Cytotoxic Effects of $PM_{2.5}$ and its Main Metal Components on Vascular Endothelial Injury and Atherosclerosis

Abstract

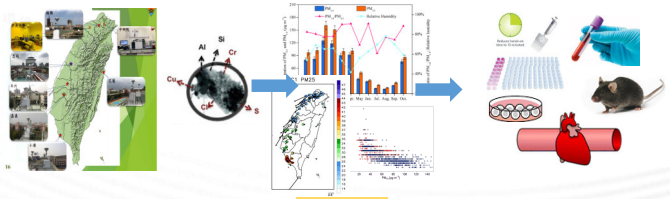
Introduction: Epidemiological evidence indicates that the death toll associated with inhaled fine particulate matter ($PM_{2.5}$) is attributed primarily to cardiovascular disorder rather than pulmonary effects. Exposure to $PM_{2.5}$ had been proved as an important cardiovascular risk factor, especially the cytotoxic effects of metal elements. However, these cytotoxic effects and safety concentrations of key metal elements for cardiovascular injury remain unclear.

Methods: According to the analysis of metal elements from $PM_{2.5}$ in Taiwan at 2017-2021, we selected the critical metal that fulfilled the following 2 criteria: (1) Time distribution: the relative content ratio is relatively high in the autumn and winter seasons of each year; (2) Spatial distribution: the concentration is different from industrialized city and agricultural city in Taiwan. Using different biochemical approaches to identify the cytotoxic and safety concentration of selected metals on the platforms of endothelial cell culture *in vitro* and atherogenic *ApoE*$^{-/-}$ mice model *in vivo*.

Results: In this work, we found that at least four metal elements including Manganese, Lead, Copper, and Tin with a higher concentration ratio in autumn and winter seasons and increasing in highly industrialized cities. Furthermore, endothelial cells exposed to these metal compounds (including chloride compounds and sulfate compounds exceeding 40mg/m^3) could directly cause free radical generation and inhibit their proliferation. Among these metal compounds, both copper chloride and copper sulfate exhibit the most cytotoxic effects. Both manganese sulfate and lead sulfate could immediately inhibit the tubular formation ability. Under the long-term cumulative effects of metal compounds with lower concentrations (~40ng/m^3), these metal mixtures could cause inflammation and death of endothelial cells. Furthermore, *ApoE*$^{-/-}$ mice were intratracheal instillation to expose $PM_{2.5}$ from 0 to 100 μg/mouse every week for 18 consecutive weeks, we found that $PM_{2.5}$ inhalation increased the serum concentration of heavy metals, especially Copper and Lead, and further cause the expression of inflammation adhesion ICAM-1 in luminal endothelium and promote the plaque formation in *ApoE*$^{-/-}$ mice.

Conclusion: Our findings shed new light on the physiological significance and safety concentration of heavy metals on $PM_{2.5}$-induced oxidative stress and apoptosis, which can contribute to endothelial dysfunction and plaque progression.

Methods



Results

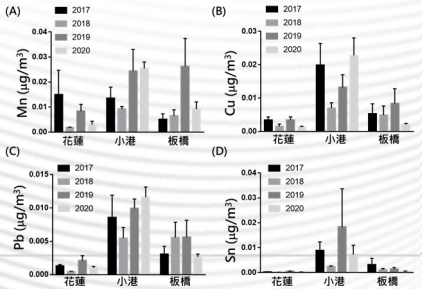


Figure 1. The average concentration (μg/m^3) of the metal elements Mn(A), Cu(B), Pb(C) and Sn(D) of $PM_{2.5}$ in three locations (Hualien/Xiaogang/Banqiao) in each winter.

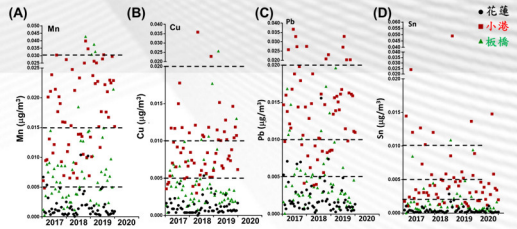


Figure 2. The average concentration of the four $PM_{2.5}$ heavy metal elements Mn(A), Cu(B), Pb(C) and Sn(D) in in the winter of 2017-2020 at three locations in Taiwan (Hualien/Xiaogang/Banqiao).

