LAUNCHING A WORLD WIDE RESEARCH STUDY

MECHANISMS DEVELOPED BY MAMMALS EXPOSED TO LOW DOSES OF IONIZING RADIATION

1. WHY A WORLD WIDE STUDY?

Background

There is recognition among many radiobiologists that the "highest tolerated dose" approach to preventing cancer is flawed at the biological level. Evolutionary theory tells us that organisms adapt and select for resistance within the cells of their body. For many years, this mechanism of protection has been known, but the focus of research has been mainly on the cellular level, in an attempt to identify genes responsible for that resistance. Radiation has been a constant presence on Earth since the beginning of life: our cells have been withstanding this presence and have been naturally adapting to it. Nevertheless, some reviews on the biological effects of low dose exposures on atomic bomb survivors have reported a potential increase in cancer incidence. Seemingly contradictory reports give strength to new evidence suggesting that reductionism approaches in biology are unsatisfactory, and that emergent properties of biological systems need to be considered, where the function of the whole system cannot be understood by determining the function of its parts.

Bystander effects are a clear example of interaction among cells and cellular systems: the signal induces a response in surrounding untargeted "undamaged" cells, causing extreme effects such as death or long-term genomic instability. On the other hand, "undamaged" cells may communicate to "damaged cells" to help then recover: a possible mechanism for adaptive response. Tumours respond differently than normal tissues from the same patient. Smokers respond differently than non-smokers.

Biological effects induced by exposure to low doses of ionizing radiation (IR) are often contradictory, probably because at this dose range intracellular homeostasis and micro-environmental changes are determinant in the outcomes of radiation. In fact, biological responses are qualitatively different following exposure to high- and low-LET, low- and high-doses. Different mechanisms are also involved in *in vitro* and *in vivo* models and at different time-points after irradiation.

Presently, both radiotherapy and radiation protection are based on fundamental assumptions about the biological effects of radiation which should be further investigated. The linear non-threshold model (LNT) at the low dose interval has been widely challenged, but the results of this research are difficult to integrate, likely due to the wide range of experimental systems utilized, and also due to the difficulty in obtaining experimental data in the very low dose range.

Opportunities

New concepts of how radiation interacts with biological systems are bound to suggest new approaches to protection involving probiotics, and new avenues for development of novel radiosensitisers for tumour therapy. The identification of mechanisms other than DNA damage as being involved in radiation response means that new intervention points for protection or for therapy are possible

The possibility of new targets for treatment of other degenerative disease including diseases of the neural system is real. Clearly a mechanism induced and/or modulated by epigenetic factors but having a genetic basis, which increases the mutation tolerance of a system, has the potential to provide novel genetic and biochemical targets for therapy and biomarkers for disease progression.

The identification of sensitive biomarkers for radiation exposure could also result from identification of the signal molecule(s) or of keys in signal transduction.

Understanding how cells "decide" what response is appropriate following radiation or chemical exposure, could also lead assays for identifying "at risk" groups of humans or biota and suggest intervention points for preventative medicine and environmental remediation. There are several potential applications of research in this area. Already, as discussed in the background, it is known that there is considerable individual variation in response to radiation and that certain genotypes are more prone to particular responses.

Attempts are underway worldwide to identify the genes (using linkage analysis) or epigenetic mechanisms which characterize radiation-induced genomic instability responses. This area would be very much helped by a greater understanding of the nature of radiation-induced bystander effects and their role in inducing and perpetuating genomic instability.

Bystander effects leading to genomic instability are part of an epigenetic mechanism permitting or resulting in adaptive or degenerative changes in populations of cells or organisms subject to environmental stressors. They induce transmissible effects in progeny by apparently epigenetic means, thus they may underlie pathogenesis in degenerative diseases or be important to health and safety in situations where toxic agents, under critical conditions, are present in the environment.

Induction and trans-generational perturbation of bystander effects, adaptive response and genomic instability appear to defy explanation at the gene or individual cell level. Rather it is necessary to consider emergent properties of systems and organized social responses in tissue, to disease, stress or toxins.

