Changes in Liver Metabolic Gene Expression after Radiation Exposure
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INTRODUCTION
The health of the liver, especially the rate of its metabolic enzymes, determines the concentration of circulating drugs as well as the duration of their efficacy. Most pharmaceuticals are metabolized by the liver, and clinically-used medication doses are given with normal liver function in mind. A drug overdose can result in the case of a liver that is damaged and removing pharmaceuticals from the circulation at a rate slower than normal. Alternatively, if liver function is elevated and removing drugs from the system more quickly than usual, it would be as if too little drug had been given for effective treatment. Because of the importance of the liver in drug metabolism, we want to understand any effects of spaceflight on the enzymes of the liver.

RESULTS

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RESULTS

OF 86 drug metabolism genes examined, expression of 52 were unchanged by any treatment condition (determined by a relative expression change of less than 2-fold). Expression of some genes was changed in an apparently dose-dependent fashion, for example Abcb1b and Mt2, while in other cases, there is little correlation of expression with dose (Cyp17a1, Cyp19a1). Some genes exhibited a post-exposure temporal pattern that is consistent regardless of dose (Cyp17a1, Cyp51A1, Adh5).

The cytochrome p450 gene tested exhibited a broad range of responses. Cyp17a1 (produces cholesterol and steroid hormones) showed an early increase in expression, followed by a reduction, followed in turn by a return to increase. Cyp2c29 (pesticide-metabolizing and 28 (CYP2C9) (cytochrome P450 family) exhibit a similar pattern over time, with the four-hour data not significant. Cyp1b1 (cytochrome P450 family) shows no significant changes; the same was true for Cyp701 (CYP2B10), Cyp2d1 (data not shown).

Both Ephx1 (acts on polycyclic aromatic hydrocarbons) and Adh5 (metabolizes steroids and lipid peroxidation products) showed increased expression by 7 days after 6 Gy exposure. Expression of the related Adh5 was unaffected (data not shown).

The ABC transporter gene tested exhibited a range of responses. Abcb1b (MDR efflux pump, also involved in lipid and steroid transport) showed significant expression increases at 4 hours after treatment with higher doses, with a return to baseline expression over time. Abcb4 (transports phospholipids into bile) showed a small increase over 7 days after treatment even at the 50 mGy dose. Abcb1 showed no significant changes (data not shown).

Expression of the metallothionein 2 gene was strongly affected by all radiation doses, particularly at the earliest time point. Expression levels returned to near control by 7 days after exposure. The left and right panels show the same data, but the graph on the right has been scaled differently to include all the data.

CONCLUSION
Although this was a preliminary study and the gene expression results have yet to be verified at the protein level, some interesting trends are evident. It has previously been shown that gamma radiation causes physiological oxidation (Ding, et al., 2005). Many of the affected genes in this study are involved in reduction or removal of oxidized compounds. The greatest expression changes were in Mtb (metallothionein) and Cyp17a1, one of the cytochrome p450 enzymes. In these two cases, large expression increases were seen in response to high and low + high exposures. Metalllothionein is usually thought to remove heavy metals from the body, but may also play a role in inflammation and oxygen free radical regulation (Sato et al., 2002). Expression of this gene is regulated by redox state (which can be affected by radiation exposure) in addition to metal concentrations and glucocorticoids. Increases in metalllothionein expression have also been reported in livers of fish exposed to 75 mGy γ radiation (Olivivk et al., 2010). Cyp17a1 encodes an enzyme that adds a hydroxyl group to progesterone, which can then be converted to testosterone, estrogen or glucocorticoids. It can also contribute to the metabolism of administered medications that have complex ring structures, like hormones or promethazine. It is interesting to note that expression of the related Cyp19a1 was not significantly by all treatments, like 52 other genes that were examined.

It seems likely that radiation exposure triggers a variety of homeostatic mechanisms, which could include alterations of gene expression. Better understanding of these pathways could aid in development of new countermeasures to ameliorate or prevent radiation-induced damage to cells and tissues.

REFERENCES


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