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Letter to the Editor

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Abstract

Response to Ling et al. regarding "An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and normal tissue responses"

We are pleased that our past manuscript entitled, "An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and normal tissue responses" has stimulated such interest in the field [1]. As with our previous response [2], we would like to re-emphasize that we consider our manuscript as providing a framework for critically testing ideas at the experimental level. While we welcome pro-offered theoretical arguments in favor or against our presented hypotheses, we point out that such arguments need to be brought forward with new and robust experimental data in support of (or against) our stated hypotheses. Alternatively, we would also welcome additional physico-chemical models that might provide more plausible explanations for the FLASH effect. However at this time, we believe the best path forward will ultimately rely on rigorous biological data that will substantiate the validity of any model based explanation of the physical, chemical, and biological based differences of FLASH radiotherapy versus conventional dose-rate modalities. With this preface we provide a brief response to the issues raised.

Point 1.

Regarding Figure 2, both panels seem to suggest that the presence of hydroperoxides in tumors and normal tissues are at different time points after the radiation delivery. This is clearly wrong as hydroperoxides are generated immediately in both tumors and normal tissues upon being irradiated. The Editors may wish to advise the authors to submit a revised version of Figure 2.

Author response:

The x-axis is time and it is not continuous from left to right, which is why there is no scale shown. However, as stated in the text we assume that in each mode of delivery, essentially the same level of hydroperoxides are generated with the same dose of radiation. However, the dose delivered in one treatment session is much, much greater with FLASH.

Figure 2 focuses on the differential dissipation of these hydroperoxides after the delivery of the radiation. With the current, conventional delivery of radiation, the initial level of

hydroperoxides at the end of the “pulse” will be much less than with FLASH. Thus, the peroxide-removal-systems of both tumor and normal tissue will have only a small difference in the rate of removal of these hydroperoxides. However, we propose that with FLASH, the level of hydroperoxides at the end of the “pulse” is so high that the reserve capacity to remove hydroperoxides is greatly exceeded in tumor tissue, but not so in normal tissue. Thus, in tumor tissue the rate of removal of these hydroperoxides is much slower. These hydroperoxides have more time to initiate new chains of oxidation, exacerbating the oxidative damage inflicted at the end of the pulse.

Point 2.

The presentation and the comparison of the left and right panels of Figure 2 is misleading. The right panel is for one radiation pulse at conventional dose rate, which is approximately 4 × 10–4 Gy, whereas the left panel is for a dose of 10 Gy delivered at Flash dose rate. 10 Gy at conventional dose rate will generate the same level of hydroperoxides as 10 Gy at Flash dose rate. The same criticism applies to the right panel of Figure 1 which compares the number of ionizations generated by doses that are different by 4 orders of magnitude.

Author response:

We agree completely that 10 Gy whether delivered by FLASH or conventionally will yield essentially the same level of hydroperoxides, assuming no limiting reagents. The point is that with FLASH, the 10 Gy is given in one treatment session, whereas with conventional radiation therapy, the 10Gy is given in many fractions of several days or weeks. Thus, immediately after delivery of the radiation in a treatment session, there would be a great difference in the number of hydroperoxides.

Point 3.

Whereas point number #4 in the Summary section implies that complete oxygen depletion is a prerequisite, the subsequent paragraph, especially the sentence “Importantly, inundating the system that removes the copious organic hydroperoxides generated by FLASH irradiation is the means by which the differences in redox metabolism between cancerous and normal tissues can be maximized”, seems to suggest oxygen depletion may not be necessary.

Author response:

Data to date suggest oxygen plays an important role, differences that have not been found at exposures using conventional dose rates. We do agree that oxygen depletion is not likely going to provide a complete explanation of the FLASH effect, but based on current evidence it is difficult to dismiss entirely. Our point is that oxygen could well be depleted at the end of a FLASH “pulse” (session).

Point 4.

In Fauvadon's original paper which first reported the Flash effect, they considered and dismissed oxygen depletion as being a factor as the lung is well oxygenated [3]. How would the present model provide an explanation to Fauvadon's observation?

Author response:

Oxygen depletion in Favaudon's model while dismissed in the lung, would still be projected to provide the same relative benefits. We point out, that as long as the dose and volume irradiated are compatible with a transient and radioprotective hypoxia that precludes the production of certain damaging free radicals and downstream signaling in vivo, the benefits of FLASH would be projected to be "relatively" tissue independent, but dependent in part on local oxygenation.

Point 5.

Lastly, the model of Figure 2 and the associated discussion seem to imply that Flash dose rate radiation induces greater damage to the tumor relative to conventional dose rate radiation.

This is inconsistent with experimental data of Fauvadon [3] and others who observed similar tumor control at the two dose rates.

Author response:

No, our data is not inconsistent; conventional and FLASH dose rates are iso-efficient at tumor control, and significant new data (under review) indicates this to be the case after single dose and fractionated irradiation regimens for orthotopic brain tumors, in addition to the published data of Fauvaudon [3]. We propose that initial damage levels when compared between normal tissue or FLASH for a given mode of irradiation are equivalent, but the capability of normal tissues to remove damaging hydroperoxides more efficiently than tumors after FLASH defines the therapeutic index, an effect that is not observed with conventional dose rate irradiation. The FLASH effect was and continues to be defined at the in vivo level, and represents the culmination of many complex biochemical and biological signaling cascades that cannot be accurately modeled by simple chemical systems. Data to date point to a remarkable normal tissue sparing by ultra-high dose rate "FLASH" irradiation. Our physico-chemical model was proposed to provide a possible explanation for some of the beneficial and protective effects of FLASH on normal tissue.

We realize our very simple radiation chemistry/biochemistry model needs much more detail and refinement. Our simple approach did not consider that the dose is being delivered to a crowded protein solution. Thus, some of the simple assumptions on the production of superoxide etc. provide only a first generation estimate. Our proposal is that a good deal of the oxygen consumed will end up being present as hydroperoxides. The level could be quite high, greatly exceeding the reserve capacity of the peroxide-removal-system of tumor tissue compared to normal tissue. Toxicity resulting from these hydroperoxides is not just a function of the initial concentration, but also how rapidly they are removed [4]. We propose

that FLASH seeds a much greater amount of hydroperoxides into tissue, and that compared to normal tissue, the limited peroxide-removal-system of tumor tissue results in these hydroperoxides being removed much more slowly, substantially increasing their toxicity.

Without further data that tests these ideas, the field will be left with only theoretical arguments, trying to explain one of the most remarkable if not unexpected effects in radiobiology for decades. For now, we await and welcome the generation of additional data sets that can point to a more plausible if not accurate explanation of the FLASH effect.

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