010; Strak et al., 2010). Yet the literature is of mixed opinion on whether these outcomes are caused by direct NP translocation out of the lung or by indirect mediators. Work with CeO_2 NP in vitro has shown induction of a proinflammatory phenotype when directly placed onto human aortic endothelial cells, which putatively contributes to vasoconstriction and atherogenic lesion development (Gojova et al., 2009). Likewise, 45 nm silver NPs elicited concentration-dependent endothelial cell cytotoxicity and endothelial nitric oxide synthase (eNOS) activation in vitro, and altered vasoreactivity with isolated rat aortic rings ex vivo (Rosas-Hernández et al., 2009). Cardiac myocytes exposed to TiO_2 NP exhibited dose-dependent oxidative stress responses, changes in cell function, and alterations in myofibrillar structure in vitro (Helfenstein et al., 2008). And, combustion-derived diesel exhaust NPs inhibited acetylcholine-induced relaxation in isolated rat aortic rings when directly exposed ex vivo (Mills et al., 2011). Importantly, in many of these direct exposures of internal cells to NPs, the doses are quite high – it is notable that many effects are only observed in vitro with concentrations of 10–100 μg/ml, when ambient concentrations are 10–100 μg/m^3, representing a difference in concentration of 10^6. It is less clear as to whether NPs translocate out from the lung at sufficient levels to drive cardiovascular effects systemically without considering an indirect pathway.

Indirect molecular mediators appear involved in NP-induced cardiovascular outcomes. Dispersing deep and broadly within the lung, NP-stimulated pathology drives the release of bioactive mediators into the circulation, which can include a mix of inflammatory cytokines, oxidatively-modified lipids, and prothrombotic factors. Circulating IL-6, monocyte chemoattractant protein-1, and C-reactive protein, for example, were all acutely elevated in rats after 4-weeks of inhaled CB exposure despite there being no evidence of particle translocation (Niwa, Hiura, Sawamura, & Iwai, 2008). Instead, CB NPs were found concentrated within alveolar macrophages believed to be responsible for the increased circulating cytokines. Oxidized LDL has also been found increased acutely in the blood of animals (for seven days) and humans

(for two hours) exposed to the NP fraction of combustion exhaust (Lund et al., 2011). Oxidized low-density lipoprotein (ox-LDL) interacts with leptin-like oxidized low-density lipoprotein receptor-1 (LOX-1) on vascular endothelial cells, promoting oxidative stress with accompanying sub-endothelial macrophage accumulation. Moreover, LOX-1 mRNA expression also increased acutely in the circulation, a recognized biomarker of progressive atherosclerosis. Evidence of systemic oxidative damage has been found after SWCNT instillation into the lungs of mice, which was found to increase mitochondrial DNA damage in the lung and heart out at least 1 week after exposure, with evidence of brachiocephalic atherosclerosis (Li et al., 2007). And in a recent larger population epidemiological study, fine particulate matter levels, and not other common air pollutants (nitrogen dioxide, ozone or sulfer dioxide), was predictive of blood LOX-1 levels using data from the Multi-Ethnic Study of Atherosclerosis (Ni et al., 2021). Notably, in a broader review of the topic of particulate matter and cardiovascular effects, Møller et al. noted that while pulmonary and systemic inflammation often occur in controlled particulate exposure studies of vascular toxicity, they are not always seen, suggesting that systemic vascular effects may occur due to pathways more subtle than canonical inflammation signaling (Møller et al., 2016).

Alterations to vasoactive factors like endothelin-1 and nitric oxide that impair blood flow are also increased acutely after NP inhalation (Knuckles et al., 2012; Kodavanti et al., 2011). As well, genes involved in complement and coagulation pathways have been found heightened in the circulation five days after mouse inhalation of TiO_2 NP for 11 days (Halappanavar et al., 2011). Indeed, the prothrombotic potential for vessel occlusion is of paramount concern following pulmonary particulate exposures in general (Budinger et al., 2011; Li, Yu, Jon Williams, & Liu, 2010). More recently, we have added that proteolytic byproduct peptides are also shed into the circulation acutely following pulmonary MWCNT aspiration in mice (Mostovenko et al., 2019). Characterized as a peptidomic response, we detected hundreds of peptide fragments induced in the lung with linearly correlated release into the circulation. Importantly, an isolated peptide fraction from the blood of MWCNT exposed animals promoted endothelial inflammation, vasodilatory dysfunction, and inhibition of angiogenesis, highlighting a specific role for molecular factors like bioactive peptides without any direct NP exposure. Overall, there is growing evidence to support multiple indirect mediators of systemic toxicity following NP inhalation exposure, which we discuss in a later section.

3.4. Systemic organ impacts involved in detoxification and clearance

Importantly, the toxicological profile of pulmonary NP exposure extends well beyond the lung via the cardiovascular and lymphatic systems. Generally smaller and more spherical, MeNPs in particular translocate to other organ systems, principally those involved in detoxification and clearance like the liver, kidneys and spleen (Kermanizadeh, Gaiser, Johnston, Brown, & Stone, 2014). Hepatic toxicity is generally greater with <50 nm NPs due to their translocation, but also varies with the toxic nature of the metal ion(s) involved (Buckley et al., 2017; Rosário et al., 2021; Nayek, De Silva, Aguilar, Lund, & Verbeck, 2021 & Nayek, Lund, & Verbeck, 2021). Low-solubility NPs, for example made of Ag, Ir, TiO_2 or CdO, all translocate from the lung and accumulate in liver and kidneys. Buckley et al. studied a size-dependence directly with Ir-NP inhalation, selected for its low solubility and capacity for radio-tracing (Buckley et al., 2017). While retention in the lung was similar for acute Ir-NP ranging in size from 10 to 75 nm, translocation to the liver and kidneys was increased with decreasing NP size. Interestingly, they found that smaller Ir-NPs continued to accumulate in higher amounts in the liver (studied beyond 100 days); however, kidney accumulation plateaued by 30d, suggesting greater liver vulnerability with time. Nayek et al. directly imaged Ag-NP present within the liver and kidneys after subacute inhalation exposure, a common material used for its antimicrobial properties in consumer goods and beauty products (Nayek, De Silva, Aguilar, Lund, & Verbeck, 2021). Interestingly, they found a size bias with smaller NPs distributing more to the liver while larger agglomerates appeared preferentially in the kidneys. Correspondingly, the smallest Ag-NPs resulted in more pronounced liver than kidney pathology, to include pro-inflammatory cytokine upregulation (IL-6, IL-1b, TNF-α) and oxidative DNA damage. However, liver lesions or fibrosis was not detected within the short 5-day exposure and sampling timeframe. In contrast, a subchronic 6-week inhalation exposure to 15 nm CdO-NPs produced prominent liver pathology, with significant neutrophil infiltration, hydropic dystrophy and areas of necrosis (Dumkova et al., 2016). Comparatively, the kidneys were less changed, with no overt cytology and only a modest thickening of filtration membranes and lamina, again supporting greater liver vulnerability. Dose is further important in determining secondary organ injury. Han et al. assessed this with 0.2 g/kg vs. 1.0 g/kg instilled doses of 10–25 nm TiO_2 NPs in the rat (Han et al., 2020). Insoluble TiO_2 was found within both liver and kidneys by 3-days after either dose, with the lower dose producing disordered cytology and lipid peroxidation in liver but mild increases in kidney membrane thickness as consistent with studies mentioned above. However, within the same timeframe, a 5-fold higher dose produced frank necrosis in both organs along with dose-dependent genotoxicity. These studies reflect the complexity in assessing secondary organ injury with NP exposures, whereby pathology is dependent on the interaction of dose and duration of exposure on top of size, with most studies addressing just one of these factors.

Further influencing the process of secondary organ toxicity is NP solubility. Liver and kidney injury is evident even with NPs that dissolve before making it to these secondary exposed organs. For example, in a chronic 10 mo. exposure study with NiO-NP (common in welding fumes; 23 nm nominal size), liver and kidney dysfunction were evident through higher blood bilirubin and proteinuria levels along with increased DNA fragmentation, despite mild pulmonary pathology compared with insoluble NPs (Sutunkova et al., 2019). Interestingly, secondary organ histological findings were similar to that reported with insoluble CdO or Ag NPs, with structural disturbance to hepatocyte and Kupffer liver cell cytology and enlarged membranes and damage to the tubular epithelium in kidneys. Yet, NiO-NPs could not be found in either tissue, expectedly due to its solubility. Dose of exposure further influences how potentially soluble NPs are processed. For example, 10 nm ZnO when inhaled subchronically at a lower 20 $\mu g/m^3$ concentration could hardly be detected within the lung, having been endocytosed by the epithelium and found in lysosomal bodies where the NPs dissolved under acidic conditions (Vysloužil et al., 2020). Yet, at a much higher 625 $\mu g/m^3$ concentration, substantial lung buildup was evident after the same 12-weeks, with endocytic clearance being overwhelmed and limited pH-dependent dissolution in the lung. This correspondingly resulted in a lower accumulation of Zn ion within the liver and kidneys as more of the metal was retained in the lung.

