1090 ENHANCING DNA DAMAGE AND MICRONUCLEI PRODUCTION IN HUMAN CANCER CELL LINES THROUGH RADIOTHERAPY-ACTIVATED NBTXR3 NANOPARTICLES

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Background Radiotherapy-induced DNA damages play a key role in the induction of the antitumor immune response, through cell death and cGAS-STING pathway activation. The radioenhancer NBTXR3, composed of hafnium oxide nanoparticles, is designed for intratumor injection in patients. Upon exposure to radiotherapy (RT), NBTXR3 enhance radiation dose delivery within cancer cells. Phase II/III trial findings in locally advanced Soft Tissue Sarcoma patients demonstrated the superiority and clinical advantages of RT-activated NBTXR3 over RT alone, exhibiting an excellent safety profile. Numerous preclinical investigations have confirmed the immunomodulatory properties of NBTXR3, including increased CD8 infiltrates in tumors, restoration of anti-PD1 sensitivity, and induction of abscopal effect, among others. Nonetheless, few data are currently available to evaluate the impact of NBTXR3+RT on DNA damages. Here, we investigated the impact of RT-activated NBTXR3 (NBTXR3+RT) on DNA double-strand breaks (DSBs) and micronuclei (MN) production in human cancer cell lines.

Methods The impact of NBTXR3 activated by radiotherapy on DNA damages production in cancer cells was evaluated by yH2AX assay and micronuclei formation in different human cell lines. Six-wells plates containing cells were treated (or not) with NBTXR3. The following day, cells were irradiated (or not) by a single dose of X-ray. For DSBs analysis, cells were collected 1h and 24h after RT and yH2AX level was assessed by flow cytometry. For MN production, cells were collected 3 days after RT, and MN production was evaluated using the MicroFlow In Vitro kit.

Results yH2AX and MN analyses showed no effect of NBTXR3 alone on DNA damages, whatever the cell line considered. As expected, RT induced a significant increase of DSBs and MN. Interestingly, NBTXR3+RT increased DSBs formation 1h after RT compared to RT and DSBs were not completely repaired 24h after RT, with more unrepaired DSBs persisting after NBTXR3+RT treatment. In parallel, analyses showed an increase in MNs formation with NBTXR3+RT compared to RT alone 72h after RT in most of tested cell lines.

Conclusions Previous reports indicate that NBTXR3+RT induced a significant abscopal effect in competent mice harboring CT26.WT tumors. Our in vitro findings demonstrate that a single dose of 4Gy with NBTXR3+RT can promote DSBs and MN generation in tested cell lines. These results suggest that the immunomodulatory properties previously observed in vivo with NBTXR3+RT could be linked to increased DNA damage, particularly MN production, which is known to play a crucial role in activating the cGAS-STING pathway, promoting IFN-b secretion, a pivotal factor in immune response priming.

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