Skin inflammation and psoriasis may be linked to exposure of ultrafine carbon particles

Air pollution has become the largest environmental risk to human health, estimated to kill seven million people worldwide every year. Data from the World Health Organization (WHO) showed that 91% of the world population was exposed to air contamination with air quality not meeting the WHO guidelines in 2016. A number of adverse health consequences have been associated with air pollution, including stroke, heart disease, lung cancer, chronic obstructive pulmonary disease, and acute respiratory infections (Chi et al., 2019; Chi et al., 2018; Craig et al., 2008; Zhou et al., 2018).

Although natural sources, such as forest fires and dust storms, contribute to air pollution, the contribution from human activities is much larger than that from natural sources. These human activities include but not limited to fuel combustion from motor vehicles, heat and power generation, industrial facilities, municipal and agricultural waste incineration/burning, and residential cooking, heating, and lighting with polluting fuels (Cui et al., 2019; Liu et al., 2018; Pant et al., 2018; Shirmohammadi et al., 2006; Wang et al., 2018).

Airborne particles represent a major type of air pollutants that have been linked to an increasing range of health effects, particularly to respiratory and cardiovascular systems. According to their mean aerodynamic size, airborne particles can be classified into three groups: coarse, fine, and ultrafine particles. Their defined size ranges are 10–2.5 μm, 2.5–0.1 μm, and less than 0.1 μm, respectively. Because of their small size and large surface-to-volume ratio, ultrafine particles are believed to pose a higher health risk than larger particles. The small size of particles facilitates their penetration into epithelial and endothelial cells, diffusion into blood and lymph circulation, and accumulation in different organs or tissues such as bone marrow, spleen, heart, and even the nervous system (Kim et al., 2018; Oberdörster et al., 2005). The large surface-to-volume ratio makes these particles more biologically active, causing proinflammatory effects and oxidative stress (Oberdörster et al., 2005; Win et al., 2018).

Ultrafine carbon particles are often studied to understand the basic toxicity of ultrafine particles. The use of carbon particles excludes the toxic effects from composition variation of ambient ultrafine particles. Several studies have demonstrated that ultrafine carbon particles can reduce cell viability and up-regulate proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6 in vascular endothelial, human monocytes, and A549 lung cancer cells (Cocci et al., 2016; Yamawaki and Iwai, 2006). However, these studies used carbon particles at much higher levels than environmental levels and short exposure time that was not appropriate to study developmental toxicity. Therefore, there remains a knowledge gap in understanding developmental toxicity of ultrafine carbon particles at environmental levels. Because of their ability to differentiate into many types of cells, stem cells have been widely used to study various toxicities (e.g. developmental toxicity) of environmental pollutants (Fu et al., 2017; Li et al., 2017; Liu et al., 2020).

Cheng et al. (2020) employed human embryonic stem cell (hESC) differentiation systems, via embryoid body (EB) formation into keratinocytes, to study the developmental toxic effects of ultrafine carbon particles. Stem cells were exposed to ultrafine carbon particles at five different concentrations ranging from 1 ng/mL to 10 μg/mL. The equivalent internal exposure was estimated to be 7.3 ng/mL (after one-day exposure) and 2.67 μg/mL (after one-year exposure), using 25 μg/m³ as the average ultrafine particle concentration in the air. The exposure of cells to ultrafine carbon particles was carried out from day 0 until the end of the differentiations. To examine developmental toxic effects of ultrafine carbon particles, the authors measured hESC viability, studied the expression of the core pluripotency markers (OCT4, SOX2, and NANOG), and tested accumulation of carbon particles in EBs. In addition, authors analyzed the expression patterns of typical progenitor (KRT8, KRT18, and ΔNP63) and mature keratinocyte (KRT14, KRT5, KRT16, and COL7A1) markers, and determined the expression of two psoriasis-related genes, S100A7 and S100A8.