Looking beyond MeNPs, size remains a dominant factor in secondary organ toxicity. Silica NPs in the <50 nm range, much like TiO_2 or other insoluble NPs, can readily leave the lung and translocate to the liver. Cao et al. used ultrasound shear wave velocity imaging to monitor liver edema that worsened over weeks after 20 nm silica NP installation in live animals (Cao et al., 2017). Effects were dose dependent, with hepatic injury enhanced when the silica was coated with a plastic film, which appeared to enhance passage from the lung. Interestingly, Fournier et al. found that inhaled 20 nm polystyrene nanoplastic as well rapidly translocated out of the lung, with detection in spleen, heart and even the uterus after just 24 h (Fournier et al., 2020). What's more, they showed that inhaled nanoplastics could even transverse the placenta and embed in fetal tissues, stunting fetal growth. Even without direct translocation to secondary organs, non-MeNPs can induce acute-phase inflammatory responses within the liver via indirect molecular mediators, as demonstrated with carbonaceous nanoscale soot material (Ganguly et al., 2017). Inflammatory markers were

up in both liver and heart with inhalation of 10–14 nm carbon nanoparticles, which importantly could not be reproduced by injecting the material directly into the blood, affirming a secondary molecular mediator as the driving factor in acute hepatotoxicity. Given sufficient time, <50 nm carbonaceous NP do translocate from the lung to the liver just as MeNPs. Modrzynska et al. demonstrated this with 14 nm carbon black, which accumulated in the liver to a similar degree as TiO_2 and CeO_2 of the same approximate size (Modrzynska et al., 2018). All three NPs ended up in Kupffer cells and sinusoids over several weeks after instillation. Yet, CB was considerably more genotoxic in the liver, with the level of DNA strand breaks being 3.9-fold and 2.4-fold higher than with TiO_2 and CeO_2, respectively, after 180 days. CB generated orders of magnitude more reactive oxygen species than either metal oxide, demonstrating how NP type governs systemic toxicity under conditions of similar size-dependent translocation.

How secondary organs are impacted differs when moving to NPs with at least one dimension exceeds the nanometer scale as with ENPs like nanotubes and fibers. Breakthrough from the lung is largely limited to the lymphatics, the degree to which depends on the general shape and agglomeration tendency of the NP. Knudsen et al. examined across 11 different instilled MWCNT types and found that short and thin fibers tended to agglomerate more and where more readily phagocytosed and cleared to the lymphatics by macrophages (Knudsen et al., 2019). Longer and more rigid nanotubes tended to get lodged in the lung interstitium. However, all types exhibited some degree of translocation to secondary organs, though minimal even when assessed up to a year from exposure. Because of this, nanotubes and fibers were found less impactful on detoxification secondary organs like the liver than were smaller, spherical NPs. Nanotubes and fibers clear the lung more prominently via the lymphatics and with time end up more in the spleen where they appear to exhibit dose-dependent and prolonged immune system modulation (Migliaccio et al., 2021). Soluble metal content within the nanotubes, however, can amend this generalization, with cobalt found to be particularly influential on hepatotoxicity (Knudsen et al., 2019). Spherical <50 nm NPs can also act more as nanotubes when they form large aggregates in situ. Barium sulfate behaves in this way when instilled into the lung (Molina et al., 2019). While nominally 25 nm particles, they end up forming large aggregates of up to 2 μm in size in the lung and are thus primarily cleared via macrophage phagocytosis to the lymphatics over long periods extending out at least 2 years. NPs were not largely evident within the liver or kidneys over this time; however, slow dissolution of the NP resulted in barium ion accumulation in the liver as well as bone. Moving to graphene, a planar material with only 1 nanoscale dimension, we see mucosillary clearance and passage through the gut becoming the dominant means of excretion (Mao, Hu, Pan, Xie, & Petersen, 2016). Yet this too is a potential oversimplification, as a small (<1%) fraction of the material escapes the lung and can be viewed within liver and spleen after 4-weeks. This is similar to the low percent of nanotube material that makes it to secondary organs, which reflects a portion of a graphene sample that fractures into a more fiber-like fraction. These examples all demonstrate the challenge in generalizing NP toxicity. The general expectation that high-aspect NPs tend to show limited hepatotoxicity can be amended by the dissolution of metal content; that the ready translocation of <50 nm sized NPs can be superseded by a materials ability to agglomerate; or that the general tendency of a planar particle to clear the lung much like non-nanoscale materials can be influenced by diversity in shape within a sample.

Less well studied were the impacts of demographic factors such as age and sex on secondary organ injury. Aging influences clearance capacity of NP from the lung, as demonstrated by Gaté et al. with acutely inhaled TiO_2 exhibiting delayed clearance from the lung within three months of exposure in aged animals (Gaté et al., 2017). Correspondingly, younger animals exhibited greater phagocytic clearance of TiO_2 to the lymphatics. Aging alone is associated with chronic inflammation in the lung and other organs, which degrades the ability to address an acute NP exposure (Pomatto et al., 2018). This also includes diminished enzymatic capacity to address oxidative insult and misfolded protein accumulation in the lung as well as detoxification organs like the liver in aged animals. So, while NP inhalation in the young animal (6 mo.) was capable of heightening clearance activity, there was generally no added capacity left in these processes to address the added burden of an NP insult in aged animals (21 mo.). Sex varies both the total load accumulated in the lung at the same NP aerosol concentration and altered downstream effects on secondary organ systems. Females exhibit significantly greater accumulation of nanoscale vs. microscale particulate as males for the same concentration (Sayers et al., 2016). Moreover, sex differences impact immune system inflammatory responses both in the lung and in secondary organs like the liver. In a model of acute and subchronic Ni-NP exposure, You et al. showed that males exhibit greater inflammation and immune cell infiltration into the lungs than female animals (You, Lee, Taylor-Just, Linder, & Bonner, 2020). NP effects carried further to secondary organs like liver and spleen, where inflammatory cytokine responses were higher in males than females. Female sex hormones have known anti-inflammatory activity but also appear to enhance macrophage-dependent clearance and inflammation resolution (Villa, Rizzi, Vegeto, Ciana, & Maggi, 2015). Overall, these limited findings substantiate the need to consider sex and age factors in assessing secondary organ toxicity from inhaled NP exposures. Indeed, the interaction of sex and age on secondary outcomes has largely not been studied, raising the question as to whether a sex bias remains throughout the lifespan or perhaps susceptibility shifts between the sexes as hormone levels fall with age.

4. Nanoparticle exposure and the brain

Beyond those involved in detoxification and clearance, the brain is a secondary organ of NP toxicity of considerable interest given its prominence in regulating all that we do and who we are. Particular focus is given to the impact of NP exposure on the brain with its privileged protective blood brain barrier (BBB), its vulnerability to neurodevelopmental impairment and its susceptibility to chronic pathology impacting the higher order functions that as humans our lives depend on.

