Title *

Development of an adverse outcome pathway based on toxicogenomic data for ENM-induced risk of developing atherosclerotic plaques

Abstract *

Adverse lung effects following pulmonary exposure to engineered nanomaterials (ENMs) are well documented in rodents. With the aim of understanding the molecular changes accountable for these effects, we investigated the global transcriptional changes in the lung of mice pulmonary exposed to multi-walled carbon nanotubes, carbon black, TiO_2 or graphene by intratracheal instillation. Besides aiding the identification of ENM-specific changes, this also enabled a cross-evaluation of processes and changes common for all investigated ENM exposures.

Despite the large variances in physicochemical properties of the ENMs tested, they all induced a strong and persistent pulmonary acute phase response. The most differentially regulated gene across all exposure types was the acute phase protein serum amyloid A isoform 3 (*Saa3*), with the other isoforms (*Saa1* and *Saa2*) also being strongly induced. We furthermore established strong correlations between pulmonary *Saa3* mRNA levels, plasma SAA3 protein levels and pulmonary neutrophil influx after exposure. This indicates a significant impact of the pulmonary derived *Saa* expression on plasma protein levels.

Increased plasma levels of SAA protein are a predictor of cardiovascular disease in epidemiological studies. A proposed mechanism is through a replacement of ApoA-1 with SAA on the HDL lipoproteins, which impairs HDL's ability to mediate cholesterol efflux from macrophages. This results in reduced reverse cholesterol transport, sequestering of peripheral cholesterol, and transport of cholesterol from HDL to macrophages, thereby facilitating the transformation of macrophages into foam cells.

We have developed an AOP illustrating this hypothesis. This AOP was accepted into the OECD AOP program in June 2017.

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