

## Genomic signatures for radiation-induced mouse lymphoma

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### Abstract

Although radiation can directly induce DNA damage and is a known human and animal carcinogen, the number of genetic changes in radiation-induced tumors, and the pathways responsible for generating them, are unknown. We have used high density BAC arrays covering >95% of the mouse genome for analysis of genomic patterns of aberrations in spontaneous and radiation-induced mouse lymphomas. 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. The number of copy number abnormalities does not correlate with the latency or pathology of the tumors. We propose that specific early events following radiation exposure induce changes in “caretaker” genes that control specific downstream pathways involved in DNA damage repair. The nature of these early events may determine the overall genomic signature observed in the resulting tumor.

Whole genome BAC CGH array analysis was carried out to compare the patterns of genomic instability in radiation-induced tumors from *p53*<sup>+/-</sup> and *p53*<sup>-/-</sup> mice. In an attempt to recognize global patterns of genetic alterations in these tumors, we carried out unsupervised cluster analysis of the whole genome BAC profiles generated from these tumors. For this purpose, the genome was divided into bins of variable size based on the gain/loss frequency of all samples, and tumors showing gene copy number losses within a particular bin were denoted in green, while those regions showing gains were represented in red. Unsupervised cluster analysis showed that on average, there were many more genetic changes in tumors from irradiated *p53*<sup>+/-</sup> mice than in those from *p53*<sup>-/-</sup> mice. Detailed inspection of these patterns identified a large number of chromosomal changes that were specific to tumors from mice with at least one functional *p53* allele. For example, gain of the *c-Myc* locus and loss of *Fbxw7* were only found in tumors from *p53*<sup>+/-</sup> mice. In summary, array CGH analysis of radiation-induced lymphomas from *p53* heterozygous mice demonstrates that these tumors show considerable genetic instability. In contrast, similar tumors from *p53* null mice show less genetic instability.