4.1. Blood-brain barrier impairment

NP vascular impairment extends to the neurovascular unit of the brain, which brings the potential for acute and chronic neurological impairment. The BBB is an intricate assemblage of cerebrovascular endothelial cells anchored together by tight-junction proteins, abluminal pericytes that facilitate barrier integrity, which is all ensheathed by astrocytes to facilitate glucose uptake and serve as a line of defense (Fig. 2). Barrier integrity is dynamic, and a wide variety of neuropathies are associated with a more “open” BBB that is thought to be pathogenic and a contributing factor in ongoing dysfunction. In our model of acute pulmonary MWCNT exposure in mice, we identified pronounced BBB disruption, with small-molecule fluorescein and macromolecule albumin leakage into the parenchyma (Aragon et al., 2017). Yet accompanying the compromise barrier, we observed dose-dependent neuroinflammatory responses, including pronounced reactive astrogliosis and microglial recruitment to the neurovascular unit. Interestingly, the higher dose of MWCNT provoked reactive astrocytes to acutely migrate close to the vessel lumen, as in early glial scar formation, suggesting a protective response in the mouse brain that was not observed in the lower MWCNT exposure (Mostovenko et al., 2021). Furthermore, glial reactivity extended farther from the vessel wall at the lower dose, suggesting greater potential for parenchymal perturbation. Indeed, we observed greater synaptic perturbation at the lower MWCNT dose, with an increased density of excitatory synapses extending farther from the vessel lumen than with the higher dose. This was accompanied by a robust decrease in inhibitory synaptic density for an overall hyperexcited

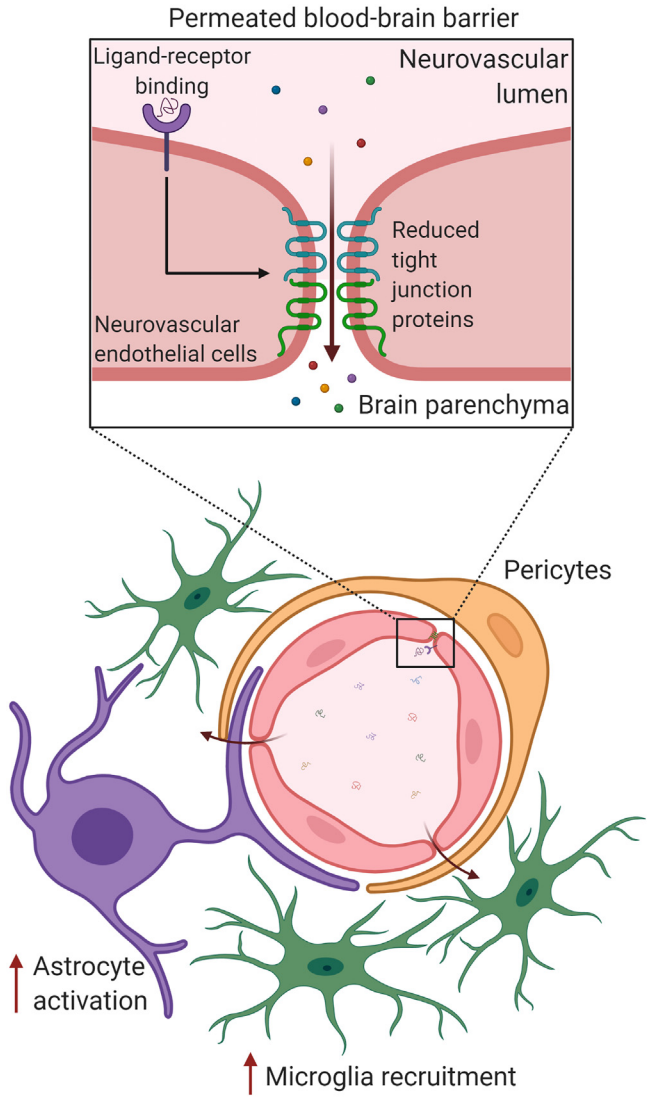

Fig. 2. Vulnerability of the blood-brain barrier with inhaled nanoparticle (NP) exposure. Dysfunction of the BBB has been found following pulmonary MeNP and carbonaceous NP exposures. The targets include tight junction disruption, leakage into the parenchyma, activation of adjacent astrocytes and recruitment of microglia to the neurovascular unit. Cell surface receptors on cerebrovascular endothelial cells are susceptible to induced circulating ligand peptides, cytokines and oxidized macromolecules that degrade barrier integrity.

phenotype that, together with BBB disruption and neuroinflammation, are all characteristic of early pathogenesis in Alzheimer's disease. Looking longer term, subchronic exposure of aged Fischer rats (19 months) to 10 mg/m^3 TiO_2 aerosol (<100 nm) for 28 days (6 h/d, 5 d/wk) exacerbated age-associated modulation of BBB integrity (Disdier et al., 2017). Again, BBB alterations were accompanied by significant pro-inflammatory responses to include up-regulated IL-1β, vascular endothelial growth factor, interferon-γ, interferon-γ-inducible protein 10, and fractalkine, which again was consistent with neurodegenerative disease pathogenesis (Disdier et al., 2017). Interestingly, no pro-inflammatory markers were detected in the blood of these animals, and no TiO_2 NPs were detected in the brain, reinforcing the role of yet unknown indirect mediators.

UFP-containing air pollutants have also been shown to elicit effects on the human as well as animal brain, including BBB disruption, with active research investigating a role in priming for neurodegenerative disorders and brain cancers (Ljubimova et al., 2013; Raaschou-Nielsen et al., 2011; Wu, Yao, & Cai, 2012). In ApoE$^{-/-}$ mice subchronically exposed to a mixture of gasoline and diesel engine vehicle exhaust (100 μg/m^3, 6 h/d, 7d/wk., for 30d), BBB disruption was observed with decreased expression of tight-junction proteins and P-glycoprotein associated transport (Lucero, Suwannasual, Herbert, McDonald, & Lund, 2017;Lund et al., 2009; Oppenheim et al., 2013). These effects were partly mediated by matrix metalloproteinase (MMP)-9 (Lund et al., 2009; Oppenheim et al., 2013) and modulation of lectin-like LOX-1 expression, known to affect MMP-9 levels in vascular endothelial cells. Furthermore, neutralization of LOX-1 protected against subchronic vehicle emissions-induced BBB disruption, lipid peroxidation, and partially reduced overall ROS production (Lucero et al., 2017). Of further importance, a high-fat diet was found to further compound the effects of subchronic vehicle exhaust emissions on cerebrovascular permeability, exacerbating changes in tight-junction and MMP-9 protein expression as well as plasma ox-LDL and LOX-1 levels (Suwannasual, Lucero, McDonald, & Lund, 2018). Mechanistically, mixed high-fat diet and vehicle exhaust also significantly increased circulating angiotensin II and expression of angiotensin II receptor type 1 (AT1) in the cerebral microvasculature subchronically, which is known to increase BBB permeation (Suwannasual, Lucero, Davis, McDonald, & Lund, 2019). Supporting this, when plasma from exposed animals was applied on endothelial cells in vitro, expression of tight-junction proteins claudin-5 and occludin was significantly reduced. Those effects were attenuated with AT1 receptor antagonist pretreatment, confirming angiotensin II-AT1 involvement in regulation of BBB disruption following NP exposure.

While the focus of the present review is on indirect mediators of systemic pathobiology, when discussing the brain, it is also important to consider that inhaled NP and UFP may also circumvent the lung and go directly to the brain through the nasal cavity (Block & Calderón-Garcidueñas, 2009). The olfactory region is topped with a thin, porous bone called the cruciform plate, through which olfactory receptor neurons project and may transport NP and UFP along axons to the olfactory bulb if not other areas of the brain (Oberdörster et al., 2004). Attention to the olfactory pathway originated with the transport of metals to the brain, as found with different NPs and UFP, (Tjälve & Henriksson, 1999). Yet, many of the metals under study, such as those from welding fumes, were water-soluble within the nasal mucosa, and there has been limited evidence for the translocation of actual NPs along this pathway in humans (Boyes & van Thriel, 2020). Detailed modeling of NP deposition in casts of the human olfactory region demonstrate a significant NP-size deposition dependency, with only the smallest (< 10 nm) particles being retained in appreciable amounts (Garcia, Schroeter, & Kimbell, 2015). Thus, exposure to smaller NPs may very well result in direct transport to the brain as well as potential indirect effects through a lung-brain axis, which can confound the assessment of NP neurotoxicity if not considered as part of a study design (e.g., comparing aspiration into the lung vs. nasal instillation or inhalation).

