Gene expression and cytokine monitoring for biodosimetry and radiation sensitivity screening (GYMBRASS)*

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Introduction

The radiation environment in deep space is very different from the one on Earth and consists mainly of the galactic cosmic rays and solar particle events. Although present at only minor fractions, high-charge and high-energy particles ("heavy ions") constitute the main risk for the crew's health due to their large ionization power [1]. In contrast to low linear energy transfer (LET) radiation such as X- or γ-rays, the relationship between the early biological effects of heavy ions and the probability of cancer development in humans, is not well understood. Therefore, large uncertainties exist in estimating cancer risk as well as other adverse health effects (e.g. cataract, vascular diseases and cognitive defects) during deep space exploration. This is considered as one of the major hurdles for safe manned interplanetary space exploration [2].

Due to obvious mass constraints and physical reasons related to the very high energy of the particles of space radiation, shielding is only practical to a certain extent. Therefore, other radiation protection measures, such as on-board biodosimetry and therapeutic countermeasures should also be considered. Another possible, more preventive measure, although ethically questionable, could be to select-out those crew applicants for interplanetary missions with high resistance to the induction of early as well as late effects of radiation exposure.

Our study aims at identifying new biomarkers for radiation exposure to low- and high-LET radiation. We will focus on the use of gene, exon and/or cytokine expression signatures in human peripheral blood mononuclear cells (PBMCs) as biomarkers. These data will be integrated with those from DNA double strand break (DSB) repair kinetics in order to identify biomarkers of individual radiosensitivity.

Results and discussion

Comparison of radiation-induced gene expression after irradiation of PBMCs with 1 Gy of X-rays or C-ions

Using microarrays, we analysed genome-wide gene expression changes in non-stimulated, cultured PBMCs 8 h after irradiation with 1 Gy of X-rays (250 kV, 15 mA; n=10) or C-ions (LET = 50-75 keV/µm; n=4). Data analysis revealed that the changes were very similar between the different types of radiation. Because of the different number of donors for both experiments, yielding very different ANOVA *p*-values, we used rank-rank hypergeometric overlap analysis to detect and to visualise overlap trends between both gene expression profiles. This showed that there was a very high degree of overlap (minimum hypergeometric *p*-value ~10^{-63}) among the genes that are upregulated by both X-ray as well as C-ion irradiation.

Radiation quality-specific gene expression changes

Besides overlapping genes, we also identified gene expression signatures that were only responsive to either X-ray or C-ion irradiation. Whether these signatures can be used as biomarkers for prediction of exposure to radiation of different qualities is still under investigation.

Analysis of individual DNA repair kinetics by γH2AX

To identify biomarkers for individual radiation sensitivity, we will integrate gene/exon/cytokine expression data with data from individual DNA repair kinetics based on microscopic analysis of γH2AX positive DSB foci. First results show that there are indeed differences in radiation-induced foci formation among the donors.

Conclusions and perspectives

Our preliminary data indicate that there is a high degree of overlap in gene expression changes in PBMCs that are irradiated with similar doses of high- and low-LET radiation, although specific expression signatures were identified for both radiation qualities. We also analysed transcriptional changes at the level of single exons, which indicate that exon expression signatures are also useful as biomarkers of exposure and may explain differences in inter-individual radiation sensitivity.

Further experiments using multiplex protein assays will be performed to verify cytokines as possible biomarkers. Integration of DNA repair kinetics from individual donors with their radiation-responsive expression profiles will be performed as a final step of the project.

References

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