

## **Physiological Effects of Low Radiation Doses**

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Low and very low radiation doses have numerous effects on the physiology of cells and tissues. These effects have traditionally been exploited in low dose radiotherapy of a wide variety of diseases, such as painful degenerative joints and acute or chronic inflammations such as ankylosing spondylitis. Only recently, first attempts of proper radiobiological research in this field have been made. In general, it was found that those effects of low radiation doses are not related to the characteristic radiation effects which cause cell death and chromosomal aberrations, i.e. double strand breaks of the DNA but are caused by gene activation and repression or the induction of unspecific stress responses.

Radiation doses which elicit those effects are lower than those at which significant cytotoxic effects occur, usually in the order of 0.2 Gy or less. The clinical effects of radiotherapy using low radiation doses may occur very rapidly and may be very dramatic, e.g. in radiotherapy of mastitis and sweat gland abscesses. A single dose of 0.2 Gy given in the early stages of a developing abscess may resolve pain, swelling and inflammation completely within a few hours this way avoiding the need to give antibiotics or use surgical intervention.

Radiation doses in this order of magnitude have been shown to lead to expression of the early stress response genes within less than 30 minutes. These are the earliest observed effects, the other effects which have been observed to occur later are likely to be consequences of this early, rather unspecific stress response. Those effects include the induction of various repair mechanisms, the decreased activity of inducible nitrous oxide synthase and the reduced expression of certain cell adhesion molecules which play a key role in the process of inflammation. The results of this research suggest that radiation effects are by no means specific but that radiation, in particular low and very low radiation doses act as an unspecific stress to the cells which activates a range of processes which are not radiation specific but specific to the special physiology of the responding cell.

This observation has far-reaching consequences for the interpretation of the effects of radiations on tissues and organs, in particular in the interpretation of the development of side effects and complications in radiation oncology. The popular textbooks of radiobiol-

ogy still ascribe the development of acute and chronic side effects of cancer radiotherapy to the inactivation of specific organ stem cells which is related to the induction of unstable chromosome aberrations which itself appears to be related to complex double strand breaks of the DNA which themselves are characteristic for ionizing radiation. Yet, recent research has demonstrated that changes in cell physiology and the expression of molecules which transfer physiological signals between cells and within cells play a much bigger role in the development of acute and chronic normal tissue effects than the inactivation of stem cells.

Does this new research have any implications for our understanding of the genetic and carcinogenic risks from low radiation doses? The present framework of radiobiological thinking is based on the target theory: each track of high energy charged particles transversing the nucleus of a cell has a small but non-zero probability of causing, by the production of low energy secondary particles some complex damage to the double helix of the DNA which the physiological repair processes acting in the cell are not capable of repairing properly. This leads to unrepaired or misrepaired breaks, unstable chromosome aberrations, stem cell inactivation and cell death. This is the molecular, radiobiological basis for the linear non-threshold hypothesis which claims that a single particle crossing the nucleus of a cell may be the cause of cancer. This molecular process of interaction of radiation with the DNA which is adequately described by the target theory is responsible for many radiation effects on cells and is the primary mechanism by which radiotherapy cures cancer. But is it important for all possible effects of radiation including heritable mutations and induction of cancer?

Recent research in the long-term changes of cell physiology and proliferative capacity of cells which survived irradiation has provided clear evidence that there are other processes, much more unspecific and indirect, which may play a much bigger role than direct hits to a critical target. These radiation effects are called radiation-induced genomic instability. There is growing evidence that these radiation effects may be involved in the induction of critical mutations and carcinogenesis.

Radiation-induced genomic instability is the term to describe the observation that stem cells in vitro and in vivo which survived a low or intermediate radiation doses become genetically unstable for many cell generations. This instability leads to the persistent appearance of new mutations which, in contrast to the cytotoxic mutations of direct interaction of radiation with the DNA are point mutations or small deletions, i.e. those types of

mutation which permit unlimited proliferation of the mutated cell which is essential for a cell to become a cancer stem cell. There is growing evidence that this new mechanism plays a much bigger role for radiation carcinogenesis than the direct induction of a mutation by irradiation. Radiation-induced genomic instability does not require direct interaction of radiation with the nuclear DNA as has been demonstrated by microbeam irradiation and may be related to the oxydative stress responses which may persist for many cell generations after irradiation.

These new observations of radiobiological research relate the induction of cancer by radiation to physiological effects of low radiation doses which are independent of direct radiation effects on the DNA. This means, however, that the target theory arguments and the microdosimetric arguments in favour of the non-threshold theory of radiation risks are no longer valid. Radiation carcinogenesis appears more as a rare consequence of an unspecific disturbance of the complex interplay of cell physiology by some unspecific stress. It will require completely new paradigms and models to predict the probable dose dependence of radiation risk based on these new radiobiological observations. Until this is available - and research is only just beginning - the estimation of the health risks of low radiation doses should be based more on common sense than on mathematical models which are likely to be incorrect.