4.2. Neurodevelopmental outcomes

Little has been researched regarding the impact of ENPs on neurodevelopment, likely due to the emphasis on ensuring safety principally for occupational exposures. Yet, children are potentially exposed to ENPs through consumer products during gestational and postnatal development. For example, prenatal subacute exposure to TiO_2 NPs in mice caused significant consequences in the brains of offspring with neurobehavioral abnormalities (Hougaard et al., 2010). Yet, the impact of UFP in air pollution on neurodevelopment has gained considerable attention for its potential to induce life-long behavioral and cognitive outcomes in children (Costa et al., 2017; Newman et al., 2013; Suglia, Gryparis, Wright, Schwartz, & Wright, 2008; Volk, Hertz-Picciotto, Delwiche, Lurmann, & McConnell, 2011; Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013). Modeled perinatal research in rodents dosed with <200 nm UFP traffic-related air pollution, there was considerable BBB disruption, associated hippocampal microbleeds detected, decreased neurogenesis and decreased AMPA receptors

(Morgan et al., 2011; Woodward et al., 2018). Believed to be involved was the stimulation of the toll-like receptor 4 pathway through increased IL-1α and TNF-α signaling, which is known to impact the barrier and neurogenesis (Hanamsagar & Bilbo, 2017; Valero, Paris, & Sierra, 2016). In utero subacute air pollution toll-like receptor 4 signaling also alters microglia morphology during embryonic brain development, particularly in males, and promotes a delay in neuronal maturation (Bolton et al., 2017). Following UFP exposure, the offspring exhibited significant impairment in contextual memory, depressive-like behavior, and reduced food-seeking. Several more studies have shown that gestational NP exposure results in persistent behavioral deficits in adult offspring, more so in males (Bolton et al., 2012; Bolton et al., 2013; Bolton, Auten, & Bilbo, 2014). Similar findings were observed with subacute gestational CB exposure, where six-week old offspring also exhibited frank astrogliosis around the cerebrovasculature (Onoda, Takeda, & Umezawa, 2017) and a decreased inhibitory interneuron density (Umezawa et al., 2018), despite the lack of overt signs of pulmonary inflammation within the dams.

Neurodevelopment vulnerability to UFP is also a consideration in the pathogenesis of autism spectrum disorders (ASD). Mice exposed to traffic-related concentrated ambient UFPs (CAPs) at post-natal days 4–7 and 10–13, equivalent to third trimester human neurodevelopment, produced a pattern of developmental neurotoxicity notably similar to mechanistic underpinnings of ASD (Allen et al., 2017). This period is characterized by BBB maturation (Xu & Ling, 1994), gliogenesis (Catalani et al., 2002), and gray matter growth (Baloch et al., 2009; Bockhorst et al., 2008). Exposed animals showed increased microglia and astrocyte activation at post-natal days 14 and 270 (Allen et al., 2014; Allen et al., 2014; Allen et al., 2017). Glutamate, glutamine and GABA levels were all altered in frontal cortex of both male and female CAPs treated animals and in the hippocampus of males with a shift to hyperexcitation (Allen et al., 2014; Allen, Liu, Pelkowski, Palmer, et al., 2014; Allen, Liu, Weston, Prince, et al., 2014) akin to the glutamatergic disbalance in children and adults with ASD (Allen et al., 2017). Per sex-dimorphic neuroanatomical effects, only males were found to exhibit learning and memory dysfunction while females displayed behaviors consistent with altered motivation (Cory-Slechta, Allen, Conrad, Marvin, & Sobolewski, 2018). Male animals also exhibited social communication deficits and reduced serum testosterone (Sobolewski et al., 2018). Males also showed ventriculomegaly and reduced myelination and size of the corpus callosum pointing to under-connectivity of the two hemispheres consistent with social and language deficits and altered hand preference found in children with ASD (Allen et al., 2017; Allen, Liu, Pelkowski, Palmer, et al., 2014).

Interestingly, when subacute CAPs exposure was shifted to early gestation, the sex-dimorphic findings also changed, pointing to distinct windows of neurodevelopmental vulnerability. Ventricular areas were enlarged only in females when observed at postnatal days 57–61, and the corpus callosum was enlarged specifically in CAPs-exposed males. Females, not male, also exhibited a 106% increase in iron deposition in the corpus callosum, which was positively correlated with increased MBP and negatively correlated with microglia cell count (Klocke et al., 2017). Iron required for oligodendrocyte maturation and myelin biosynthesis (Badaracco, Siri, & Pasquini, 2010; Connor & Menzies, 1996) has also been associated with air pollution-associated risk for cognitive impairment with adult neurodegeneration (Bartzokis et al., 2007), suggesting that iron homeostasis may also play a role in CAPs-induced neurotoxicity.

4.3. Adult neurotoxicity and neurodegenerative disease

On the opposite end of the age-spectrum, NP exposure may also contribute to the pathogenesis of neurodegenerative diseases (Block & Calderón-Garcidueñas, 2009; Oudin et al., 2016). Diesel engine UFP emissions have been of particular concern, recognizing that upwards of 90% of the particle fraction is on the nanoscale (Kittelson, 2001). Acute diesel exhaust particulate (250–300 $\mu g/m^3$ for 6 h) induced neurotoxicity, with greater inflammatory cytokine expression and lipid peroxidation in neurodegenerative disease-relevant brain regions after a day (Cole et al., 2016). Alzheimer's and Parkinson's related pathology was then evident with subchronic diesel particulate exposure along with increased Aβ42, phosphorylated Tau [pS199], and α-synuclein neuropathology in rats (Levesque, Surace, McDonald, & Block, 2011). Mice exposed chronically to NPs (< 200 nm) from traffic pollution showed neurite atrophy, decreased myelination, and increased microglia activation in hippocampus (Woodward et al., 2017). In combination with aging (18-month old animals), chronic traffic NP exposure impaired memory, with a 30% reduction in short- and long-term novel object recognition test performance. Even in models of familial Alzheimer's (5XFAD mice), chronic diesel exhaust particulate enhanced Aβ42 accumulation with reduced brain function (Hullmann et al., 2017). Yet chronic diesel exhaust-derived UFP has also been shown to increase depression- and anxiety-like behaviors in mice (Ehsanifar et al., 2019), with more research needed to investigate psychiatric outcomes.

Neuroinflammation appears to be an underlying consequence of modeled UFP exposures (Ehsanifar et al., 2019; Levesque et al., 2011; Levesque, Surace, et al., 2011). Chronic UFP exposure induces Nrf-2 activation in conjunction with neurocognitive deficits (Guerra et al., 2013). These effects were accompanied by moderate oxidative stress in the brain as measured by reduced antioxidant enzyme heme oxygenase 1 and mitochondrial superoxide dismutase SOD-2 mRNA levels in disease-relevant striatal and hippocampal regions. Similarly, chronic diesel exhaust UFP also upregulates neuronal nitric oxide synthase levels in the brain (Ehsanifar et al., 2019). Such stress responses are accompanied by persistent microglial activation, whether from subchronic direct motor vehicle exhaust or chronic mixed urban traffic UFP exposures alike (Babadjouni et al., 2018; Mumaw et al., 2016). Interestingly, these studies found no change in circulating cytokine levels, supporting the involvement of other indirect mediators.

NP-induced neurotoxicity is additionally associated with metal content, with the impacts of manganese and lead well known in neurodegenerative and neurodevelopmental disorders, respectively. In human adults, chronic inhalation of manganese containing NPs, for example in welding fumes, can cause severe neurotoxicological consequences (Bailey, Kerper, & Goodman, 2018). In fact, there are a multitude of industrial processes that can result in manganese NPs, including mining, ore-crushing, metallurgical operations, dry-cell battery production, etc. Repeated studies have shown dose-dependent cognitive deficits, particularly in working memory, in workers exposed to Mn-containing fumes (Al-Lozi et al., 2017; Bowler et al., 2006; Bowler et al., 2007; Bowler et al., 2011; Park, Bowler, & Roels, 2009; Roels et al., 2012). Manganese in the NPs exists as different oxides and in combination with fluorine and potassium, which have been shown to increase manganese solubility in the lung. In the case of manganese, it is solubility concerns that relate to induced neurotoxicity, driving reactive oxygenated species production and inflammatory cytokines in the brain (Tjalkens, Popichak, & Kirkley, 2017). Manganese-driven oxidative stress in neurons drives calcium dysregulation and eventual apoptotic cell death (Ijomone, Aluko, Okoh, Martins, & Aschner, 2019). Manganese selectively accumulates in dopaminergic neurons with repeated rat exposure to welding fume NPs (Sriram et al., 2010), though exactly why is still not known; however, this neuronal death produces the idiopathic Parkinsonian symptoms associated with manganism. Yet it should be considered that NPs contain other metals that have their own role in developing neurocognitive outcomes. Zinc, magnesium, lead, lithium and even iron blood levels can influence mood and anxiety levels (Mlyniec, Gaweł, Doboszewska, Starowicz, & Nowak, 2017), supporting the potential that a broader range of metal NPs can drive neurobehavioral consequences.

