Radioactive materials play an important socio-economic role in most developed countries. In addition to their industrial uses, especially in energy generation, there is increasing utilization of ionising radiation in the therapeutic and diagnostic procedures of modern medicine. Ionising radiation is also present in the natural environment where it may also have a socio-economic impact. Since ionising radiation is a proven human carcinogen it is clearly important to improve our knowledge of the risks involved in its use – this applies particularly to health effects that result from low dose exposure of the public and workers. Since epidemiological studies have insufficient power to directly measure excess cancer after these low doses it is necessary to project risks from high dose studies. Establishing the biological validity of these projections is an increasingly important issue in radiological protection research. Accordingly, the experimental studies outlined here utilized a combination of experimental models of cancer induction and molecular biology techniques to investigate the mechanisms and genetics of radiation carcinogenesis. The work was initiated in FP4 and is currently being extended in FPS; there is close collaboration with the GENRAD consortium.

The mechanisms and genetics of radiation tumorigenesis (MAGELLANS)

Challenges to be met

The specific challenges to be met in the project are best illustrated by the following questions. First, radiation is a proven carcinogen but where does it act in the complex multi-stage process of cancer development operating over many years and what are the implications for low dose risk? Second, we know from radiotherapy observations that rare human genetic conditions pre-dispose to radiation-induced cancer but should we expect more common genetic variation that might distort population-based estimates of low dose risk? At this stage in knowledge it is necessary to seek proof-of-principle evidence on these questions using relevant experimental models of cancer-induction. The project was designed ahead of FP4 to make full use of information expected from human and mouse genome research. In the project the partners are seeking detailed knowledge of radiation induced susceptibility to radiation-induced myeloid leukaemia, lymphoma, skin tumours and breast cancer in selected mouse models.

Achievements

Induction of myeloid leukaemia and lymphoma: Changes in the normal structure of chromosomes are frequent in myeloid leukaemia and lymphoma arising in humans and mice; both these tumour types are thought to originate in bone marrow cells. Chromosomal studies relating to radiation-induced myeloid leukaemia in the mouse have shown that the crucial radiation-induced damage during multi-stage tumour development occurs in primitive, normal bone marrow cells. This damage is consistently expressed in bone marrow cells and tumours as loss of a small segment of chromosomal DNA and the segment has been isolated in fragments and reconstructed. Using genome information and technology the likely target genes have been positioned in this chromosomal region and analysed further to determine their importance for tumour initiation. Similar progress is being made for lymphoma development but, here, the critical DNA loss occurs on a different chromosome.

The picture emerging from this sub-project, and indeed from others in the same EU programme, is that radiation is principally acting very early in multi-stage carcinogenesis as a DNA-deleting agent for tumour-specific genes in single cells. There is already good knowledge of this mechanism of DNA damage and, overall, the research is adding important support to the view that cancer induction by radiation does not occur through an unusual mechanism. On this basis, cancer risk will tend to rise with dose without a low dose-threshold where risk can be discounted.

Genetic susceptibility to myeloid leukaemia, skin tumours and breast cancer: Previous studies with mouse models had provided some evidence of common, genetic variation in radiation cancer risk but little specific information. As given below, work on this sub-project has added substantially to knowledge. In the case of myeloid leukaemia, a single heritable gene distributed amongst mouse strains appears to be the major determinant of risk. The evidence suggests that the variant gene acts to reduce the ability of bone-marrow cells to respond adequately to DNA damage in certain chromosomal regions; the gene appears to be tissue-specific in its action. The chromosomal location of the gene has been estimated and work on its identification is underway. The genetics of skin-tumour susceptibility is more complex involving the interaction of a number of common variant genes, some of which have been located. Importantly, there appears to be shared genetic mechanisms for susceptibility to radiation and chemical carcinogens. One susceptibility gene which produces an
altered hormone-related protein has been isolated and its mechanism of action is under investigation; studies on a new mouse genetic model are also underway. Finally, a third sub-project on genetic variation in the genes that control response to radiation damage in DNA led to an external collaboration on breast cancer risk. This work which involved gene location, isolation and characterisation showed that partial deficiency in a single key gene was associated with tissue radiosensitivity, chromosomal instability and breast cancer risk. Further work on the origins and impact of this variant gene, which is not common, is being shared with GENRAD.

The principal outcome from work in this area is evidence that variant genes influencing radiation cancer risk can be, but are not always, common. They tend to be tissue-specific in their action and frequently work in concert; cross-sensitivity to other carcinogens will probably apply to some variant genes. Overall, the work adds support to the view that, for genetic reasons, tissue-specific cancer risk after radiation will not be uniformly distributed in the human population. Also, that we should expect much of the common genetic variation in low dose cancer risk to be inherited in a complex fashion – predictions on the response of most individuals are likely to remain most difficult.

Selected references
A cancer modifier role for parathyroid hormone-related protein. 
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Analysis of loss of heterozygosity in lymphoma and leukaemia arising in F1 hybrid mice locates a common region of chromosome 4 loss. 
Elevated breast cancer risk in irradiated BALB/c mice associates with unique functional polymorphism of the Prkdc (DNA-PKcs) gene. 