RIBE (Radiation Induced Bystander Effects), RIAR (Radiation Induced Adaptive Response) and RIGI (Radiation Induced Genomic Instability) are indicative of a widely operating mechanism in biological systems. They reflect the emergent complex control at tissues' level and the modulation of cellular signalling, which challenge the gene dominated views in biology and which could be harnessed for therapeutic gain as well to shed new light on problems in radiation protection, low dose risk and evolutionary biology.

Given the knowledge about the genetic basis of susceptibility to RIBE, RIAR and RIGI, and the range of chemical and physical toxic agents (including radiation) that may induce these mechanisms, it would seem like a promising area of radiobiology to explore these linked phenomena.

In particular, the low dose range is of interest for occupational and population exposure, and for this reason many researchers are working to understand which mechanisms are involved at this level.

It may be of concern to compare results obtained from a network of different laboratories utilizing comparable experimental methods: the same type and dose range of irradiation, the same *in vitro* or *in vivo* models, the same biological end-points in order to make advancement in understanding which

response mechanisms occur following: *in vivo* or *in vitro*, high- and low-LET, low- and high-doses, early- and late effects.

2. WHY LOWRAD ?

LOWRAD is an affiliated Non Governmental Organization to the World Council of Nuclear Workers, WONUC. WONUC has a deep interest in radiation protection and in the assessment of the hazards associated with the biological effects of low and very low doses of ionizing radiation for at least three reasons. The nuclear industry workers represent, along with radiology, nuclear medicine and radiotherapy professionals in hospitals, the largest group of workers for whom exposure to ionizing radiation is the main occupational hazard. Their families usually live in the vicinity of nuclear plants and they will be in charge of the implementation of any regulations.

For these reasons they are very much concerned by the controversies which have arisen over the past few years with regard to the effects of low and very low doses of ionizing radiation on human health and biotopes. Two pitfalls must be avoided: fuelling unjustified anxiety on doubtful bases or underestimating the risks associated with exposure to ionizing radiation.

3. PROGRAMME

Within the frame of the Lowrad organization we are presently launching a call for research programmes in the low dose range of ionizing radiation, under the wide subject "**MECHANISMS DEVELOPED BY MAMMALS EXPOSED TO LOW DOSES OF IONIZING RADIATION"**

As previously reported, available data on indirect effects of low doses are often contradictory because different biological mechanisms are involved in different experimental conditions. To fruitfully utilize results from the research groups within the proposed consortium, the type of radiation, range of doses, biological models and analysed end-points have to be discussed previously.
Mechanisms may be studied on animal models and on *in vitro* cells, but population studies are essential, taking into account that the ultimate scope is to improve the knowledge on the risk for populations exposed to low and very low doses of ionizing radiation, including nuclear workers and other occupationally or environmentally exposed groups

First step:
Selection of research programs and partners

The interested research teams should address an expression of interest and a proposed work program comprised of a **maximum of 5 + 1 pages**, including summary, research objectives, research team, state of the art with bibliography (2 page max.), 3-5 previous team publications on the subject, and proposed tasks with bibliography. The additional page should be for budget.
The email to submit proposals is lowradworldstudy@gmail.com. This email is managed by the coordinating committee partners at the Nuclear and Technological Institute in Portugal.
Dead line is the **15 January 2008.**

Second step:
The selected participants will be invited for a working meeting on the 15th February, 2008, at the Nuclear and Technological Institute, Lisbon, Portugal.

Third step
Call for financial support (European Union, Japan, Department of Energy of USA, Nuclear Industry).

4. THE IMMEDIATE AND LONG TERM INTEREST AND APPLICATIONS

The aim of LOWRAD is to better understand the mechanisms of low dose responses in radiobiology, helping to regulate the working conditions of radiation-exposed workers based on the latest scientific findings.
Thus the LOWRAD will promote on a dedicated web site the scientific debate on methods and on intermediate results and a two-way dialogue between researchers, regulators and representatives of nuclear workers. It is foreseen, at the end of the launched research program, a working meeting to verify how the obtained results will be practically utilized for regulation. A special issue of the International Journal of Low Radiation will be dedicated to the repercussions of the study.

5. PUBLICATION

Research papers will be published in the International Journal of Low Radiation – IJLR, a journal indexed at SCI, or in other peer-reviewed scientific journals, and presented during annual LOWRAD International Conferences. A final report as well as an executive summary will also be made public in the LOWRAD website.

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