MULTIWALLED CARBON NANOTUBES, A PHYSICAL BARRIER TO CELL DIVISION

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Fibrous particles are extensively employed in a wide variety of industries, including construction, textile or medical industries due to their unique physical properties. However, at the nanoscale, these fibers have been associated with acute toxicological effects [1], raising significant health concerns. Asbestos is the best-known carcinogenic fiber, since it has been demonstrated that exposure to asbestos increases the risk of development of mesotheliomas and lung carcinomas [2]. The pathogenicity of fibers like asbestos has been attributed to specific physical characteristics, particularly their thinness, length and biopersistence, factors that enhance their ability to persist in biological tissues and cause harmful effects. The fiber pathogenicity paradigm recognizes fibers' geometry as their most important toxicological characteristic [3].

In the last decades, fiber toxicology research has increased, and several types of synthetic and natural fibers have been classified as carcinogenic or probably carcinogenic for humans according to IARC. Among these fibers, multiwalled carbon nanotubes (MWCNTs) have focused significant attention due to their widespread application in industry [4]. However, their fiber-like structure and their biopersistence in lung tissues raise concerns regarding their potential to induce adverse health effects, particularly in an occupational context. Several epidemiological and animal studies suggest that MWCNTs may induce mesothelioma in a manner similar to crocidolite asbestos [5]. However, the molecular mechanisms underlying this process remain a subject of debate.

In this study, we focused on the molecular mechanisms by which MWCNTs promote cell transformation *in vitro*. We employed a combination of cellular biology techniques, along with flow cytometry and microscopy to investigate the effects of MWCNTs exposure during cell division. Our results demonstrate that exposure to these fibers induces cellular phenotypes indicative of chromosome instability (CIN), including an increase in the frequency of binucleated cells and micronuclei after 48 and 72 hours of exposure. Additionally, we observed abnormal mitotic structures in MWCNTs-treated cells. Specifically, we observed lagging chromosomes upon cell division and a significant increase of aberrant mitotic spindle morphologies. Finally, flow cytometry analysis of DNA content, combined with Cdt1 protein detection, revealed an accumulation of tetraploid cells in MWCNTs-treated samples.

Taken together, our findings establish a model in which MWCNTs interfere with the cell division process by acting as physical barriers for the mitotic and cytokinesis machinery. This phenomenon leads to errors in chromosome segregation due to interference with mitotic spindle microtubules and to tetraploidization by disrupting the contractile ring resolution. These abnormal cell divisions trigger polyploid cell generation, which in turn exacerbates genomic instability in subsequent divisions, thereby promoting cancer progression.

References

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Figures

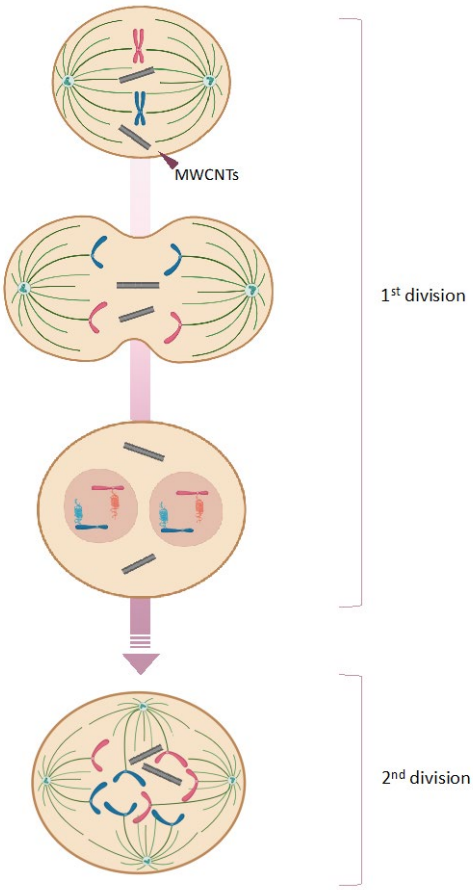

Figure 1. Proposed model explaining the mechanism by which MWCNTs interfere in cell division.