INDUCTION OF LYOSOMAL MEMBRANE PERMEABILIZATION BY RADIOTHERAPY-ACTIVATED NBTXR3 NANO Particles

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Background For many decades, radiotherapy (RT) has been a widely used approach for treating cancer worldwide. Currently, approximately 50% of cancer patients undergo radiotherapy as part of their treatment. However, the effectiveness of RT is limited due to the harm it can cause to healthy tissues. To overcome this limitation, we have developed nanoparticles of functionalized hafnium oxide (NBTXR3) with a high electron density. These nanoparticles greatly enhance the interaction with ionizing radiation, resulting in a higher deposition of energy within cells. The clinical advantage of combining NBTXR3 with radiotherapy (NBTXR3+RT) over radiotherapy alone has been established in patients with locally advanced Soft Tissue Sarcoma through the Act.in.Sarc study (NCT02379845), a randomized controlled phase II/III trial. Additionally, our preclinical research has demonstrated that NBTXR3+RT not only destroys tumor cells but also triggers an immune response against the tumor, resulting in a substantial abscopal effect associated with an increase in CD8 infiltrates within the tumors. Nevertheless, we currently have relatively few elements on the early cellular events that could trigger or explain the performances of NBTXR3+RT to modulate antitumor immune response.

Methods We carried out a series of in vitro studies, including immuno-fluorescence, flow cytometry, confocal microscopy, and RNAseq experiments on different cancer models.

Results We have observed that NBTXR3 nanoparticles, once taken up by cells through endocytosis, predominantly merge with lysosomes. After subjecting the cells to radiation therapy (RT), we observed a significant disruption of the lysosomal membrane (known as lysosomal membrane permeabilization or LMP) in the cells treated with NBTXR3+RT, whereas no such LMP was observed in cells treated with RT alone. Furthermore, in addition to the LMP, we detected a significant elevation in lipid peroxidation, which is a characteristic biomarker of ferroptosis.

Conclusions Recent studies show that ferroptosis has the direct capacity to kill cancer cells and has a potential antitumor effect. The results presented here suggest that the lysosomal membrane permeabilization (LMP) induced by NBTXR3+RT may promote lipid peroxidation and, consequently, ferroptosis. These findings highlight the distinctive nature of the biological responses triggered by NBTXR3+RT and could potentially explain, at least in part, the immunomodulatory capabilities of these nanoparticles.

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