5. Indirect mechanisms of systemic toxicity

The health impacts of NP inhalation exposures extend to the circulation and beyond to other organ systems (Table 1, Fig. 1), yet not always with solubilization or NP transport to the periphery, directly or facilitated by macrophages. Studies where systemic effects occur through indirect mediators have been highlighted above. Traditional cytokine/chemokine activation in the blood is evident only in some cases, transiently, and often at levels insufficient to explain extrapulmonary inflammation and organ injury. Reactive oxygenated species and induced oxidative stress also manifests in other organ systems, yet not always with a pro-oxidative state in the blood. In this next section, we review the state-of-knowledge on indirect mediators of extrapulmonary NP toxicity. The composition of augmented factors in the circulation can include classical cytokine ligands as well as novel vasoactive peptides derived from proteolytic processing in the lung, sometimes accompanied by lipid and protein peroxidation products and extracellular vesicles (EVs) (Fig. 3). We review the evidence for these circulating factors and arrive at the importance for a multivariate approach to analyzing blood compositional change in understanding the toxicological profile of different NPs.

5.1. Oxidative species and reactive products

A defining characteristic of NPs is their high surface area-to-volume ratio, which enhances composition-based particle reactivity. Especially for MeNPs or metal-bound NPs, redox cycling may be readily promoted (Shannahan, Kodavanti, & Brown, 2012), leading to ROS production and oxidative stress in exposed tissues (Shvedova, Pietroiusti, Fadeel, & Kagan, 2012). Oxidative stress occurs particularly with NPs having: (i) transition metal content or contaminants, (ii) bound free radical intermediates, and (iii) adsorbed redox-active molecules on the NP surface (Shvedova et al., 2012). NPs containing iron, copper, chromium, vanadium, and silica are especially reactive through Haber-Weiss and Fenton-type reactions. Silicate NPs also present free radical intermediates like SiO and SiO_2 on their surfaces, which promote hydroxyl and superoxide free radical formation. Additionally, with a large surface area, carbon-based NPs can adsorb ambient reactive species like ozone and nitrogen dioxide that provide additional oxidative potential (Manke, Wang, & Rojanasakul, 2013). Yet, the high surface area-to-volume ratio does not entirely explain the reactivity of a NP in tissues. For example, CB of different mean diameters produced similar cellular antioxidant responses, suggesting that some oxidative effects are independent of NP surface properties (Koike & Kobayashi, 2006). Of further consideration, fullerenes and carbon nanotubes can scavenge hydroxyl radical through interactions with dangling bonds at sites of defects in the carbon framework (Fenoglio et al., 2008). Thus, the oxidative potential across different NPs is rather difficult to predict without empirical determinations.

Within the lung, NP contact can result in accumulation of ROS as well as reactive nitrogen species that can overwhelm intracellular antioxidant capacity and oxidatively damage proteins, lipids, and DNA (Shannahan et al., 2012). Under these conditions, ROS causes lipid peroxidation of polyunsaturated fatty acids (Barrera, 2012). Oxidized lipids then promote the polymerization of membrane components, modification of transmembrane potential, release of mitochondrial calcium, and pro-apoptotic signaling through caspases-3 activation and DNA fragmentation (Bertin & Averbeck, 2006). However, the cellular response is graduated. As ROS levels start to increase, nuclear factor-erythroid factor 2 activation triggers defensive transcriptional responses to enhance antioxidant capacity. If ROS increases further, inflammatory responses are activated via c-Src, p38 MAP kinase, and NF-κB signaling cascades (Wu & Tang, 2018). These cascades may further progress to involve mitochondrial stress-associated pro-apoptotic signaling and eventual cell death. Indeed, inhibition of the NF-κB pathway was found sufficient to alleviate NP-mediated inflammation and fibrosis pointing to this as a critical initiation step (Chen et al., 2014). This cascade was nicely documented by Pardo et al. in a study of single *versus* repeated mouse exposure to inhaled roadside particulates (Pardo, Porat, Rudich, Schauer, & Rudich, 2016). ROS levels in the lung were dependent on the number of repeated exposures; however, nuclear factor-erythroid factor 2 activation only increased with the single dose

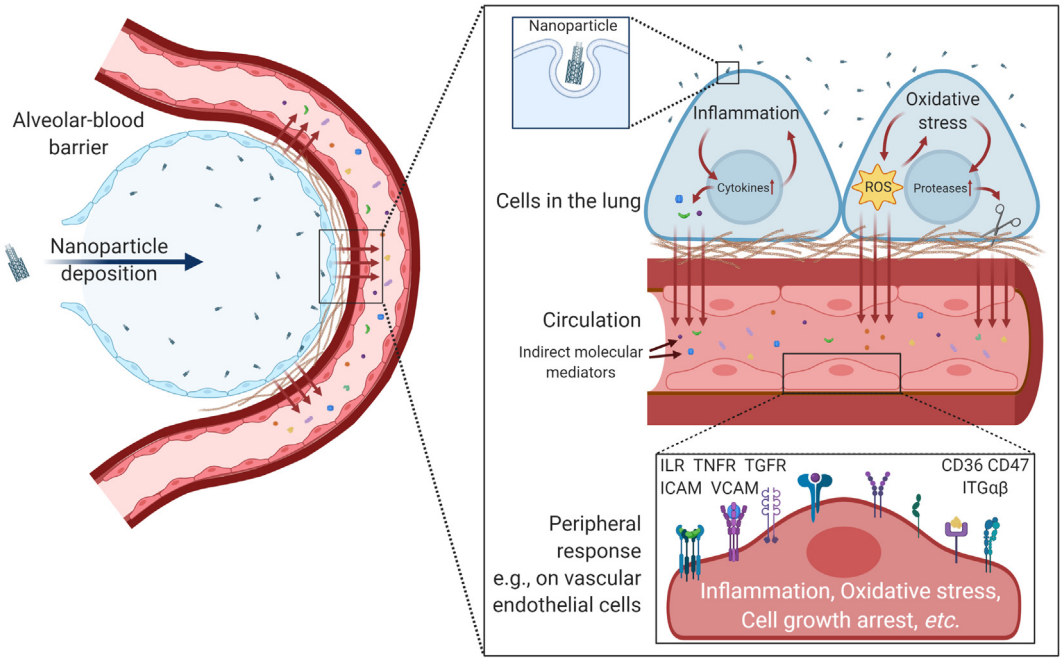

Fig. 3. Indirect mechanism of systemic toxicity following nanoparticle (NP) inhalation. As illustrated, NPs penetrate deep into the lung to interact with cells of the alveolar-blood interface and resident immune cells. There, NP stimulation triggers oxidative stress and inflammation with the generation of oxidative products, the activation of matrix proteases, and the release of pro-inflammatory cytokines. Signaling proteins and peptides, oxidized lipids and protein products, and secreted extracellular vesicles are released across the alveolar-blood interface into the circulation. These indirect mediators interact systemically with the cardiovascular system, altering function, and negatively influencing extrapulmonary organs.

and was driven down at the higher level of ROS with repeated doses. This coincided with enhanced antioxidant capacity in the lungs of singly-dosed animals, while glutathione, heme oxygenase 1 and other antioxidant defense genes were all decreased in the lungs after repeated exposures. The latter group exhibited pronounced lipid and protein oxidation in the lung not evident in single-exposure animals. Moreover, repeat-exposure animals exhibited significant increases in pro-inflammatory IL-6 and TNF-α in the blood that was not detected in those animals exposed just once, pointing to co-morbid systemic outcomes.

