Project Title: Identification of genetic modifiers of susceptibility to radiation-induced lymphoma

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The specific aims of this project were as follows:
Aim 1: Identify mouse genetic loci that affect the survival time of mice post radiation
Aim 2: Identify somatic genetic alterations that are indicative of tumor suppressor and oncogene loci involved in radiation-induced cancers.
Aim 3: Identify candidate radiation susceptibility genes by gene expression microarray analysis of the radiation response in normal tissues or in tumors from the strains used for aims 1 and 2.

Progress to date:
Aim 1: 250 F1BX mice have been followed up to completion of tumorigenesis. The genotypes of these 250 mice are currently being analyzed using microsatellite markers. We have completed the genotypes of chromosome 3, 4, 9 and 16. Primary data shows that there exist radiation-induced tumor susceptibility loci on chromosome 3, 4 and 9.
Aim 2: A total of 88 tumors from p53+/- and 59 tumors from p53-/- mice have been analyzed by CGH using the complete 19K BAC array. In tumors from p53+/- mice, the majority of radiation induced tumors exhibit one of three "signatures" based on gene copy number changes. Some exhibit extensive scrambling of the genome, with very high numbers of recurrent gains and losses. Two other signatures are characterized by excess gains but relatively few losses, or vice versa. Changes in spontaneous tumors often involve whole chromosomes, whereas radiation induced tumors exhibit a high frequency of localized deletion/amplification events. However, there is no clear signature between spontaneous and radiation-induced tumors from p53-/- mice in contrast to the results obtained in tumors from p53+/- mice. There were remarkably more genetic changes in tumors from p53+/- mice compared to those from p53-/- mice.
These have resulted in the identification of several genes, including *Fbxw7, Pten, Hipk2*, Aurora-A, and a novel gene named *GeMac*, involved in radiation carcinogenesis.
Aim 3: Gene expression microarray analysis has been carried out in 3 normal tissues and 12 radiation-induced tumors. Unsurpervised cluster analysis shown more than 5000 genes have been altered in tumors. More tumors and normal tissues will be required.

In summary, this project has been in our opinion very successful, and has resulted in the identification of several genes, including *Fbxw7*, *Pten*, *Hipk2*, Aurora-A and a novel gene named *GeMac*, involved in radiation carcinogenesis. Ten publications have appeared related to this work, and several additional papers are submitted or are in preparation. In particular, our latest data indicate that *Fbxw7*, in addition to being a tumor suppressor gene for radiation-induced lymphoma, is also a germline modifier of susceptibility. A polymorphism has been identified in *Fbxw7* that confers increased risk of developing radiation-induced tumors, not only lymphomas but also a range of epithelial tumor types. This latter result is particularly exciting, and validates the approach of using mouse models to find genes and pathways that control susceptibility to radiation effects in cancer induction.

Publications related to this grant:

1. Li J, Jiang T, Mao JH, Balmain A, Peterson L, Harris C, Rao PH, Havlak P, Gibbs R, Cai WW. Genomic segmental polymorphisms in inbred mouse strains. Nature Genetics, 36:952-4 (2004).

2. Mao JH, Perez-Losada J, Wu D, Delrosario R, Tsunematsu R, Nakayama KI, Brown K, Bryson S, Balmain A. Fbxw7/Cdc4 is a p53-dependent, haploinsufficient tumour suppressor gene. Nature. 432: 775-9 (2004).

3. Perez-losada J, Mao JH, Balmain A. Control of genomic instability and epithelial tumor development by the p53-Fbxw7/Cdc4 pathway. Cancer Research, 65: 6488-92 (2005).

4. Perez-losada J, Wu D, DelRosario R, Balmain A and Mao JH. p63 and p73 do not contribute to p53 tumor suppressor activity in vivo. Oncogene, 24:5521-5524 (2005).

5. To MD, Perez-Losada J, Mao JH, Balmain A. Crosstalk between Pten and Ras signaling pathways in tumor development. Cell Cycle, 4: 1185-1188 (2005).

6. Mao JH, Li J, Jiang T, Li Q, Wu D, Perez-Losada J, DelRosario R, Peterson L, Balmain A and Cai WW. Genomic instability in radiation-induced mouse lymphoma from p53 heterozygous mice. Oncogene, 24: 7924-34 (2005).

7. Mao JH, Saunier EF, de Koning JP, McKinnon MM, Higgins MN, Nicklas K, Yang HT, Balmain A and Akhurst RJ. Genetic variants of *Tgfb1* act as context-dependent modifiers of mouse skin tumor susceptibility. Proc Natl Acad Sci U S A, 103: 8125-8130 (2006).

8. To MD, Perez-Losada J, Mao JH, Hsu J, Jacks T, and Balmain A. A Functional Switch From Lung Cancer Resistance to Susceptibility at the *Pas1* Locus in *Kras2*^{LA2} Mice. Nature Genetics 38: 926-30 (2006).

9. Mao JH, Wu D, Perez-Losada J, Jiang T, Li Q, Neve RM, Gray JW, Cai WW, and Balmain A. Crosstalk between Aurora-A and p53: frequent deletion or downregulation of Aurora-A in tumors from p53 null mice. Cancer Cell 11:161-73 (2007).

10. Wakabayashi Y, Mao JH, Brown K, Girardi M, and Balmain A. Promotion of Hras-induced squamous carcinomas by a polymorphic variant of the *Patched* gene in FVB mice. Nature 445: 761-765 (2007).