The mechanism of the toxicity of lanthanides nanoparticles to selected immune cell subsets

In recent years, there has been a growing interest in the potential application of lanthanide compounds. Lanthanides occur in everyday objects and there are also present in environment. Multimodality of lanthanide nanoparticles i.e. upconversion nanoparticles makes them promising diagnostic and therapeutic agents. Therefore, for biomedical applications the lack of their toxicity is essential. Thus, the main aim of this study is to investigate the mechanism of lanthanide doped nanocrystals $NaGdF_4:Yb^{3+}/Er^{3+}$ toxicity. Many research groups tend to pay more attention to toxicity investigation for cancer cells than normal cells.

In this work, the investigation of lanthanide nanomaterials toxicity focused on immune system cells. Additionally, the investigation of toxicity was expanded by functionalized nanoparticles to check whether the nanoparticles surface protection reduce cell death.

In this study the toxicity of bare $NaGdF_4:Yb^{3+}/Er^{3+}$ nanocrystals was examined in 8 normal and 4 tumor cell lines. The most sensitive cells were mouse macrophages J774A.1 and RAW264.7. Therefore, events leading to death caused by lanthanide nanoparticles were investigated in mice macrophages. $NaGdF_4:Yb^{3+}/Er^{3+}$ nanoparticles disturbed mitochondrial homeostats, perturbed autophagy and led to mitochondrial dependent apoptosis. It has been proved that the presence of nanoparticles is not sufficient to cause cell death. The inhibition of cell acidification by lysosomal inhibitors ammonium chloride and Bafilomycin A1 resulted in apoptosis reduction. Furthermore, inhibitors reduced mitochondrial damage and peroxide induction. Obtained results proved that lysosomal acidification is a crucial factor which determinate the toxicity of $NaGdF_4:Yb^{3+}/Er^{3+}$nanoparticles. Nanoparticles lysosomal localization may not only interfere with their function but also lead to permeabilization and release of lysosomal content to the cytoplasm.

The cytotoxicity of bare $NaGdF_4:Yb^{3+}/Er^{3+}$ nanoparticles was reduced by surface functionalization with SiO_2, $SiO\text{-}NH_2$ and PEG2000 groups. The decrease in toxicity is the result of weak nanoparticles interaction with cells or the delayed degradation of nanoparticles in lysosomal environment.