Involvement of *Mth1* in the toxic and carcinogenic effects of cobalt and zinc oxide nanoparticles

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We have previously shown that short-term exposure to low doses (between 0.05 and 1 µg/mL) of cobalt and zinc oxide nanoparticles (CoNPs, ZnONPs) are able to induce reactive oxygen species (ROS) and oxidative DNA damage (ODD) in mouse embryonic fibroblast cells (MEFs). This ODD was found also to have a prominent role in the transforming effects of the NPs found under chronic exposure scenarios, and characterized by morphological cell changes, significant increases in the secretion of metalloproteinases (MMPs) and anchorage-independent cell growth ability; all cancer-like phenotypic hallmarks.

The MutT homolog 1 (Mth1), is a pyrophosphorylase that effectively sanitizes oxidized dNTP pools to prevent incorporation of damaged bases into DNA. In this work, we sought to assess the role of *Mth1* in the toxic and carcinogenic effects of chronic Co and ZnONPs exposure. Thus, *Mth1* knock-down was carried out in MEF cells chronically exposed to the NPs for 12 weeks by using MISSION® constructs carrying shRNA sequences targeting mouse *Mth1*. Knock-down cells were then exposed to the NPs for 2 more weeks, and cytotoxic and carcinogenic end-points were evaluated and compared to the empty vector controls.

Results demonstrate a *Mth1* expression knock down of about 90% efficiency, and Mth1 was found to be involved in the toxic and carcinogenic effects of Co and ZnONPs, as the absence of expression is associated with a phenotype with higher sensitivity to both NPs and oxidant agents, and with a reduced aggressiveness of the transformed phenotype.

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