Radiation Protection Dosimetry
Vol. 99, Nos 1–4, pp. 257–259 (2002)
Nuclear Technology Publishing

THE GENETICS OF RADIATION-INDUCED OSTEOSARCOMA

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INVITED PAPER

Abstract — Individual genetic variation can influence susceptibility to the carcinogenic effects of many environmental carcinogens. In radiation-exposed populations those individuals with a greater genetically determined susceptibility would be at greater risk of developing cancer. To include this modification of risk into radiation protection schemes it is necessary to identify the genes responsible for determining individual sensitivity. Alpha-particle-induced osteosarcoma in the mouse has been adopted as a model of human radiation carcinogenesis, and genome-wide screens have been conducted for allelic imbalance and genetic linkage. These studies have revealed a series of genes involved in determining the sensitivity to radiogenic osteosarcoma formation.

INTRODUCTION

The risk of an individual developing cancer after exposure to ionising radiation is currently estimated by extrapolation of epidemiological data correlating tumour outcome with the received dose in large irradiated cohorts. Estimates of risk derived from these data assume the radiation response is identical in all exposed individuals. However, the many inter-individual differences in the human genome may contribute to variation in individual radiation response[1–7]. Thus, quite different outcomes may arise between individuals receiving comparable radiation doses, making it necessary in future risk assessments to consider the individual genetic variability.

Radiation-induced osteosarcoma has been used as a model system to begin the task of identifying which genetic factors influence individual sensitivity. Radiation-induced osteosarcoma has been described in a series of irradiated cohorts, including retinoblastoma patients, painters of luminescent dials, and ankylosing spondylitis sufferers[8–10]. These epidemiological studies have revealed a range of genetic effects. At one extreme, retinoblastoma patients show an incidence of radiation-field osteosarcoma far in excess of that predicted for the applied radiation dose[11]. This is due to the presence of highly penetrant germ-line mutations of the Rb1 tumour suppressor gene. At the other end of the range a multitude of common low-penetrance modifying genes can influence susceptibility[1–7,12]. Thus, even though more traditional dose–response relationships are observed in the osteosarcoma cohorts, some individuals receiving high doses did not develop osteosarcoma, whilst others receiving low doses did[8–12]. Conventionally, such discrepancies are completely explained by invoking the stochastic nature of radiation-induced carcinogenesis. However, genetic differences amongst the irradiated subjects may provide an alternative explanation. Current estimates suggest that close to one in every 1000 bases in the human genome is polymorphic, leading to an almost infinite interindividual genetic variability. Evidence is accumulating that gene–gene interactions amongst these polymorphic genes may have profound biological effects on the predisposition to both radiogenic and spontaneous carcinogenesis[1–7,13].

Genetic studies in radiation-exposed human populations have allowed the identification of some of the highly penetrant gene mutations that influence radiation cancer susceptibility. These tumour genes include the aforementioned suppressor gene Rb1[11], as well as p53[14,15], patched[16], and ATM[17,18]. Other such genes may be identified through the rigorous screening of differences arising in the tumour cell genome. Such a strategy is not practical for the identification of the low-penetrance modifying genes. Here a more realistic approach is to use animal models of radiation carcinogenesis that allow saturation screening for genetic factors. Both of these strategies have been used to identify genes involved in radiation-induced osteosarcoma in the mouse, and have been able to identify a number of tumour genes as well as loci that modify susceptibility[12].

A GENETIC SCREEN FOR NEW TUMOUR GENES INVOLVED IN RADIATION OSTEOSARCOMAGENESIS

A characteristic of both tumour suppressors and oncogenes is that the number of copies (alleles) of the gene in the genome is frequently altered during oncogenesis. The resulting allelic imbalance (AI) can be quantified and used as a means of locating the gene(s) involved. A genome-wide screen has been conducted

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for AI in osteosarcomas induced in (BALB/c × CBA) F1 hybrid mice by parenteral application of the alpha-emitting radionuclide thorium-227. Allelic imbalance was detected by DNA microsatellite allelotyping. A total of ten loci showing imbalance in more than 50% of tumours were selected for more detailed analysis.

Four of the loci thus identified were found to correspond to known oncogene/suppressor genes that have been previously implicated in human osteosarcomagenesis. We have mapped two other loci to the corresponding syntenic regions of the human genome, and established that they too are involved in human osteosarcoma. The remaining 4 loci have not yet been mapped in sufficient detail. It is concluded that the genetic alterations, and hence carcinogenic mechanism, in sporadic human osteosarcoma and radiation-induced osteosarcoma in the mouse are astoundingly similar.

A GENETIC SCREEN TO IDENTIFY GENETIC CONTROL OF SUSCEPTIBILITY TO RADIATION OSTEOSARCOMAGENESIS

Inbred mouse strains reveal different sensitivities to the carcinogenic effects of ionising radiation. It has been established that the basis for this difference in sensitivity is genetic variation between the strains. The BALB/c strain has a greater sensitivity than the CBA strain, with shorter latency and a higher incidence of osteosarcoma following identical treatment with osteosarcomagenic doses of thorium-227. Polygenic control of osteosarcoma susceptibility has been shown by demonstrating that the sensitivity of (BALB/c × CBA) F1 hybrid mice is intermediate to the two parental strains. This is also confirmed by studies of sensitivity in genetically heterogeneous backcross BALB/c (BALB/c × CBA) animals where sensitivity was segregated. Some backcross animals exhibit parental BALB/c or CBA sensitivity, whilst others were comparable to the F1 hybrids.

The segregation of osteosarcoma sensitivity seen in the backcross animals has allowed us to conduct a genetic linkage screen to identify the genes responsible for modifying susceptibility. A genome-wide quantitative trait locus (QTL) analysis revealed the existence of five loci whose inheritance conferred increased sensitivity to osteosarcomagenesis. Animals inheriting all 5 loci developed tumours far more rapidly and with an almost 100% incidence. In contrast, animals lacking all five loci were relatively resistant to radiation-induced cancer, having a much longer latency and a lower incidence rate.

CONCLUSIONS

Study of the genetic mechanism of radiation-induced osteosarcoma has revealed the involvement of a set of loci harbouring tumour suppressors or oncogenes. Our current estimate is that a minimum of 10 genes are involved. These loci are indistinguishable from those involved in sporadic human osteosarcoma. At the same time, it has been established that a set of at least five genes determines the sensitivity of mice to radiation-induced osteosarcoma formation. Initial evidence suggests that at least one of these genes is also involved in determining human sensitivity to ionising radiation.

Whilst our studies focus primarily on an experimental model, sufficient overlaps have been established with the human system to suggest that radiogenic tumours arise by comparable mechanisms in both species. This commonality will allow us to test human radiogenic cancers for both susceptibility genes and gene alterations detected using murine models of radiation carcinogenesis.

ACKNOWLEDGEMENT

This work is supported in part by funding from the radiation protection programme of the European Commission (Contracts F14P-CT95–0008b and FIGH-CT99–00001).

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