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Long-fibre Carbon Nanotubes induce Pleural Mesothelioma *via* silencing and/or loss of key Tumour Suppressor Genes

Abstract *

Exposure to asbestos fibres causes pathological changes in the pleural cavity including malignant mesothelioma. Length-dependent retention of asbestos fibres in the pleural cavity is crucial for disease development. Chronic inflammation plays a key role in carcinogenesis and epigenetic events, rather than driver mutations, are considered to be major causative factors. Manufactured carbon nanotubes (CNT) are similar to asbestos in terms of their high aspect-ratio and thus may pose an asbestos-like inhalation hazard, however the molecular mechanisms underlying their carcinogenic potential have not been fully explored. Using a model of direct injection into the pleural cavity, we compared the molecular changes which occur at the mesothelium after exposure to short/long asbestos fibres and short/long CNT over 20 months.

We show a common pro-oncogenic activity of long CNT and long asbestos throughout disease progression. Key molecular events encompass changes in gene expression/signaling pathway activation, oxidative DNA damage, increased mitosis and proliferation. Instillation of long CNT into the pleural cavity of mice induces chronic inflammation and pro-oncogenic changes leading to development of mesothelioma, with deletion of *p19/Arf* and silencing of *p16/Ink4a* and *NF2*. Epigenetic changes induced by pathogenic fibres occur at the pre-neoplastic stage of disease and thus may play a role in progression of pleural inflammatory lesions to malignant mesothelioma.

These data demonstrate that exposure to long CNT induces development of pleural mesothelioma, replicating the pathogenesis of human disease and highlighting commonality in the hazard mechanism of long pathogenic fibres at the molecular level. Epigenetic changes precede malignant transformation of both asbestos- and CNT-induced inflammatory lesions. Crucially, our findings reinforce concerns that long CNT may pose an asbestos-like hazard, leading to malignant mesothelioma.

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