Pardo et al. did not, however, measure whether oxidized macromolecule byproducts were increased in the circulation. Indeed, most studies of peripheral organ toxicity following modeled pulmonary NP exposure lack assessment of oxidized macromolecules in the blood, as reviewed elsewhere (Dugershaw, Aengenheister, Hansen, Hougaard, & Buerki-Thurnherr, 2020; Moller et al., 2010; Shvedova et al., 2012; Yu et al., 2020). These studies instead propose NP translocation or proinflammatory cytokine release from the lung into the circulation as the causal agents of systemic oxidative stress. For example, Nichols et al. found significant ROS production and mitochondrial respiratory dysfunction in cardiac tissue following nano-TiO_2 inhalation in mice, demonstrating a reversal of effects with phospholipid hydroperoxide glutathione peroxidase treatment (Nichols et al., 2018). Yet, they attributed the oxidative insult to nano-TiO2 translocation. However, lipid peroxidation products are also potent stimulants of tissue inflammation, and their role as indirect mediators of extrapulmonary toxicity needs to be considered, perhaps concomitant with cytokine release. Oxidized macromolecules have considerably longer half-lives than typical ROS species, and so have greater potential to induce oxidative effects outside the lung that can be independent from NP translocation (Shannahan et al., 2012). Unfortunately, it is difficult to measure such oxidative byproducts in the circulation. Common blood oxidant stress biomarkers include the thiobarbituric acid reactive substances (TBARS) assay, which measures levels of malondialdehyde and lipid hydroperoxides. Peroxidation of arachidonic acid in lung tissue can also result in the release of prostaglandin F_2-like compounds, with 8-iso-prostaglandin-$F_{2\alpha}$ (8-isoprostane) primarily assayed (Chen, Arjomandi, Balmes, Tager, & Holland, 2007). The release of oxidized proteins can also be detected through an increase in blood protein carbonyl levels (Shacter, 2000). However, all these assays are influenced by oxidative stress and background processes occurring throughout the body, challenging the determination of a causal role. Indeed, the few studies that have looked at oxidized macromolecules in the periphery are unable to demonstrate causation. For example, Pirela et al. studied the pulmonary and systemic effects of inhaled printer-emitted NPs in rats (Pirela et al., 2019). They found modest lung injury and inflammation with a mild increase in lactate dehydrogenase levels and significant, though not pronounced, cytokine and chemokine activation along with increased alveolar macrophage and neutrophil counts. In the blood, they found a significant increase in 8-isoprostane levels at multiple doses as early as one day after exposure, reflecting the potential for systemic oxidative damage. Analysis of heart tissues, however, showed no evidence of injury or inflammation to affirm systemic effects. Yet in a later publication, the same group reported that printer-emitted NPs promoted global metabolic changes within the circulation involving glycerophospholipids, unsaturated fatty acids, and sphingolipids that are in-kind modulated under pro-inflammatory conditions associated with cardiovascular disease (Guo et al., 2019). Thus, further directed research is needed to demonstrate a casual role for oxidized macromolecules as indirect mediators conveying NP toxicity from the lung to peripheral organs.

5.2. Cytokines and chemokines

The deposition of NPs deep within the lung largely circumvents mucociliary clearance and promotes an inflammatory reaction with immune-cell stimulating cytokine and chemokine release (Fujii, Hayashi, Hogg, Vincent, & Van Eeden, 2001). Yet the story is more complicated, with different particulates promoting varied degrees of T helper cell 1 (more prominent with vehicle emissions) or 2 immune responses (Hamilton, Holian, & Morandi, 2004). This is further complicated by the varying degree to which particulate-driven inflammation in the lung is accompanied by an increase in circulating pro-inflammatory factors. For example, Inoue et al. showed that diesel exhaust particulate, separated from the soluble organic fraction, promoted greater inflammation in the lung and pro-inflammatory cytokine and chemokine release into circulation (Inoue et al., 2006). Yet this was limited to mice co-treated with lipopolysaccharide, while circulating cytokines were not significantly increased by diesel particulate treatment alone. Similarly, Wang et al. showed that urban pollution fine particulate alone produced no significant increase in circulating IL-6, but in a co-exposure with ozone they observed a particulate dose-dependent increase in serum IL-6 (Wang, Jiang, Zhao, & Song, 2013). Moreover, Hullmann et al. showed pronounced neurological effects of repeated diesel exhaust particulate inhalation in mice with no significant pulmonary histopathology or increases in serum levels of IL-1, IL-6, IL-17, keratinocytes-derived chemokine, MIP-1, or monocyte chemoattractant protein 1 (Al-Lozi et al., 2017). In human exposures, Mills et al. showed that acute diesel exhaust produced significant cardiovascular outcomes related to vascular tone and fibrinolysis; however, again there was no change in proinflammatory IL-6, C-reactive protein or TNF-α (Mills et al., 2005). Thus, while release of pro-inflammatory cytokines and chemokines into the circulation is possible with particulate inhalation, which can drive cardiovascular deficits (Hadei & Naddafi, 2020), it cannot be assumed that particulate alone is able to induce these factors in the blood as a causal factor of other systemic effects.

In contrast, pulmonary MeNP exposure appears to more readily evoke blood cytokine responses than does diesel engine emissions exposure. For example, Holland et al. reported that instillation of 20 nm silver NPs resulted in significant increases in circulating IL-1, IL-6, IL-10, IL-13, IL-17, IL-18, MIP-1, and TNF-α after a day and as long as a week, yet lung tissue injury was surprisingly minimal (Holland et al., 2015. The silver NP did not readily dissolve, appearing prominently within the lung at one week, yet the particles were actively being phagocytosed by pulmonary macrophages, which may have caused the release of cytokines into the blood. They also found significant cardiovascular inflammation and depressed vascular reactivity consistent with the circulatory responses observed, though breakthrough of the silver NP into the circulation or vascular tissues was not assessed and so could not be ruled out. We already discussed that MeNPs are more likely to make it to the periphery owing to their smaller size. This was the case in a study by Du et al. where instilled silica NP exposure also prompted significant increases in circulating IL-1, IL-6, C-reactive protein and TNF-α, but the silica NPs were also found in the bloodstream and cardiac tissues making it hard to disentangle the contribution of direct and indirect effects (Du et al., 2013). Interestingly, Coccini et al. compared the toxicological profile of cadmium-doped silica NPs with non-doped silica NPs, finding that after instillation of both there was an increase in circulating IL-6, but the translocation of the cadmium-doped silica NPs produced significant renal toxicity that entirely absent with non-doped silica NPs (Coccini, Barni, Mustarelli, Locatelli, & Roda, 2015). This emphasizes that in this case the particle translocation with nephrotoxic cadmium is a key determinant, not the capacity to increase circulating cytokines with or without NP transport from the lung.

Yet it cannot be overlooked that dose plays a significant role, with many modeled exposures being performed at exaggerated levels of NP exposure. For example, Erdely et al. showed that mice which aspirated a 40-μg bolus of ultrafine CB, SWCNT or MWCNT exhibited significant increases in serum cytokines and chemokines (IL-6, CCL11, CXCL1, CCL22), more so with MWCNT than the other two NPs (Erdely et al., 2009). Later, they extrapolated that for an average 10.6 $\mu g/m^3$ MWCNT concentration in industrial manufacturing facility under

typical ventilation conditions: a 40 μg deposition in the mouse lung would equate to 20,000 8-h workdays of exposure, roughly 76 years of a work life (Erdely et al., 2013). Yet, if a high dose was the major determinant, then it is of note that with a high 100 μg bolus instillation of MWCNT in the rat, Thompson et al. observed no significant change in serum IL-6 (Thompson et al., 2016). Instead, they measured a significant decline in gp130, an antagonist to the IL-6 receptor, which may have had a pro-inflammatory effect in the periphery. It is hard to reconcile these findings, since the two models differed in species used, the administration type, and the vehicle used. To the later point, Thompson et al. used saline while Erdely et al. devised a dispersion media containing serum albumin and the phosphocholine DPPC to minimize nanotube aggregation and facilitate better dispersion within the lung, which seemingly would make for a more potent exposure. Additionally, cytokine release into the periphery may occur transiently as a short-duration, acute response. Erdely et al. first reported a significant rise in circulating cytokines 4-h post 40 μg CB, SWCNT and MWCNT exposure (Erdely et al., 2009); however, measures of the same mediators were not significantly different by 24 h post exposure (Erdely et al., 2011). Similar findings were found by Urankar et al. 24 h after an even higher dose (100 μg) aspiration of three different types of MWCNT, where only serum eotaxin levels reached significance with one type of MWCNT; yet, they still reported significant cardiovascular consequences (Urankar et al., 2012). Thus far, modeling studies with non-MeNPs have been less than conclusive in defining a role for cytokine factors, pointing towards other indirect mediators.

