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Inflammasome Activation by Nanomaterials

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Introduction

Nanomaterials (NMs) may interfere with the immune system. One of the suggested pathways is via inflammasome activation. The aim of this in vitro study was to determine the effect of a series of nanomaterials on inflammasome activation.

Conclusions

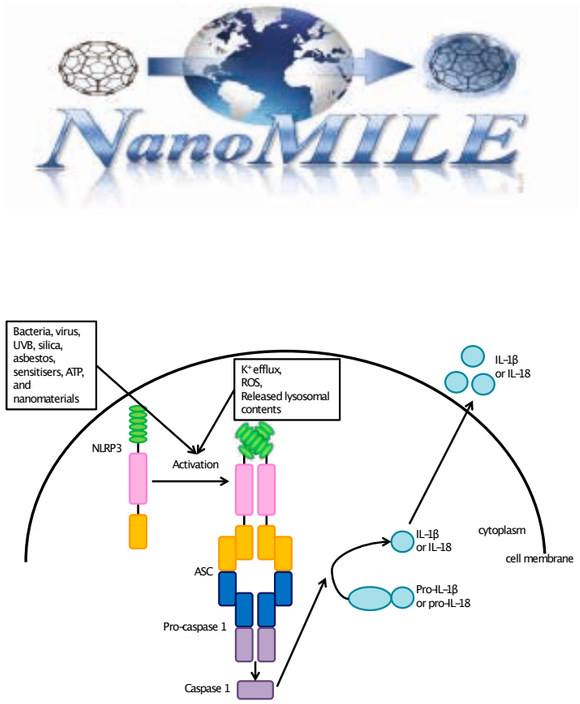
- CeO_2 and SiO_2 NMs caused dose-related, NLRP3 and ASC dependent increase IL-β production
  →Inflammasome activation
- TiO_2 and ZnO NMs did not affect IL-β induction
  →Dependent on chemical composition
- Micro-sized CeO_2 particles did not affect IL-β induction
  →Dependent on size
- SiO_2 NMs increased IL-1β production accompanied by pronounced NLRP3- and ASC-dependent decrease in viability
  →Pyroptosis (programmed and inflammatory cell death induced by caspase-1)

What is an inflammasome?

Inflammasomes are intracellular protein complexes that upon sensing danger signals can initiate inflammatory responses, including the production of IL-1β.
They consist of:

- NOD-like receptor (nucleotide-binding oligomerization domain-like receptor, of which NLRP3 is the most fully characterized)
- ASC (apoptosis-associated speck-like protein)
- Pro-caspase 1

When activated, inflammasomes cleave pro-caspase-1, resulting in caspase-1. This enzyme can in turn cleave pro-interleukin-1 beta (IL-1β) or pro-interleukin-18 (IL-18) into their mature (active) forms (Figure 1).



Figuur 1: Mechanism of NLRP3 inflammasome complex formation (Modified from: Tschopp and Schroder, 2010. Nature Reviews Immunology 10, 210-215 and Bryant and Fitzgerald, 2009. Trends in Cell Biology 19(9), 455-464).

Methods

In this study THP-1 derived macrophages are exposed to several NMs. THP-1 cells are human monocytes, which are known for excellent inflammasome activation. Normal as well as NLRP3- or ASC-deficient THP-1 cells were differentiated into a macrophage phenotype by exposure to 100 ng/ml phorbol 12-myristate 13-acetate (PMA) for 3 hours. After exposure for 48 hours to 100µl NM dispersion (concentration ranges from 4 µg/ml to 128 µg/ml), the cell viability (with WST-1) and IL-1β production (with ELISA) were measured.

