**Silica nanoparticles induces cell death in lung epithelial cells through mitochondria and endoplasmic reticulum pathways.**

Tien-Hui Lu[1,2], Ling-Mei Tsai[1], Dong-Zong Hung[2], Cheng-Chieh Yen[3], Chin-Chuan Su[4], Yi-Chang Su[5], Chun-Fa Huang[5], Shing-Hwa Liu[8], Ya-Wen Chen[1,2]

[1]Graduate Institute of Basic Medical Science, [2]Department of Physiology, China Medical University, Taichung, Taiwan

[2]Toxicology Center, China Medical University Hospital, Taichung, Taiwan

[3]Department of Occupational Safety and Health, Chung Shan Medical University, Taichung, Taiwan

[4]Department of Otorhinolaryngology, Head and Neck Surgery, Changhua Christian Hospital, Changhua, Taiwan

[5]School of Chinese Medicine, China Medical University, Taichung, Taiwan

[6]Toxicology Center, China Medical University Hospital, Taichung, Taiwan

**Abstract:**

Silica nanoparticles ($SiO_2$-NPs) are widely used in nanotechnology industry and applications in various products. Previous studies have indicated that nanoparticles can induce oxidative stress damage causing cell death. Alveolar type II epithelial cells are known to be vulnerable to oxidative stress. However, the toxic effect of $SiO_2$-NPs on alveolar type II epithelial cell damage remains unclear. In this study, we investigate the effect and possible mechanisms of $SiO_2$-NPs on rat type II epithelial cell line (L2)

for 24–48 h. The results showed a decreased in cell viability and an increased in annexin-V binding in a time- and dose-dependent manner. Meanwhile, after $SiO_2$-NPs exposure, the amount of silicon uptake and ROS production was correlated with the concentration of $SiO_2$-NPs at 24h, and the malondialdehyde (MDA) level increased in a dose-dependent manner at 48h. $SiO_2$-NPs also caused mitochondrial-dependent apoptotic signals, including the increasing of caspase-3 activity, disruption of the mitochondrial membrane potential, up-regulation of Bax and down-regulaton of Bcl-2 protein expression, activations of caspase cascades and cleave poly(ADP-Ribose) polymerase (PARP). Moreover, treatment of L2 cells with $SiO_2$-NPs resulted in endoplasmic reticulum (ER) stress, such as activating the protein expression of C/EBP homologous protein (CHOP), X-box binding protein 1(XBP-1), caspase-12, and decreasing the glucose-regulated protein 78/94 (GRP-78/-94) protein expression. These results suggest that $SiO_2$-NPs trigger an oxidative stress, and induce alveolar epithelial cells apoptosis through mitochondria and endoplasmic reticulum pathways.

*Keyword: Silica nanoparticle; Lung epithelial cells; Apoptosis; ROS; Mitochondria; ER-stress*