

Stem cell transplantation for prevention and treatment of deterministic radiation effects

Workshop-Report

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A workshop on "Stem cell transplantation for the prevention and treatment of deterministic radiation effects" was held at The Faculty of Medical Sciences, University of Groningen, The Netherlands, on 25th November 2002. This workshop was organised by Working party 4 "Mechanisms and treatment of deterministic effects from accidental radiation exposure" of the thematic network NET-EULEP (contract co-ordinator Professor J. Hopewell, University of Oxford, UK). In total, 18 participants attended the workshop, representing scientists from the field of stem cell biology, haematology and radiation biology from both EC funded and non-EC funded projects.

The objectives of the Workshop were to:

- i) provide a forum for the scientists to introduce both experimental and therapeutic models of deterministic normal tissue effects relevant to radiation exposure
- ii) introduce novel developments in the field of stem cell research and the preparation for therapeutic applications in general
- iii) provide a platform for the discussion of potential approaches for the exploitation of stem cells and stem cell techniques for the modification of normal tissue radiation effects
- iv) foster contact between the various research groups in order to establish co-operation aiming at submission of an application for research funding under the EC framework 6 programme

The Workshop programme (Appendix 1) comprised brief presentations by the speakers, with the majority of time allotted to discussions, which were both informative and constructive. This was the basis to achieve optimum interactions between the participants.

The first part of the workshop was devoted to recent results in research on haematopoietic and mesenchymal stem cells.

In the initial presentation by **G. De Haan**, the potential relevance of haematopoietic stem cells in the aging process of tissues was discussed. Recently established culture conditions for the isolation and amplification of multi-potent haematopoietic stem cells from adult bone marrow were introduced.

P. Charbord reported on mesenchymal stem cells, which in the adult can be found in bone marrow. This represents a source for endothelial cells, adipocytes, osteo- and chondroblasts and muscle cells, as well as cells of neuro-ectodermal origin, like neurons, astrocytes or oligodendrocytes, and from endodermal origin (hepatocytes). Questions possibly to be addressed in studies with radiation exposure relate to changes in growth and/or proliferation potential of mesenchymal stem cells. Also, the relevance of stromal bone marrow cells for haematopoietic stem cells were discussed.

In the second part of the workshop, models of radiation injury in normal tissue were presented, which may be exploited for studies into the potential of stem cells for the amelioration of deterministic radiation effects.

R. Coppes described irradiation studies on salivary glands in rats. Two pathogenic mechanisms of radiation-induced damage were indicated; early effects due to dysfunction of saliva secreting cells and later effects as a result of "classical" cell loss. It was suggested that only the later effects might be a target for stem cell transplantation.

First results from experiments into the effect of bone marrow stem cell transplantation as well as stem cell mobilisation by G-CSF were presented.

W. Dörr presented an experimental model of radiation-induced oral mucositis and the pathogenesis of this acute radiation effect. He described the role of stem cells, as a functional concept, for mucosal repopulation and regeneration. The efficacy of keratinocyte growth factor administration on the mucosal radiation reaction, illustrates an additional role of mesenchymal stem cells. This factor is exclusively produced by mesenchymal cells. Moreover, a model of in-vitro reconstituted oral mucosa was presented as a tool for additional studies into the stem cell biology of oral mucosa.

The radiation response of the urinary bladder can be studied by cystonometrical measurements in mice, as demonstrated by **W. Dörr**. In the acute response phase, functional changes in urothelial cells are the predominant mechanism, and the supply of stem cells may be beneficial there. As the acute reaction significantly influences the manifestation of late effects in this organ, there may also be benefit for chronic changes. Moreover, because the late radiation response is associated with urothelial cell depletion and irregular regeneration, stem cell supply at this point in time may ameliorate the consequences of radiation exposure.

M. Martin focused on the pathogenesis of late fibrotic changes in irradiated skin. The central role of transforming growth factor $\beta 1$ (TGF- $\beta 1$) was emphasized. Also, the involvement of myofibroblasts and keratinocytes was described. A model of in-vitro reconstituted skin was presented, similar to that of oral mucosa. Techniques for isolation and characterisation of skin stem cells were introduced.

Radiation effects in spinal cord, i.e. radiation myelopathy, can be studied in the rat. **M. Rezvani** explained the possible pathogenetic mechanisms of this radiation effect. In the first studies on the effect of transplantation of neural stem cells, a significant amelioration of radiation-induced myelopathy was observed.

As a model to study the effect of mesenchymal stem cell transplantation after total or partial body exposure to ionising irradiation, the NOD/SCID hu mouse can be used, as demonstrated by **D. Thierry**. The localisation of the mesenchymal stem cells within the injured organs can be determined by histological and cytological analysis. The homing clearly depends on the type of cells transplanted. The combination of ex-vivo expansion of haematopoietic stem cells with the infusion of mesenchymal stem cells was studied in a non-human primate model. The localisation and potential of these cells in irradiated animals is determined.

J. Wondergem reported on a model of cardiovascular radiation damage after radiation exposure. Vasculo-connective cells, i.e. endothelial cells, smooth muscle cells and fibroblast play a predominant role in the pathogenesis. The potential role of transplantation of multipotent stem cells in order to replace damaged endothelial cells and myocytes was explained.

In conclusion, the Workshop brought together stem cell scientists, cell biologists and normal tissue radiobiologists for exchange of information and cross-fertilisation. It provided a platform for exchange of ideas on the interaction of the disciplines involved, aiming at the modulation of deterministic normal tissue effects of radiation exposure by exploitation of current knowledge in the field of stem cell science. This relates to haematopoietic and mesenchymal stem cells, but also to multi-potent stem cells of individual tissues.