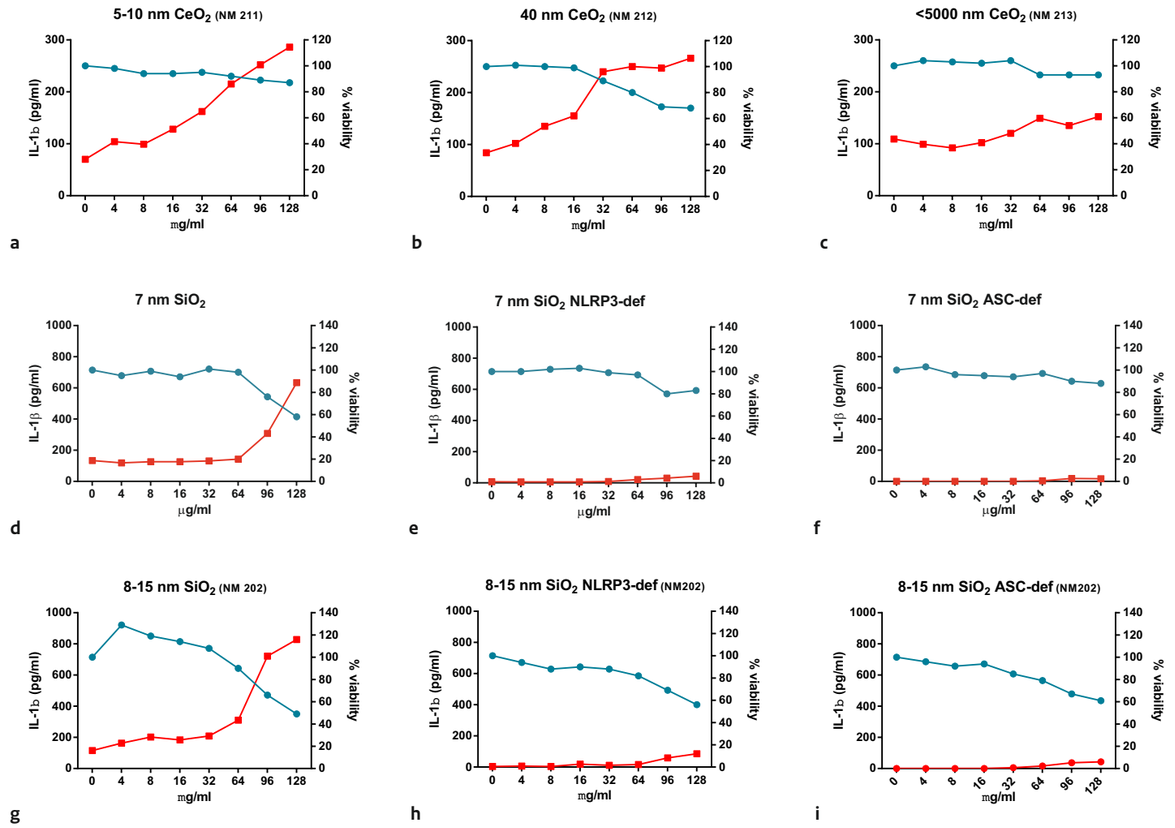


Figure 2: IL-1β concentration (red lines) and viability (blue lines) of normal, NLPR-deficient and ASC-deficient THP-1 cells after 48 hours of exposure to CeO_2 and SiO_2 NMs.

Results

- CeO2 NMs caused a dose-related increase IL-β production (red lines) in normal THP-1 derived macrophages (Figure 2a and b)
  - Micro-sized CeO_2 particles did not affect the IL-β production (Figure 2c)
- SiO_2 NMs caused a dose-related increase IL-β production (red lines) accompanied by decreased cell viability (blue lines) in normal THP-1 derived macrophages (Figure 2d and g)
  - These effects were not observed in NLRP3- and ASC-deficient cells (Figure 2e, f, h and i)
- TiO_2 and ZnO NMs did not affect the IL-β production in normal cells (data not shown)

Future studies

Future studies will include measurement of IL-18 and testing series of NMs that differ in one single characteristic, such as size, surface charge or redox potential. In addition, effects of ROS inhibition by NAC, caspase-1 inhibition by Z-WEHD-FMK, and ATP inhibition by apyrase on IL-1β production will be studied.

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