# Silica nanoparticles-induced necrosis and exocytosis of von Willebrand factor in primary human endothelial cells is surface area-dependent [Abstract]

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## Silica nanoparticles-induced necrosis and exocytosis of von Willebrand factor in primary human endothelial cells is surface area-dependent

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Next to a widely distribution in our environment nanoparticles (NP), including silicon dioxide ($SiO_2$) NP are manufactured on industrial scale and are increasingly used in a broad spectrum of biomedical applications, such as cancer therapy, medical diagnostics and drug delivery. However, despite promising clinical approaches of nanotechnology, potential exposure risks to humans have to be considered. Although the intake of ultrafine particles occurs through the gastro-intestinal tract and the skin, inhalation is the most important uptake route for translocation to the systemic circulation. In this context, several toxicological studies have shown an interaction of NP with endothelial cells (ECs) linking air pollution with nanoscaled particles to increased cardiovascular disease. Although NP-induced dysfunction of ECs is contigent on several mechanisms, involving inflammatory cytokines and the activation of coagulation, the molecular pathways are poorly understood.
In order to gain a closer mechanistic insight into NP-EC interactions, we evaluated the impact of well characterized $SiO_2$ NP with defined size, surface modifications and shape on primary human umbilical vein endothelial cells (HUVEC). Cytotoxicity assays using the tetrazolium reduction (MTT) and lactate dehydrogenase (LDH) release revealed that silica NP-induced toxicity depends on the size and the dose of applied NP. Rather we showed that it is the surface area of $SiO_2$ NP that is the crucial parameter of toxicity and not its volume, mass or concentration. Furthermore, FACS analysis and assessment of caspase-3/7 activity excluded apoptosis and correlated cytotoxicity with necrotic processes. To determine whether NP induce procoagulatory cascades in HUVEC, we next analyzed the release of von Willebrand factor (VWF). Immunofluorescence studies showed that stimulation with fluorescent-labeled NP led to endothelial Weibel-Palade Body (WPB) exocytosis and the formation of VWF ultralarge fibers (ULVWF). Interestingly, high resolution microscopy techniques demonstrated that cellular uptake and perinuclear localization of $SiO_2$ NP not only affect viability and the release of coagulatory factors but also cell proliferation and migration.