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Impact of an integrated in vivo-in vitro approach for evaluating the hazardous pulmonary effects of nanomaterials and the underlying mechanisms

With the promising benefit of nanotechnology and the rapid rise of engineered nanomaterial production, potential human exposure to nano-scaled respirable particles has become a major concern. Animal exposure studies have shown that pulmonary exposure to nanoparticles, such as carbon nanotubes (CNTs) and nano-scaled cerium oxide (nCeO2), can deposit the particles deep in lung tissues and cause adverse health effects. Unique physicochemical properties of the nanoparticles greatly influence their adverse effects. With the identification of the specifically affected lung cells at the site of particle accumulation, we have developed multiple in vitro models to assess the cytotoxic, fibrogenic, and carcinogenic potential of nanomaterials using relevant human cell culture models. All in vitro doses were physiologically relevant and based on in vivo doses that induced significant pulmonary disorders in animal models. Acute (days), sub-chronic (weeks), and long-term (several months) exposures to CNTs, nCeO2, and nFe2O3 were shown to cause dose- and time-dependent cytotoxic (cell damage) and fibrogenic (collagen production) effects, as well as neoplastic and/or malignant transformation (anchorage-independent growth, apoptosis evasion, increased migration, invasion, angiogenesis, and tumor formation), consistent with the in vivo animal data. In vitro assessment tools further allow detailed mechanistic investigations of key signaling pathways and mediators involved in the pathological processes (e.g. p53, transforming growth factors, and matrix metalloproteinases), which may serve as predictive biomarkers for the in vivo responses. Impact of the integrated in vivo-in vitro approach also includes that it supports the utility of the in vitro models as rapid screening tools for risk assessment of nanomaterial-induced pathologies.

Primary author: WANG, Liying (National Institute for Occupational Safety and Health, Morgantown, WV, USA)

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