AsiDNA protects the normal tissue against chemo- and radio-induced toxicity

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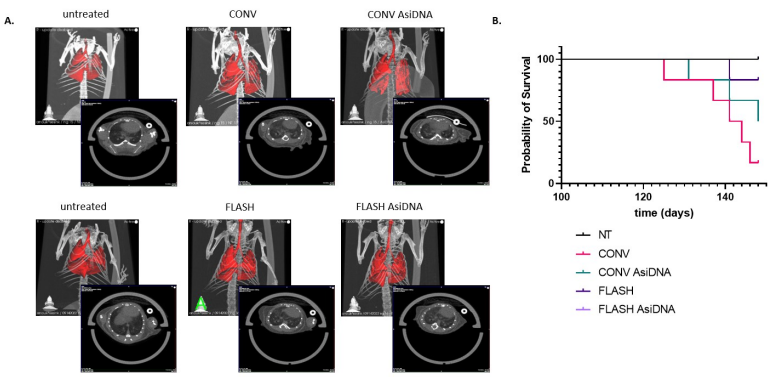
Abstract

Background/Aims: Radiotherapy and chemotherapy are customary implemented in cancer treatments with curative intent. However, the associated severe side effects often interfere with the completion of the initial treatment plan. Although the current standard of care reduced the frequency of severe injuries, their efficacy is still suboptimal. Previous studies have shown that AsiDNA, a short double-stranded DNA molecule able to interfere with DNA repair, sensitizes tumour cells, with no increased normal cells sensitivity, to chemo- and radio-therapy1,2. These observations led us to assess the potential of AsiDNA to protect healthy tissue from treatment induced toxicities.

Methods: In vitro, we monitored by flow cytometry cell cycle arrest induced by AsiDNA, which allows us to identify key proteins involved in this arrest followed by Western blot conformation. Furthermore, we monitored cell survival of normal cells treated upon AsiDNA and/or chemotherapeutics or radiation treatment. In vivo, we combined AsiDNA treatment with FLASH- and conventional- radiotherapy (FLASH versus CONV-RT)3,4 in BL6 mice followed by long term survival and the monitoring of lung fibrosis formation.

Results: In vitro, AsiDNA enters healthy cells, revealed by the PARylation of cellular proteins, but induces its nuclear targets engagement (H2AX and HSP90 phosphorylation) only in dividing cells, in which it induces G1/S cell cycle arrest. We revealed that this arrest is DNA-PK/p53/p21 dependent. The association of AsiDNA to antitumour treatments increased survival of healthy proliferative cells. In vivo, we confirm that FLASH-RT delays the onset of lung fibrosis compare to CONV-RT. If AsiDNA delays RT-induced lung fibrosis, the most striking result is the strong radio-protection we obtained if AsiDNA is combined to FLASH-RT versus CONV-RT.

Conclusion: These findings suggest that, likely through AsiDNA-induced cell cycle arrest of highly dividing cells in vivo, the combination of AsiDNA with FLASH-RT attenuates radiation induced toxicity, thus providing an opportunity to increase the therapeutic window.



CT assessment and survival of radiation induced pulmonary fibrosis. (A) Lung micro-CT of BL6 mice 4 months post Conventional (CONV) or FLASH radiotherapy treatment with or without prior AsiDNA treatment. Images are obtained using micro-CT imaging, high resolution and 100µm reconstruction. Representative images are shown with the 3D lung reconstruction of connected Hounsfield Units -800 till -200 (left) and CT axial slice (right) obtained using vivoquant software. (B) Kaplan-Meier representation of animal surviving fraction displayed in days post treatment and/or radiation.

References

1. Herath, N. I. et al. Preclinical Studies Comparing Efficacy and Toxicity of DNA Repair Inhibitors, Olaparib, and AsiDNA, in the Treatment of Carboplatin-Resistant Tumors. Front. Oncol. (2019) doi:10.3389/fonc.2019.01097.

2. Ferreira S, Foray C, Gatto A, Larcher M, Heinrich S, Lupu M, Mispelter J, Boussin FD, Pouponnot C, D. M. AsiDNA is a radiosensitizer with no added toxicity in medulloblastoma pediatric models. (2020) doi:10.1158/1940-6207.CAPR-20-0054.

3. Favaudon, V. et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci. Transl. Med. (2014) doi:10.1126/scitranslmed.3008973.

4. Montay-Gruel, P. et al. Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s. Radiother. Oncol. (2017) doi:10.1016/j.radonc.2017.05.003.