Cheng et al. first measured hESC viability and found that hESC viability was not reduced for all five studied concentrations after 72 hr of exposure, suggesting that the carbon particles at those concentrations were not cytotoxic. The expression of OCT4, SOX2, and NANOG, three core pluripotency makers vital to hESC self-renewal, was then determined. Only SOX2 was substantially down-regulated when the concentration of carbon particles was equal to or higher than 10 ng/mL. This implicates that the proliferation and differentiation ability of hESC may be affected by ultrafine nanoparticles.

The authors then used EBs, in vitro three-dimensional cell aggregates with the ability to differentiate into the three primary germ layers (endoderm, ectoderm and mesoderm) and even all cell types, to examine the impact of ultrafine carbon nanoparticles on the hESC differentiation. The authors found visible carbon aggregation within EBs exposed to 10 μg/mL carbon particles, implicating that ultrafine carbon particles could be potentially bio-accumulated in the developing embryo. The authors further analyzed the expression level of the lineage-specific markers of endoderm,
mesoderm, neuro-ectoderm and non-neuro-ectoderm in day 9 EBs by qRT-PCR. Up-regulation of non-neuro-ectoderm genes (SMYD1, WISP1, KRT18 and DSC3) was observed, indicating that non-neuro-ectoderm lineages may be affected by carbon particles.

Cheng et al. further explored the effect of ultrafine carbon nanoparticles on the process of differentiation of hESCs to keratinocytes, one of neuro-ectoderm epidermis lineages. Using qRT-PCR, they analyzed the changes in keratinocytes’ progenitor markers (KRT8, KRT18 and ΔNP63) and mature markers (COL7A1, KRT5, KRT16 and KRT14) at day 12 and day 18. Up-regulation of early stage keratinocyte markers (KRT8, KRT18 and ΔNP63) and down-regulation of late keratinocyte markers (KRT14, KRT5, COL7A1 and KRT16) were observed when particle concentration was 10 µg/mL. Results of two protein expression (ΔNP63 and KRT14) in EBs on day 18 confirmed those of gene expression. These results suggest that the development of the human skin may be affected by exposure to carbon particles.

Since the dysregulation of KRT8, KRT18 and ΔNP63 is also involved in skin inflammation processes including psoriasis (Wang et al., 2007; Shen et al., 2005), Cheng et al. investigated the expression level of S100A9 and S100A7, two psoriasis-related genes. These two genes were upregulated gradually with the increase of concentration of ultrafine carbon nanoparticles. Pro-inflammatory chemokines (CCL20, CXCL1, CXCL8 and CXCL2) and cytokines (IL-6 and IL-1β) were also up-regulated in both day 12 and day 18 treated samples, and CXCL1 was up-regulated in day 18 treated samples. These results implied that ultrafine carbon particle exposure could lead to inflammation and psoriasis in the process of skin development.

Using a hESC-based differentiation model, Cheng et al. revealed that the exposure of ultrafine carbon particles at environmentally relevant concentrations could down-regulate the pluripotency gene SOX2, lead to potential bioaccumulation of carbon particles in EBs, and disrupt the hESC differentiation towards keratinocytes by up-regulating early stage keratinocyte markers and down-regulating late keratinocyte markers. Additionally, ultrafine carbon particles could promote inflammation and psoriasis-related genes in developing keratinocytes. These findings provide a new insight into the potential toxicity of ultrafine particles towards skin development, which is meaningful for understanding developmental health effects of ultrafine particles.

In addition to elemental carbon, ambient ultrafine particles consist of other toxic components including organic compounds (Gu et al., 2019; Ma et al., 2019; Shirmohammadi et al., 2016), trace metal oxides (Soleimani et al., 2018; Wang et al., 2017; Zhang et al., 2018), sulfates (Gupta et al., 2015; Ren et al., 2018) and nitrate ions (Gammon et al., 2016; Lan et al., 2018; Liu et al., 2020a). This study used commercial carbon nanoparticles with relatively uniform size distribution as a simple model to test the developmental toxicity of ultrafine particles. Therefore, it cannot provide the toxic effects of particle size that is also vital to toxic outcomes and other components present in ambient ultrafine particles. Future studies are needed to address these issues.

REFERENCES

injury/inflammation and inhibits cell growth in vascular endothelial cells.