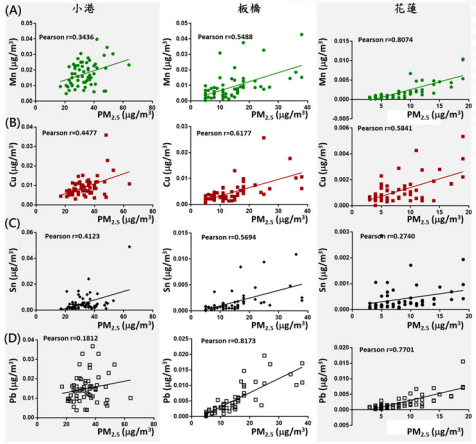


Figure 3. The correlation between $PM_{2.5}$ concentration and average concentration of heavy metal elements Mn(A), Cu(B), Sn(C) and Pb(D) in the winter of 2017-2020 at three Taiwan locations (Hualien/Xiaogang/Banqiao).

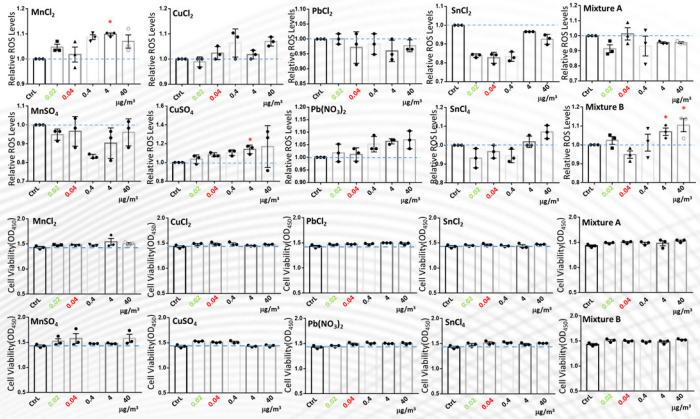


Figure 4. Low concentration of eight heavy metal compounds derived from heavy metals Mn, Cu, Pb, and Sn in $PM_{2.5}$, and their mixture A and B combination slightly increase the generation of reactive oxygen species (ROS), but no effects on the proliferation of vascular endothelial cells.

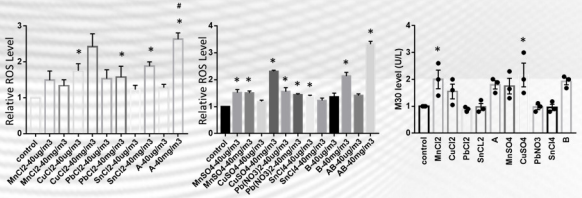


Figure 5. High concentration of eight heavy metal compounds derived from heavy metals Mn, Cu, Pb, and Sn in $PM_{2.5}$, and their mixture A and B combination induce the production of reactive oxygen species (ROS) and some compounds cause the apoptosis of vascular endothelial cells.

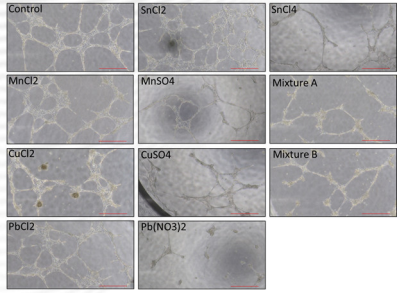


Figure 6. The effects of eight heavy metal compounds on the tubular formation of vascular endothelial cells.

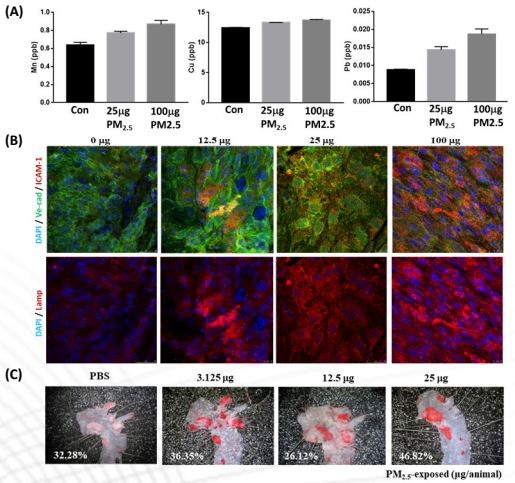


Figure 7. $PM_{2.5}$ inhalation into *ApoE*$^{-/-}$ mice increased the serum concentration of heavy metals (A), especially Copper and Lead, and further cause the expression of ICAM-1 in luminal endothelium (B) and promote the plaque formation (C).

Acknowledgement

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