Activation of the cGAS-STING pathway by NBTXR3 nanoparticles exposed to radiotherapy

Authors

Julie Marill[1], Audrey Darmon[1], Ping Zhang[1], Sébastien Paris[1]

[1]Nanobiotix, 60 rue de Wattignies, F-75012, France

Abstract

Radiation therapy (RT) is one of the most used local treatment for many cancer types. In addition to DNA breaks and free radicals production leading to numerous cell damages and cancer cell destruction, many preclinical and clinical studies have demonstrated that RT acts as an efficient modulator of tumor immunogenicity. RT can set in motion a series of processes facilitating tumor recognition by the immune system, such as induction of the immunogenic cell death (ICD). Recent studies reported that RT could also activate the cGAS-STING pathway, which plays a fundamental role in the immune response to cytoplasmic DNA, by activation of the transcriptional factor IRF3, leading to expression of interferon β. Moreover, cGAS-STING activation appears to be an important component for tumor resident Antigen-Presenting Cells (APC) activation, a crucial step for induction of CD8+ T cell response against tumor derived antigens. Interestingly, recent preclinical data showed that STING agonist and RT could synergize to control local and distant tumors.

NBTXR3 is composed hafnium oxide nanoparticles used for a single intra-tumor administration and activated by radiation therapy. The size, shape and surface of these nanoparticles have been designed to develop strong interactions with cancer cells – effective cell binding and uptake – and to persist within the tumor mass during the whole RT treatment. The high electron density of NBTXR3 is responsible for an increased probability of interaction with incoming ionizing radiations when compared to tumor tissues with low electron density. NBTXR3 increases energy dose deposition within the cancer cells which results in an enhanced tumor destruction when compared to RT alone. NBTXR3 is currently evaluated in clinical trials including soft tissue sarcoma (phase II/III), head and neck, prostate, liver and rectum cancers (phase I).

Here, we explored the ability of RT-activated NBTXR3 to increase cGAS-STING pathway response, compared to RT alone. To achieve this goal, we used human colorectal cancer HCT116-Dual cells, which stably express a secreted luciferase under the control of a minimal promoter containing five IFN-stimulated response elements. This system allows the study of IRF3 transcriptional activity, by monitoring the chemiluminescence. A significant increase of luciferase activity (from 30% to >50% ($n=5$, $p<0.05$)) was observed for cells treated with NBTXR3 and irradiated (2Gy to 8Gy), when compared to RT alone. At equivalent dose of RT, NBTXR3 showed a significant increase of cGAS-STING pathway induction that could prime a more effective antitumor immune response.