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TITLE: Transgenerational Radiation Epigenetics

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

To examine the effect of early exposure to irradiation (IR) and to look for an epigenetic signature we have irradiated pregnant females at gestation day 15. Of the pups that were born, some were sacrificed at 10 weeks for preliminary epigenetic screening. Others were used as breeders for transgenerational studies and still others have been left to take when they develop lung tumors. We have nearly finished collecting tissue from the 10 week mice as well as unirradiated controls. In addition we are nearly done collecting tissue from the F2 generation. Analysis of the tissue will start soon. We have also been weighing the mice at necropsy and have found that the average weight of the irradiated mice is less than the controls. This is an indication that there is an affect of IR on the mice in utero. We are hopeful we will also find an effect on the epigenome.

15. SUBJECT TERMS
Epigenetic biomarkers, transgenerational, lung cancer

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Table of Contents

INTRODUCTION

This study is to try and identifying the mechanistic basis by which environmental exposures such as radiation increase the risk for cancer later in life. To this end we have set up three specific aims. The first is to look for and validate an "epigenetic signature" after exposure to low dose irradiation in utero. The second aim is to see if these changes can be found in lung tumors. The third and final aim is to see if these changes persist through multiple generations.

BODY

Our stated goals for year one were primarily to set up breeder pairs of mice, irradiate pregnant females, and generate mice for all three aims. Additional goals were to collect tissues from the irradiated and non irradiated F1 offspring, and set up breeders for F2 and F3 generations.

1.1a IACUC approval was set up before the start of the study.

1.1b We have set up breeder pairs, irradiated pregnant females and generated the mice needed.

1.1c We have collected tissues from 9 irradiated (IR) and 12 control F1 mice. Collection of the final samples for this aim will be completed October 2011.

1.1d We are waiting for the final tissues to be collected. The tools available for the study of epigenetic changes have improved and expanded since the start of this award. While we are waiting we have also been keeping abreast of current technology.

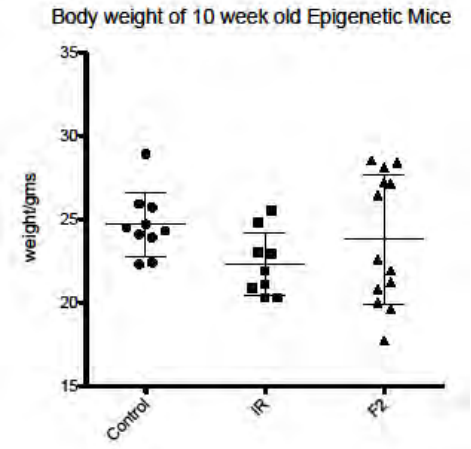
2.1a We are breeding and irradiating additional pregnant female mice to generate all the mice needed. We currently have 34 mice in the study, 17 irradiated and an equal number of control mice. The percentage of females presenting with plugs but not impregnated has been unexpectedly high (40%) and, as a result, it has taken longer than expected to get the desired number of offspring. Irradiated mice that are not pregnant are not useable in the study. Thus we are required to set up twice the number of breeders for the F1 study.

2.2b Mice will be taken in year 3 or as they exhibit signs of distress.

3.1a We have completed breeding the F2 generation of mice for Aim 3 and have collected tissue from 16 of these mice. We are currently breeding the F3 generation and have initiated collection of tissues from F3 mice. The breeding for Aim 3 is progressing quickly as we do not have to irradiate the females.

Early evidence for a transgenerational effect of radiation has been obtained. Preliminary data indicate a reduction in median body weight of F1 irradiated mice (IR) and F2 mice, as compared to unirradiated mice (see figure 1 on the following page).

Figure1



This was not due to litter size as the average litter size of both the irradiated and unirradiated is 4.2±1.8 and 4.8±1.9 respectively.

KEY RESEARCH ACCOMPLISHMENTS

*Generation and collection of tissues from mice for Aim1 nearly complete

*Generation of over half the mice for Aim 2

*Generation and collection of mice for F2 generation nearly complete and start of collection for F3 generation

REPORTABLE OUTCOMES

As well as the lung tissue for the study we are also collecting plasma, kidney, liver, spleen, testes and heart. This will create a tissue bank for other studies.

CONCLUSION

The differences in body weight of the irradiated versus the unirradiated mice shows an overall affect on the mice. However, as this study is still in its preliminary phase, and we have yet to analyze the tissue we do not have any specific conclusions on epigenetic changes at this time.

REFERENCES

None.

APPENDICES

None.