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Are iron oxide nanoparticles neurotoxic?

Among the different types of nanomaterials, iron oxide nanoparticles (ION) awaken a particular interest due to their unique properties, including superparamagnetism and high biocompatibility. These features make them very suitable for a broad variety of uses, mostly in biomedical applications, namely magnetic resonance imaging, targeted drug delivery, tumor location and magnetic hyperthermia, among others. In particular, over the last decade, ION have been used for diagnosis and treatment of several central nervous system (CNS) diseases, such as Alzheimer´s, Parkinson´s, multiple sclerosis, and primary brain tumors. This is mainly because the reduction in particle size gives ION the ability to cross the blood-brain barrier and gain access to the brain.

Recent investigations indicated that ION could cause a certain degree of neurotoxicity, but knowledge on the possible risk of exposure to ION for human brain cells is very limited and conflicting so far. In fact, many current studies on toxicity assessment are far from reaching a conclusion and providing guidance for their safe use, due to the lack of comprehensive methodological approaches to address and better understand the potential risk they may pose. Besides, ION surface can be coated to improve their properties and facilitate functionalization, but coating may also affect toxicity.

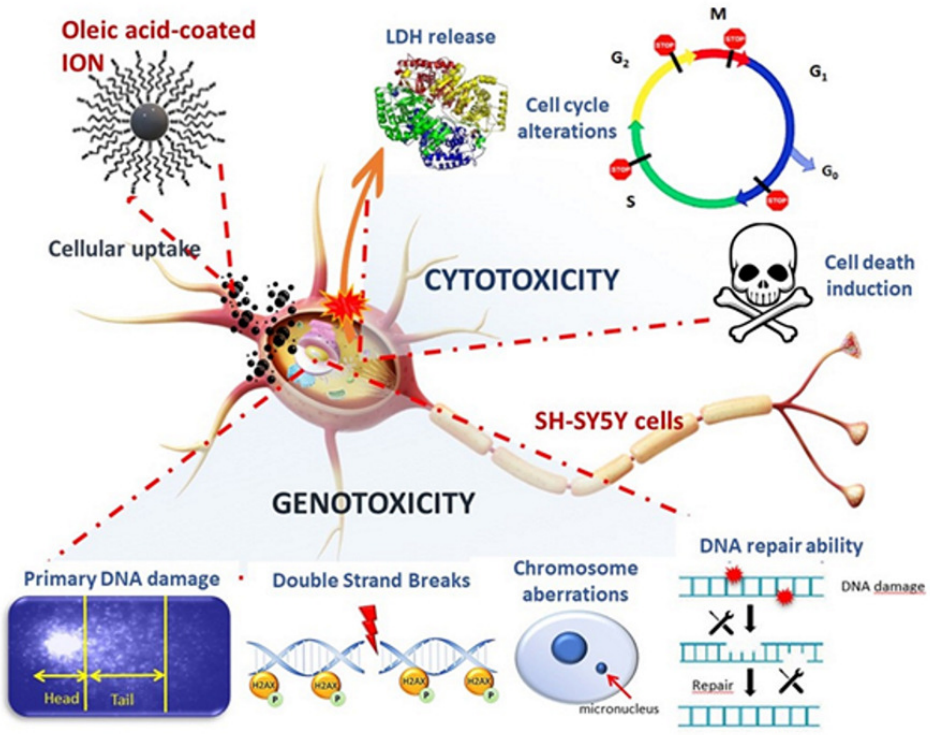

Fig. 1. Overview of the study experimental design.

Hence, the aim of this work was to evaluate the possible effects of oleic acid-coated ION (O-ION) on human neuronal cells (SH-SY5Y), in order to obtain an overall view of the potential risk, mainly at molecular and cellular levels, associated with their exposure. With this main purpose, a complete set of toxicological assays was carried out for assessing O-ION cytotoxicity (effects on cell viability, cell death and cell cycle maintaining) and genotoxicity (direct or indirect effects on the genetic material), considering also alterations in DNA repair competence and iron ion release from the nanoparticle surface. All experiments were conducted in complete cell culture medium and in serum-free medium.

Results obtained showed that O-ION exhibit a *moderate cytotoxicity* related to cell membrane impairment, cell cycle disruption and cell death induction, especially marked in serum-free medium. On the contrary, iron ion release was only observed in complete medium, indicating that cytotoxicity observed was not related to the presence of iron ions in the medium. However, O-ION *genotoxic effects were limited* to the induction of primary DNA damage, not related to double strand breaks (the most serious form of DNA damage in eukaryotic cells) and easily repairable, and this damage did not become fixed in cells in most conditions. Alterations in repair ability were observed when cells where treated with O-ION before or during a challenge with hydrogen peroxide, but not during the repair period.

This work contributes to increase the knowledge about the impact of ION on human health in general, and specifically on nervous system cells. Due to the ION promising features and great potential for the diagnosis and treatment of various CNS disorders, it is highly likely that their use will continue growing in a near future. Thus, further research is needed to address in-depth the possible mechanisms involved in ION toxicity, and to determine the conditions for their safe use in diagnostics and clinics.

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