EUROPEAN COMMISSION

nuclear science and technology

Genetics of Radiation Carcinogenesis (GENRAD)

Contract N° FIGH-CT1999-00001

Final report
(summary)

Work performed as part of the European Atomic Energy Community's research and training programme in the field of nuclear energy 1998-2002 (Fifth Framework Programme)
Generic research in radiological sciences

Directorate-General for Research
Euratom

2008

Project coordinator

Michael J. Atkinson, GSF, Germany

Project partners

Sylvie Chevillard, CEA, France

John Harrison, NRPB, UK

Ken Brown, University of Glasgow, UK

Heinz Höfler, Technical University of Munich, Germany

Introduction

Estimations of the risk of an individual developing cancer through exposure to ionising radiation are based primarily on the long-term follow-up of exposed populations. The extrapolation of dose-effect data derived from these epidemiological studies presents several problems. One growing concern about the validity of extrapolated epidemiological data is the ability of small population samples to accurately predict cancer risk in the global human population. It is now becoming increasingly clear that genetic variation plays a major role in determining the incidence of cancer. On an individual level inheritance of mutated tumour suppressor genes such as p53 or Rb1 greatly increases lifetime risk of developing cancer. On a population level national cancer rates vary dramatically, and whilst environmental and behavioural factors make a contribution, genetic factors also contribute to population risk. Currently very little is known about the genetic component of the risk of radiation carcinogenesis, preventing the inclusion of genetic risk factors in radiation protection models.

More than 10 million differences in the human genome have been recorded to date. The pattern of inheritance of these differences is not random, and it is estimated that 600 000 different human genomes exist on the planet. Genetic variation can be considered in a number of different ways. A single variation occurring in less than 1 % of the population is considered a gene mutation, whilst the same variation, if present in more than 1 % of the individuals, is considered a polymorphism. Irrespective of frequency, the variation may always be associated with a specific phenotype (highly penetrant) or may only cause the phenotype in a subset of individuals (low penetrance). Clearly, as an individual inherits many different variant genes the net phenotype is the result of complex interactions.

This new knowledge necessitates a paradigm shift in our assessment of the health effects of ionising radiation, moving from population-based to individual assessment of risk. At the moment radiosensitive individuals are recognised *post hoc*, i.e. after tumours appear. Within a population, each individual will inherit a constellation of variant and mutated genes that makes her or him inherently at greater or lesser risk to the carcinogenic effects of ionising radiation. In an ideal situation those individuals inheriting genes increasing sensitivity to radiation would be recognised and offered greater protection. However, before such refinements of radiation protection can take into account the variability of the human population, we must first identify those genes that make a contribution to individual susceptibility.

Objectives

The GENRAD consortium aimed to establish the scientific basis for the inclusion of individual genetic risk in future radiological protection models. A number of steps towards this goal were defined:

i) the establishment and validation of animal models that permit experimental verification of the genetic component

ii) conducting experimental studies using these animal models to identify which tumour types and radiation qualities are influenced by genetic effects

iii) the use of these models for the identification of low and high penetrance genes that act as modifiers of susceptibility to ionising radiation.

This knowledge will ultimately be used to develop a genetic screening platform for use in predicting the individual cancer risk inherent in an exposure to ionising radiation. This will lead to an even greater level of protection of radiation workers and the citizens of the Union, which in turn will contribute to the safer exploitation of nuclear technologies.

Development of animal models for the study of genetic effects in radiation carcinogenesis

The objectives for this part of the project are the development and testing of a number of animal models. In previous studies the partners have established a number of models systems, some of which have already been validated. However, the need for additional studies was identified in order to complete the project.

Thus, in order to study different tumour types (e.g. sarcoma, carcinoma and haematological malignancies) and radiation qualities (e.g. alpha, X and gamma radiation), a number of different animal models are required. These include specific crosses (F1, backcross, interspecific) between mouse strains for use in linkage analysis and studies of allelic imbalance (see below). To facilitate tumour development for molecular genetic studies, a number of genetically modified or mutant mouse strains are also required.

Identification of high penetrance genes modifying susceptibility

The most readily identified source of genetic variability in the radiation response are the highly penetrant dominant acting genes responsible for acute radiation sensitivity syndromes and for familial cancer syndromes. Inheritance of a mutated form of one of these genes engenders a greatly increased risk of developing cancer after radiation exposure. A genome-wide scan for loci exhibiting allelic imbalance (AI screen) is used to map and ultimately identify regions of the genome-harbouring high-penetrance genes with the potential to act through the germ-line to modify risk of radiation carcinogenesis. This screen is based on the premise that such genes manifest themselves through a change in the number of gene copies in the tumour tissue. Such a change is detectable through an assay of allelic status (allelic imbalance, AI).

Identification of low penetrance genes modifying susceptibility

A less dramatic, but equally important, source of genetic variation are the gene poly-morphisms arising through the inherent variability of the human genome. These poly-morphisms are individually responsible for only small differences in gene function and each makes only a minor contribution to overall risk. However, in individuals who by chance inherit several such polymorphisms the additive effect on risk may be appreciable. To identify these genes, linkage analysis is used to identify those genes that exert a more modest influence on individual susceptibility. This screen for low-penetrance genes is based upon the fact that in a cohort of genetically heterogeneous animals those that inherit predisposing genes will be more likely to develop cancer. Consequently, these genes will be inherited more frequently in tumour-bearing animals.

Results

Development of animal models for the study of genetic effects in radiation carcinogenesis

The consortium has studied animal models of radiation-induced cancer of the bone, haematopoietic system, lung, gastrointestinal tract, breast and skin. In each of these systems we have developed and validated model systems accessible to molecular genetic analysis, allowing the mapping and identification of modifying genes.

Identification of genes modifying susceptibility

The most significant conclusion of GENRAD is the demonstration that genetic factors do indeed exert an influence on the risk of developing cancer after irradiation. In bone and GI tract we have already identified a number of the genes involved, and learnt how natural variant forms of these genes can influence cancer predisposition.

In all of the tissues studied we have also been able to map, and in some cases identify, genes that are mutated during the development of the radiation-induced cancers. All of these genes are also strong candidates for modifying genes able to increase the risk of cancer if present as a mutated variant in the germ line.

In future studies the consortium members will continue to map and identify the genes implicated in these present studies, along the way providing yet more evidence supporting the critical role of individual genetic background as a major determinant of risk of cancer following exposure to ionising radiation.

Implications

We have provided unequivocal evidence that genetic factors, present in the germ line, modify the risk of developing radiation-induced cancer. Through our mapping studies we have been able to determine both the number and location of these modifying genes.

A radiological protection scheme that is based on dose-response extrapolations alone cannot adequately describe the contribution of such a genetic component. Consequently, future developments must begin to incorporate the biological contribution of the germ-line variability within human populations.