Addressing modeling concerns, Beard et al. assessed the correlation of blood cytokine levels with real-world exposure to carbon nanotubes and nanofibers (Beard et al., 2018). Assessing across 102 workers from 12 different primary and secondary manufacturing sites using these materials, they found no significant associations between inflammatory cytokines IL-1, IL-6 and TNF-α in serum of workers, though they did find a significant association with decreased chemokines CXCL8 and CCL11 that would suggest a suppressed immune-cell response. Indeed, this group later demonstrated in the population that the blood of workers exposed to higher levels of carbon nanomaterials exhibited greater suppression of immune cell activation after ex vivo LPS and SE-B stimulation (Schubauer-Berigan et al., 2020). In all, the role of circulating cytokines in manifesting systemic health outcomes is largely inconclusive: most studies show a minimal association with engine exhaust or urban air particulates; MeNPs seems to produce a pronounced response in circulating cytokines that is confounded by those particles breaking through into the circulation where they may act on the vasculature to drive of blood cytokine levels; high-aspect NPs like MWCNT that are more largely restricted to the lung only seem to promote cytokine release into the circulation under extreme conditions, while actual carbon nanomaterial exposure in workers seems to suppress the immune cell response in the circulation.

5.3. Vasoactive proteins and peptides

As we have thus reviewed, the pathological response to NP exposure in the lung is complex and no single released factor can fully explain the extrapulmonary burden. Indeed, omic research is revealing a wide diversity of circulatory changes, with a host of vasoactive and pro-pathological factors released to the periphery. For example, Thompson et al. used proteomic analysis to show at least 66 proteins augmented in rat blood after diesel exhaust inhalation (particle size 120–140 nm) (Thompson et al., 2019). Using ex vivo assays, they demonstrated the bioactivity of the blood molecular milieu by placing serum on naïve cells, an approach previously used with ozone as an inhaled pollutant that cannot escape the lung (Postlethwait et al., 1998; Pryor et al., 1995) and thereby affirming a causal, contributing role for indirect mediators (Mumaw et al., 2016; Robertson et al., 2013). Evident in the blood was a wider array of proteinaceous changes beyond classical cytokines that promote receptor-mediated cardiovascular responses. For example, blood levels of angiotensin increased with vehicle exhaust exposure, stimulating angiotensin receptors to augment cardiovascular function (e.g., vasoconstriction) and even compromise the BBB (Ferrario, 2006; Suwannasual et al., 2019). Inhaled vehicle emissions also promoted increases in oxidized low-density lipoprotein (ox-LDL), which is yet another vasomodulatory protein response (Suwannasual et al., 2018), and which cross-activates with angiotensin their respective endothelial receptors, LOX-1 and AT1, modulating pathways involving nitric oxide and ROS responses (Li, Saldeen, Romeo, & Mehta, 2000; Li, Zhang, Philips, Sawamura, & Mehta, 1999; Morawietz et al., 1999). However, the influence of diesel exhaust or concentrated ambient urban particulate via blood-borne ligands on the renin-angiotensin system has even wider implications by affecting the neuroendocrine stress axis that regulates everything from mood, immune function to digestion (Qiu et al., 2018; Sack et al., 2016).

Yet another vasoactive protein of importance is thrombospondin (TSP), a prominent modulator of arteriolar vasodilation that promotes anti-angiogenesis via endothelial cell-surface receptor interactions (Miller, Isenberg, & Roberts, 2010). Work by us and others have shown increased TSP levels within the circulation and extrapulmonary tissue after MWCNT exposure in the lung (Aragon et al., 2017; Mandler, Nurkiewicz, Porter, & Olfert, 2017). Mandler et al. further demonstrated a causal role for TSP whereby vasodilatory dysfunction, endothelial nitric oxide pathway inhibition, and endothelial leukocyte adhesion were all significantly muted after MWCNT exposure in TSP knockout animals (Mandler et al., 2017; Mandler, Nurkiewicz, Porter, Kelley, & Olfert, 2018). They went on to also show a role for the cell surface receptor CD47 with a knockout mouse and MWCNT treatment (Mandler et al., 2018). TSP-CD47 signaling caused eNOS uncoupling and ROS generation, with declining nitric oxide levels found after MWCNT treatment in wild-type animals. However, effects on nitric oxide levels were absent in TSP and CD47 knockout animals treated with MWCNT. Moreover, Mandler et al. demonstrated that these vasodilatory and nitric oxide responses were produced in the absence of either lung or blood activation of IL-6, IL-10 or TNF-α after MWCNT exposure, supporting an independent role for TSP in mediating NP systemic cardiovascular outcomes.

Interestingly, both ox-LDL and TSP are ligands for another endothelial cell surface receptor, CD36 (Febbraio, Hajjar, & Silverstein, 2001). Binding of ox-LDL to CD36 has been shown to deplete endothelial cholesterol from the plasma membrane, which dislocates membrane-active eNOS, reducing nitric oxide, and altering vascular responses while stimulating atherogenesis (Uittenbogaard, Shaul, Yuhanna, Blair, & Smart, 2000). TSP activation of CD36 separately drives p38 MAP kinase activation and proapoptotic signaling. TSP-CD36 interactions also inhibit myristate uptake, which reduces eNOS activity further while also influencing potentially many other myristoylation-regulated processes (Isenberg et al., 2007). However, the TSP concentration needed to activate CD36 is some two-orders greater than that needed to modulate CD47, with the latter operating more as a sensor to physiological shifts in TSP, while CD36 responds to more pathological TSP levels (Isenberg et al., 2006). MWCNT exposure in the lung indeed produced sufficient TSP-related signaling in the blood to drive CD36-mediated endothelial responses ex vivo with impaired vasorelaxation in wild-type vessels absent in CD36 knockout vessels (Aragon et al., 2016). Yet assessments of circulating TSP showed only a modest increase in MWCNT treated animals (Erdely et al., 2009). While significant, the magnitude was insufficiently elevated from physiological levels to mediate the observed CD36 dependence, suggesting an alternative exposure-induced peptide ligand.

Importantly, blood from MWCNT-treated mice that had MMP-9 knocked out was unable to initiate the ex vivo CD36-dependent vasorelaxation deficits found in wild-type animals, implicating a role for MMP-9 (Aragon et al., 2016). This supported the hypothesis that matrix remodeling in the NP-exposed lung promoted generation and release into the circulation of proteolytic fragments of which a subset would

have ligand functionality. Indeed, not only was MMP-9 expression elevated in the lung after MWCNT exposure (Erdely et al., 2009), so were a multitude of other matrix proteases and cathepsins involved in the extracellular release of proteolytic fragments (Mostovenko et al., 2019). Not surprisingly, the resulting shift in circulating peptides was equally complex, which in aggregate comprises a peptidomic response to NP exposure. Employing quantitaive peptidomic mass spectrometry, we assertained that 841 peptides (with masses between 1 and 7 kDa) were significantly altered after MWCNT exposure across matched lung lavage and serum biofluids, with 567 exhibiting correlative exchange between the two biofluids. Importantly, pre-treatment with the pan-MMP inhibitor, marimastat, directly into the lung muted most though not all of the peptide fragment release into the blood, affirming a pulmonary source, involvement of MMPs, and the co-involvement of other proteases not antagonized by marimastat (Young et al., 2021). The identified peptides were enriched with factors associated to abnormal cardiovascular responses. This was further observed in the peptidomic response within cerebral spinal fluid, which was further indicative of ongoing neuroinflammation and synaptic remodeling proximal to the neurovascular unit that was consequent ligand-mediated cerebrovascular dysfunction (Fig. 2) (Mostovenko et al., 2021). Thus, the peptidomic response was consistent with the reported impacts to the vasculature at different doses of MWCNT in the lung, providing putative biomarkers of exposure and extrapulmonary pathological effects.

Moreover, when separated from whole serum, circulating peptides induced with MWCNT exposure were able to cause ex vivo vasorelaxation deficits and inhibited endothelial angiogenesis (Aragon et al., 2016; Mostovenko et al., 2019). Among the identified peptides was a 59-mer TSP fragment derived from the type 1 repeat domain containing the CD36 binding motif, which was elevated in the blood to a concentration of 20–24 nM, sufficient to activate CD36. Synthesizing the peptide, we further affirmed its ligand functionality in inducing endothelial dysfunction at 22 nM in culture. However, the circulating peptide fraction induced with MWCNT exposure was able to stimlate other pro-inflammatory responses, including increases in endothelial Ccl2, Vcam1, Icam1, and TNF-α, that were independent of CD36 and implicated integrin signaling with c-jun-induced cytokine transcription. Other peptide fragments of fibronectin, collagens and laminins were identified and hold ligand potential for integrin receptor signaling pathways. What's more, peptides released into the circulation can be further acted upon by blood-borne proteases, further complicating the peptidomic dynamics and the associated bioactivity. Additionally, extrapulmonary responses following NP inhalation can add to the circulating peptidomic response. Circulating factors we've already discussed, from cytokines and oxidative products to angiotensin, can stimulate endothelin converting enzyme and the release of the vasoactive 21-mer peptide endothelin-1 (Yanagisawa et al., 1988). For example, inhalation exposure in rats to urban air particulates is known to increase endothelin-1 levels in the circulation (Kumarathasan et al., 2015; Thomson, Goegan, Kumarathasan, & Vincent, 2004); however, more research is needed to explore the broader complement of peptide responses generated in the periphery following an NP-induced insult in the lung.

