

Particulate matter PM₁₀ destabilizes mitotic spindle through downregulation of SETD2 function in A549 lung cancer cells

Miguel Santibáñez-Andrade¹, Rocío Morales-Bárceñas, Raúl Quintana-Belmares, Yesennia Sánchez-Pérez¹ and Claudia M. García Cuellar¹

¹*Subdirección de Investigación Básica, Instituto Nacional de Cancerología, San Fernando No. 22, Tlalpan, CP 14080, Ciudad de México, Mexico.*

E-mail: msantrade@ciencias.unam.mx

Background: Air pollution represents a global problem, impacting negatively in human health. This effect is seen predominantly in major cities, where intense traffic or industry activities are common. Particulate matter of 10 micrometers or less in diameter (PM₁₀) is considered as an agent related to pulmonary diseases, including lung cancer. Chromosomal segregation is controlled by chromosome-microtubule interactions, where SETD2 plays an important role in microtubule stability through binding to alfa tubulin (α -TUB) and promoting microtubule polymerization. Also, spindle assembly checkpoint (SAC) orchestrate a mitosis-delay signal through proteins such as BUBR1, AURORA B and SURVIVIN, to ensure genomic instability. Alterations in microtubule stability as well as in SAC cause aneuploidy, a cancer hallmark. Although PM₁₀ are associated to the generation of chromosomal alterations, the impact in chromosomal segregation mechanisms still being an opportunity area. The **aim** of this study is to evaluate the effect of PM₁₀ in the expression of SETD2, as well as the effect in the expression of SAC and mitotic genes in the control of chromosomal segregation/mitosis, using the A549 cell line (lung cancer). **Materials and methods:** A549 cells were exposed to PM₁₀ (10 $\mu\text{g}/\text{cm}^2$) for 24 h to evaluate protein levels of SETD2, α -TUB, CICLIN B, BUBR1, AURORA B and SURVIVIN by Western Blot. As controls of SAC activation, cells were exposed to taxol (100nM) and nocodazole (0.2 $\mu\text{g}/\text{mL}$). **Results:** PM₁₀ decreases the levels of SETD2 (36.6%), α -TUB (27.3%) and BUBR1 (23.3%), and increases the levels of AURORA B (22.6%) and SURVIVIN (83.6%) in A549 cells, compared with non-treated cells ($p < 0.05$). PM₁₀ also caused a decrease in mitotic index (37.3/300 cells) when compared with control group (49/300 cells). Co-localization of SETD2/ α -TUB was lower in PM₁₀-treated cells in comparison with non-treated cells (43.6/300 cells vs 82.3/300 cells, respectively). Finally, micronuclei (MN) frequency was higher in PM₁₀-treated cells in contrast with non-treated cells (36.3/500 cells vs 13.3/500 cells, respectively), being the presence of whole chromosomes more common in PM₁₀-treated MN than in non-treated MN (24.6/500 cells vs 9/500 cells, respectively). **Conclusion:** Particulate matter PM₁₀ induce missegregation and aneuploidy, through a downregulation of SETD2 and SAC components, probably inducing survival and predisposing to the generation of aneuploid transformed cells.