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Letter to the editor: Hypoxia kinetics and histology in combined radiotherapy and oxidative phosphorylation inhibition effects on antitumor immunity

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ABSTRACT

In response to the recent paper by Chen *et al* investigating the triple combination of oxidative phosphorylation inhibition, immunotherapy and radiotherapy, we would like to stress that after irradiation, a strong reduction in hypoxia (within 24 hours) can be followed by a strong increase (several days). This is especially the case with larger fraction sizes of radiation therapy, which are often applied in combination with immunotherapy, and is likely to be tumor dependent. All together this may strongly affect the synergistic effect of such a triple combination therapy.

Dear editor,

We read the recent paper by Chen *et al*[1] with interest. In their experimental studies, they analyzed the combined effect of oxidative phosphorylation (OXPHOS) inhibition using IACS-010759, together with radiotherapy and programmed cell death protein 1 (PD-1) blockade. They clearly showed, in well-designed experiments, how metabolic targeting can enhance the synergy of radiotherapy and immune checkpoint inhibition (ICI). This triplet treatment is an excellent example how, in a combined approach, radiation treatment can be used not only for local but also for systemic treatment.

A major advantage of OXPHOS inhibition is that it reduces one of the major radiation resistance mechanisms, that is, tumor cell hypoxia. Indeed, using [^{18}F]-FAZA-PET imaging, Gammon *et al*[2] found a reduction of tumor hypoxia after treatment with IACS-010759. In the discussion, Chen *et al*[1] elaborate on the effects radiation may have on the oxygenation status of tumors. They state that irradiation is associated with decreased glycolysis and increased OXPHOS, which is known to increase hypoxia by increasing oxygen demand. However, we and others have shown the kinetic process of radiation-induced changes in hypoxia, both acute and up to several days[3–5]; we found that between 6 and 48 hours after a single fraction of 10–20 Gy, hypoxia actually *decreases* drastically.[5] This decrease in hypoxia is accompanied by a strong decrease in tumor blood perfusion. The observation that hypoxia decreases despite a reduced perfusion indicates a decrease in oxygen consumption, due to a decrease in metabolic activity and indicated by a reduction in proliferative activity, as the underlying mechanism.[6] After several days, a strong increase in hypoxia is measured, accompanied by an increase in necrosis and proliferative activity. Thus, changes in oxygenation status in a tumor change rapidly over time, depending not only on a shift from glycolysis to OXPHOS, as changes in ATP requirement also change over time after irradiation. This should be taken into concern when interpreting the results.

Additionally, for their experiments, Chen *et al* used the murine 344-SQ non-small cell lung cancer *adenocarcinoma* model, which was either sensitive or made resistant to PD-1. The response they reported may well be specific for this particular tumor model, as in several studies the metabolic status of NSCLC has been found to be model dependent. For instance, NSCLC squamous cell carcinomas were found to predominantly depend on OXPHOS, whereas adenocarcinomas (used in the current experiments) generally rely more on glycolysis.[7] Therefore, the effects reported may well be histology dependent. Moreover, hypoxia-inducible factor 1α (HIF1α) is one of the main controllers of glycolysis and is upregulated after irradiation. Targeting HIF1α and thus glucose metabolism is likely to reduce the antioxidant

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capacity of tumors, thereby enabling the sensitization of tumors to radiation therapy.[8]

In conclusion, we would like to stress that changes in hypoxia, induced by radiation therapy, has a strong kinetic behavior. Due to the kinetics after irradiation, a strong reduction in hypoxia (within 24 hours) can be followed by a strong increase (several days) accompanied by massive necrosis. This is especially the case with larger fraction sizes of radiation therapy, which are often applied in combination with ICI, and is likely to be tumor dependent. All together this may strongly affect the synergistic effect of this triple therapy.

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