Radiosensitizing Effect of Iron Oxide Nanoparticles: Towards Improved Radiotherapy Outcomes

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Rationale and Objectives

Nowadays, radiation therapy (RT) is one of the core components in the treatment of cancerous tumors. Although its utilization rate is generally above 50 %, RT remains limited by the dose administered to healthy tissues surrounding the affected area. In this context, it has been demonstrated that nanoparticles can act as "radiosensitizers" capable of broadening the radiotherapeutic window of RT[1]. In recent years, radiosensitization by iron oxide nanoparticles (IONPs) has emerged as a promising approach since these nanoparticles have already reached clinical settings as contrast agents for Magnetic Resonance Imaging (MRI). Our team recently evidenced the radiosensitizing effect of two IONPs formulations, and confirmed the crucial role of biochemical mechanisms and key antioxidant enzymes in the global radiosensitization mechanism[2]. Our current efforts focus on understanding the physico-chemical parameters affecting the efficacy of IONPs as potent theranostic agents for MRI-assisted cancer treatment by RT.

Methods and Materials

We synthesized iron oxide nanoparticles (IONPs) using a polyol method adapted with our previously developed continuous flow process[3]. IONPs obtained using this method are readily dispersible in water and are subsequently formulated as stable dispersions by means of organosilane treatment and PEGylation. Details concerning these surface modification steps are available elsewhere[4]. The impact of our IONPs formulations and commercial formulations on the inhibition of the thioredoxin reductase enzyme (TrxR) was evaluated in A549 cells (50 µg Fe/mL) over varying incubation times[2]. Cells were irradiated with 225kV X-rays at a dose rate of 2 Gy/min. Uptake assays were performed on cells preincubated with molecular inhibitor or transfected cells, then cells were treated with fluorescent IONPs (50 µg Fe/mL).

Results

Our continuous flow setup enabled the preparation of IONPs with various structural features (various sizes). Carboxylated IONPs and PEGylated IONPs were prepared through an easy surface modification step and compared with commercially available IONPs formulations (Endorem® and Sinerem®). Our results confirm the link between the radiosensitizing effect of IONPs and the inhibition of TrxR. Notably, the newly developed formulations exhibited superior radiosensitizing properties compared to the commercial ones. Radiosensitization caused by our IONPs was supported by uptake assays, validating the global action mechanism responsible for the amplification of cancer cells sensitivity to RT.

Conclusions

Based on their numerous assets (biocompatibility and superparamagnetic properties), IONPs constitute promising candidates as radiosensitizing agents for image-assisted (MR or Magnetic Particle Imaging) treatment of cancer using RT.

References

(1) Shen, H.; Huang, H.; Jiang, Z. Nanoparticle-Based Radiosensitization Strategies for Improving Radiation Therapy. *Front. Pharmacol.* **2023**, *14*, 1145551.

(2) Ternad, I.; Penninckx, S.; Lecomte, V.; Vangijzegem, T.; Conrard, L.; Lucas, S.; Heuskin, A.-C.; Michiels, C.; Muller, R. N.; Stanicki, D.; Laurent, S. Advances in the Mechanistic Understanding of Iron Oxide Nanoparticles' Radiosensitizing Properties. *Nanomaterials* **2023**, *13* (1), 201.

(3) Vangijzegem, T.; Stanicki, D.; Panepinto, A.; Socoliuc, V.; Vekas, L.; Muller, R. N.; Laurent, S. Influence of Experimental Parameters of a Continuous Flow Process on the Properties of Very Small Iron Oxide Nanoparticles (VSION) Designed for T1-Weighted Magnetic Resonance Imaging (MRI). *Nanomaterials* **2020**, *10* (4), 757.

(4) Stanicki, D.; Larbanoix, L.; Boutry, S.; Vangijzegem, T.; Ternad, I.; Garifo, S.; Muller, R. N.; Laurent, S. Impact of the Chain Length on the Biodistribution Profiles of PEGylated Iron Oxide Nanoparticles: A Multimodal Imaging Study. *J. Mater. Chem. B* **2021**, *9* (25), 5055–5068.

Financial Interest Statement

The authors declare no competing interests.