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. Exposure to cosmic radiation is one aspect of spaceflight that can be modeled in ground experiments.

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, Cyp51l, Adh5).

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 Mt2 (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. Metallothionein 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 metallothionein expression have also been reported in livers of fish exposed to 75 mGy + radiation (Olivsk, 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 Cyp19a was not significantly altered 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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