Reviewer's report

Title: Dietary Flaxseed Administered Post-Thoracic Radiation Treatment Improves Survival and Mitigates Radiation-Induced Pneumonopathy in Mice

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Reviewer: Joel S Greenberger

Reviewer's report:

This is an interesting study of C57BL/6 mice with 13.5 Gy thoracic irradiation with flaxseed dietary supplement. The authors look at 2, 4, 6 weeks after irradiation, measure fibrosis, and hydroxyproline content.

The experimental model is not the model described by Travis for this mouse strain. Mice develop organizing alveolitis/fibrosis at 120 – 150 days after irradiation, and this is in fact organizing alveolitis not fibrosis. In addition, the irradiation dose of 13.5 Gy is below that usually associated with fibrosis in this model at 19 – 20 Gy. It is not clear what the investigators are measuring so that the results are going in a instructive direction.

A critical control for the flaxseed has to be included.

Specific Comments:

Abstract:

The authors should include multiple radiation doses and data out to 120 – 150 days. The mouse strain used should be stated in the abstract.

Introduction/Background:

The discussion of radiation terrorism is inappropriate for the experiments being carried out with thoracic irradiation as the current model being studied is one more associated with radiotherapy for lung cancer or esophageal cancer. The introduction discusses cytokine radioprotective drugs, which are irrelevant to the current study and should be deleted.

Materials and Methods:

C57BL/6J mice from Charles River should be described in greater detail. C57BL/6TAC compared to C57BL/6HnSD have different radiobiology and have been published by others, and the Charles Rivers strain should be discussed with respect to references 18 – 20. They have used different mice. A complete dose response curve for induction of radiation fibrosis in these mice at 120 – 150 days should be included in preliminary data or in a revised manuscript since this is critical to interpreting the current dietary supplement. Dietary treatments should include a control FS. 13.5 Gy as described with 250 KVP should be related upon. What was the dose rate? What was the shielding applied? What was the dose to
the head, and abdomen/pelvis? The other sections of the Materials and Methods section are appropriate except for the tissue harvesting and evaluation. The Optimus Imaging System should be utilized to quantitate percent organizing alveolitis/fibrosis as described by Travis. Hyroxyproline content is interesting but must be accompanied by data at 120 – 150 days with respect to organizing alveolitis/fibrosis.

Results:

Table 1 describes data with BAL at 4 months which would be 16 weeks for 112 days. Data at 150 days should be included to measure organizing alveolitis as described by Travis. Multiple irradiation doses should be tested including 19 Gy and 20 Gy previously reported by Travis to produce fibrosis/organizing alveolitis in this strain.

Figure 1 is a paradigm and could be described in the text.

Figure 2 describes FS compared to control diet. The results are quite interesting out to 6 weeks, but the data for 16 weeks, and more appropriately 150 days should also be included. One of the problems with studies of late fibrosis in this mouse strain is the failure to hold mice long enough to detect fibrosis/organizing alveolitis.

Figure 3 describes effects on body weight showing minimal differences. This is instructive as it suggests that the animals are eating the diet.

Figure 4 shows data out to 6 weeks. The study has suggested rapid death at 110 and 150 days which is just the time that these experiments were terminated for the diet group. Groups should be included in which the mice were fed FS for the entire 150 days.

Panel B shows minimal changes. It is not clear how the data in panel A (supplementary), on BAL WBC/ml relates to the other studies of cytokines and fibrosis.

Figure 5 describing lung injury, inflammation, and blood oxygenation are not particularly informative. Panel B shows thickening, but there is no specific stain for fibrosis rather HE. This could be an acute reaction and does not look like the fibrosis/organizing alveolitis seen in this mouse strain at 110 – 150 days post-thoracic irradiation.

Figure 7 shows lipid peroxidation that appears to be decreased by the short term administration of FS. This data is quite interesting.

Figure 8 fibrotic changes in mouse lungs and fibrotic index should be accompanied by Optimus Imaging. This mouse strain gets peripheral lung organizing alveolitis rather than diffuse fibrosis and would be expected to be seen in the photographs.

The results and discussion section follows the figures and tables.
Discussion:

The discussion should include mention of the new data requested, and more importantly, an analysis of fibrosis/organizing alveolitis in this mouse strain and how FS might influence the molecular pathways thought to be associated with lung lesion as described by Travis.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests below.