# Long-term exposures to low doses of cobalt nanoparticles induce cell-transformation enhanced by oxidative damage

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So far, *in vitro* studies of nanoparticles (NPs) on the toxic, genotoxic and carcinogenic potential mainly focused on acute-exposure and high-dose conditions. This makes difficult to extrapolate to human beings in real scenarios. This means that there is a serious lack of information on the genotoxic/carcinogenic potential of NPs at low doses and prolonged exposures.

To overcome this point, we have evaluated the cell-transforming ability of cobalt nanoparticles (CoNPs) after long-term exposures (12 weeks) to sub-toxic doses (0.05 and 0.1 μg/mL). To get further information on whether CoNPs-induced oxidative DNA damage is relevant for CoNPs carcinogenesis, the cell lines selected for the study were the *wild-type* mouse embryonic fibroblast (MEF *Ogg1*$^{+/+}$) and its isogenic *Ogg1 knockout* partner (MEF *Ogg1*$^{-/-}$), unable to properly eliminate the 8-OH-dG lesions from DNA. Differences between cell lines offer relevant information on the role of oxidative damage on the studied biomarker.

Our initial short-term exposure experiments demonstrate that low doses of CoNPs are able to induce reactive oxygen species (ROS) and that MEF *Ogg1*$^{-/-}$ cells are more sensitive to CoNPs-induced acute toxicity and oxidative DNA damage. On the other hand, long-term exposures of MEF cells to sub-toxic doses of CoNPs were able to induce cell transformation, as indicated by the observed morphological cell changes, significant increases in the secretion of metalloproteinases (MMPs) and anchorage-independent cell growth ability, all cancer-like phenotypic hallmarks. Interestingly, such changes were significantly dependent on the cell line used, the *Ogg1*$^{-/-}$ cells being particularly sensitive.

Altogether, the data presented here confirms the potential carcinogenic risk of CoNPs and points out the relevance of ROS and *Ogg1* genetic background on CoNPs-associated effects.