

DoReMi workshop on

“Low dose radiation effects on the immune system: current knowledge and future perspectives”

The DoReMi WP5 exploratory workshop “Low dose radiation effects on the immune system: current knowledge and future research needs” gathered around 50 participants at the Lion’s Garden Hotel, in Budapest (Hungary) on Nov 5-7, 2013. Fifteen DoReMi partners were represented, and six external experts have been invited to participate in this workshop. The workshop was co-organized by four DoReMi members. Simon Bouffler, WP5 leader provided the financial support for the invited experts from the WP5 budget. The scientific program was developed collaboratively by Serge Candéias (CEA), Udo Gaipf (UKER), Benjamin Frey (UKER) and Katalin Lumniczky (NRIRR). The local organization provided an excellent environment to foster both very good work sessions and interactions between participants.

Meeting report

After a short introduction on the expectations of this workshop, namely the effects of radiation on immune functions as well as the role of the immune system in the response to radiation, and a keynote lecture by Prof. András Falus, the workshop began with a first session dedicated to the presentation of the EURATOM funded FP7 projects DoReMi and OPERRA as well as the MELODI platform. Six scientific sessions were then organized, to present work by the participants on tumor immunity, inflammatory responses and bystander effects, basic mechanisms and pathways, risk of low dose radiation, radiation induced immune modulation and 3D models in inflammation and immunity. Although the talks were organized in distinct sessions, several of the 23 presentations could have fitted in more than one, showing the interconnection of the subjects presented. This was also exemplified by lively discussions at the end of each presentation. These discussions were also fueled by many unpublished results presented during the talks. The workshop ended with a round table discussion to gather the opinion of the participants on the importance of immunology in low dose radiation research, and the best way to integrate radiobiology and immunology to further improve radioprotection.

The radiation quality dependence of several radiation-induced effects was considered in the different presentations. A special focus was given to bystander / distal / abscopal effects mediated by cytokines, immune cells or exosomes, on the production of cytokines and the role of cytokine/cytokine receptor, on DNA lesions and DNA repair, and on the induction of distinct forms of cell death such as apoptosis and necrosis. Several presentations discussed a prominent role of NF- κ B in the inflammatory response and in the response to radiation. It was highlighted that the inflammatory and immunological status of an individual at the time of radiation exposure can modulate radiation effects; however, radiation exposure can also greatly influence the development and functional integrity of the immune cells. The importance and role of epigenetics in the radiation response was also underlined in several talks. Finally, various aspects of tumour immunology and immunotherapy of tumours were also presented.

The discussions after the presentations or during the round table highlighted several important parameters that have to be considered carefully in the design of the experiments. These are the (a) timing of the measurements (early vs. long lasting effects), and of the mode of exposure to radiation (acute vs. chronic) , (b) the age at exposure (increased sensitivity in the developing immune system), (c) individual sensitivity (to both radiation and immune disorders) , (d) the dose/dose rate used for the experiment, (e) the quality of radiation, (f) the choice of models, including the different cell/tissue sensitivity to both radiation and immune effects, (g) the proliferative status of the cells, and (h) the oxygen level in the cultures.

Round table discussion/perspectives

Within the framework of DoReMi, it is clear that studies addressing the role of the immune system in radiation response and the effects of radiation on immune functions must be conducted with the aim of improving radioprotection at low doses. Integration of immunology in low dose health effects must improve the identification of potential risks. It was however recognized that we are at the early stages of the recognition of the role of the immune system in radiobiology. We are currently in the “data acquisition” period. Indeed, a large part of the data presented in this workshop was obtained following exposure to high doses of radiation. We have to learn from these experiments, as they will be important and helpful in designing new studies specifically aiming to address low dose risk. A lot of the presented studies included experiments performed following exposure to 2 Gy. It was argued that 2 Gy, although clearly out of the low dose range, does not represent a high dose from a therapeutic point of view, or related to a whole organ/tissue/organism. It was therefore proposed that this dose could be used as a “reference” against which to study the role of the immune system in exposure to low doses.

Experimental models most suitable for use in future studies were considered and discussed. As already pointed out, we are currently in the early stages of integration of immunology in radiobiology, and we are not able to recommend one model as “gold standard” over the others. However, *in vivo* studies must be favored whenever possible, keeping in mind that experiments with germ free animals should be interpreted with precaution since their immune system is probably not experienced enough and unrepresentative of a typical normal human in the population.

The ultimate goal is to translate these results in a better evaluation of low dose health effects, including carcinogenesis as well as non-cancer effects such as cardiovascular diseases, which clearly have an inflammatory component. It was recognized that there is a great potential for immunological studies to improve understanding of radiation-associated non-cancer diseases. It could be useful to conduct epidemiological studies of cancer and non-cancer diseases in immunocompromised patients, or on the contrary in patients with an “over-activated” immune system, such as patients suffering from allergies or chronic diseases. In these studies, the same endpoints than in radioprotection could be analyzed and already existing data in the field should be considered. This aspect could be a link to the wider immunology community.

It is important to keep in mind that some of the effects of radiation on the immune system can be very long lasting, as have been observed on A-bomb survivors which show for several decades after exposure alterations in the respective ratio of immune cell populations in the blood. How were these alterations induced? Are they genuinely caused by radiation or some sort of response of general stresses? How are they maintained for such a long time? These observations highlight the need for

further mechanistic studies in order to characterize the immunological competency of exposed people, and their ability to respond to infectious challenges after exposure.

Finally, it was agreed that we have to learn from tumour patients. They have an impaired immune status not only in the tumor and its surrounding, but also often systemically. Study of immune interactions with the various cytotoxic therapies such as radiotherapy (that are commonly applied for cancer patients) might help elucidating how radiation modulates antitumor immune mechanisms on the one hand, but also how the immune status might influence tissue radiosensitivity on the other hand. These data will provide important clues regarding the implication of the immune system in the promotion/support/suppression of low dose radiation-induced carcinogenesis. Another big challenge will be to identify mechanisms that connect the DNA-damage response to immunological modulations. Understanding the radiation dose-dependence of immune system effects in the context of radiation carcinogenesis is critical.

Altogether, it was recognized that radiobiology and radioprotection will benefit from studies focused on the role of the immune system in low dose radiation response and on the effects of low dose radiation on the immune system. There is a future for radioimmunology.

Most of the presentations given during the workshop are available on the DoReMi website. We are grateful to the speakers for making them available. If you want more information, do not hesitate to contact the authors, or the organizers (doremi@stuk.fi, with "immunology workshop" as subject) who will relay your question(s).

The Organizing Committee.