5.4. Extracellular vesicle involvement

EVs are an emerging subject of cell-to-cell communication research with putative prognostic and diagnostic value for respiratory pathology (Holtzman & Lee, 2020). Circulating EVs comprise a mix of microvesicles and exosomes, both being submicron in diameter, though exosomes have an overall smaller size distribution (Lie, Johansson, Mossberg, Kahn, & Karpman, 2019). Microvesicles are generated extracellularly through budding of the plasma membrane during physiological and pathological remodeling in the lung, though shedding increases with cellular stress (Bewicke-Copley et al., 2017; Park et al., 2012; Xu et al., 2015). Exosomes are formed through the exocytosis of multivesicular bodies such as stress granules and, thus, will contain macromolecular cargo derived from various intracellular organels compartments. Integral to homeostatic functioning, and carrying a cadre of RNAs and proteins, EVs are regularly shed under stress and manipulate recipient cells over a long distance. It is possible that EVs may also transport smaller-sized NPs from the lung to the periphery. Logozzi et al. demonstrated that 20 nm gold NPs endocytosed by macrophages ended up being released again within exosomes, which may facilitate NP distribution throughout the body (Logozzi et al., 2019).

NP exposure in the lung has been demonstrated to evoke EV release to enact peripheral responses. For example, with further examination of the serum peptidomic response to MWCNT pulmonary exposure, we observed that 40% of identified peptides were fragments from known exosome-associated proteins. Both the exosome concentration and size distribution in the serum were significantly altered following MWCNT exposure, supporting that bioactive products of pulmonary pathology can be shuttled to the periphery via EVs (Mostovenko et al., 2019). While these results may be the first to imply peptide transport via circulating exosomes, the concept that EVs can act as signaling conveyors after NP insult has been considered for some time though with rather limited exploration. Nemmar et al. first pubished on the release of leukocyte-derived microvesicles into the blood after pulmonary MWCNT exposure (Nemmar et al., 2007). Moreover, they demonstrated that blood-isolated microvesicles from MWCNT treated animals induced thrombin generation to suggest increasd thrombosis risk. Zhu et al. demonstrated that pulmonary macrophages release exosome-like EVs following inhalation of magnetic iron oxide nanoparticles, a common dust component in mining (Zhu et al., 2012). They found that these EVs were quickly cleared from the alveoli, presumed to be released into the circulation. They then demonstrated that the NP exposure-induced EVs were potent activators of T-cells that would exacerbate peripheral inflammation.

Several studies have suggested circulating EVs may be useful for diagnosing ambient particulate matter exposure, principally through quantificaiton of EV-derived micro-RNA. Bollati et al. were one of the first groups to show this relationship, where they assessed blood microvessicle-derived micro-RNA from 55 steel plant workers (Bollati et al., 2015). miR-128 and miR-302c, two micro-RNAs known to be associated with cardiovascular disease, were both significantly increased, 14-fold and 5.6-fold respectively, within blood EVs from matched samples collected at the start of a work week and after 3 full work days. In a follow-up study with the same worker cohort they performed more detailed regression modeling with particulate sub-fractions and metal levels (Pavanello et al., 2016). As many as 17 different micro-RNAs were found associated across the different measures. miR-200c, miR-302b and miR-30d were associated with oxidative stress and inflammation processes, though these three were principally correlated particularly with metal levels, not specific subfractions of the particulate matter. Rodosthenous et al. separately reported 16 EV-derived micro-RNAs found significantly associated with ambient in-home particulate matter levels evaluated as a moving average across a one-year period that were not complicated by high-levels of metal components (Rodosthenous et al., 2016). Importantly, associations improved with a longer period of time, suggesting a cumulative burden. Bonzini et al. provided one of the first examinations of circulating EV counts in association with ambient particulate matter exposure in healthy subjects (Bonzini et al., 2017). They further used flow-cytometry to sub-classify EVs by their cellular origins using specific markers. Interestingly, they found no overall correlation between personal breathing zone particulate levels and total circulating EV counts, but when examining subclasses of EVs, both CD105+ endothelial-originating EVs and CD14+ macrophage-originating EVs were significantly associated. Somewhat surprisingly, however, they found no difference in this association between course and fine particulate levels, suggesting that the particulalte fraction had no influence on EV release into the circulation. That said, none of these studies seprately assessed the contribution of the UFP

fraction, which we can only speculate may have a more pronounced influence as discussed for other NP responses reviewed earlier. Of additional note, Bonzini et al. also found that the association between particulate matter exposure and circulating EV counts was significantly interactive with a subject's body mass index. The finding emphasizes the importance in considering other known risk factors for cardiovascular disease as a contributing factor in manifested indirect mediators of systemic health outcomes.

6. Conclusions and future directions

Mechanisms underlying the extrapulmonary health outcomes of inhaled NP exposures remain incompletely understood, with a wide diversity of particulates producing disparate impacts in the lung and beyond. Metal and metal oxide NPs can produce cellular effects distinct from carbonaceous NPs, influenced in part by the solubility and size of the NP, but also by the reactive nature of the bulk material or surface-adsorbed contaminants. UFP from combustion sources represents a complex mixture of both metal and carbonaceous components with mixed-mode surface reactivity and solubility properties impacting health outcomes. Thus, while we've reported that different NP/UFP exposure impact the vasculature and extrapulmonary organs like the brain, the underlying mechanisms vary and can be mixed. Too few studies compare outcomes directly between different types of NP/UFPs, yet this is needed to understand the relative peripheral impact between materials. What's more, studies tend to assess systemic burden with a single exposure duration, typically acutely or subchronic. Longitudinal studies would allow a clearer picture of how different NP/UFP exposure produce evolving pathology from acute inflammation onto chronic disease. Likewise, further studies are needed to assess how aging and sex impact the longitudinal course of disease with NP/UFP exposure, with very little known for occupational exposures and only a modest number of studies assessing environmental UFP across ages.

Additionally, we are just beginning to divulge the complex interactions of indirect factors shed from the lung into the circulation, and how they augment tissues in the periphery. It is unclear whether the different indirect mediators reviewed here are significant in only a subset of NP/UFP exposures or how the role of each mediator might evolve across time, again because few studies have compared across types of NP/UFP or looked at outcomes longitudinally. More likely, all the discussed indirect mediators contribute at different time scales, with outcomes further modulated by varied degrees of compensation within the organism. Yet while it is easy to suggest these needs for future research, the resources required to conduct such an expansion in experimental design are appreciably and requires consideration by those involved in funding decisions. The community would also benefit from establishing a common framework to standardize NP/UFP dose guidelines by type and route and aligned with target exposure scenarios while also setting the number of days to repeat exposure for acute, subacute, subchronic and chronic outcomes.

Omic analyses at the protein, peptide, lipid, and metabolite levels are also desired to reveal the complex response in the circulation after NP/UFP exposure, which again will differ with dose, duration, and type of particulate, often in non-linear and additive ways. Peripheral pathological alterations are, in part, driven by a subset of these byproducts, for example by acting as cell-surface ligands, compromising the endothelium, and releasing molecular moities or immune cell invasion into other organs. Moreover, by-products of lung pathological responses can be translocated to the periphery encapsulated within EVs, which can be endocytosed and allow micro-RNA, protein, and peptide cargo to compromise intracellular processes that influence function and cell survival. Thus, further big-data research is warranted to investigate the role of indirect factors transducing the breadth of toxicological impacts occurring different NP exposures.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was funded by grants from the National Institute for Occupational Safety and Health, United States (OH010495 to A.K.O. and M.J.C. and NIOSH/NTRC 939ZXFL to A.E.), the National Institute of Environmental Health Sciences, United States (ES014639 to M.J.C), and the National Institute on Aging, United States (AG070776 to A.K.O. and M.J.C.). The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. Illustrations were created with BioRender.com.

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