Radiation-induced NF-κB activation and expression of its down-stream target genes as biomarker of radiation quality

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Abstract:

Introduction
Activation of Nuclear Factor κB (NF-κB) and the resulting gene expression profile after exposure to different radiation qualities have been evaluated to a very limited extent. Therefore, the activation of NF-κB after exposure to low and high linear energy transfer (LET) radiation and the expression of its target genes was analyzed in human embryonic kidney (HEK) cells.

Methods
Activation of NF-κB was visualized by the cell line HEK-pNF-κB-d2EGFP/Neo L2 carrying the destabilized Enhanced Green Fluorescent Protein (d2EGFP) as reporter. The NF-κB dependent d2EGFP expression was evaluated by flow cytometry. The biological effectiveness (RBE) of NF-κB activation and reduction of cellular survival as determined by the colony forming ability test was compared for heavy ions having a broad range of LET (~ 0.3 - 9674 keV/µm). Furthermore, the effect of LET on NF-κB target gene expression was analyzed by real time reverse transcriptase quantitative PCR (RT-qPCR).

Results
The maximal RBE for NF-κB activation and cell killing occurred at an LET value of 80 and 175 keV/µm, respectively. There was a dose-dependent increase in expression of NF-κB target genes NFKB1A and CXCL8. A qPCR array of 84 NF-κB target genes revealed that TNF and a set of CXCL genes (CXCL1, CXCL2, CXCL8, CXCL10), CCL2, VCAM1, CD83, NFkB1, NFkB2 and NFKBIA were strongly up-regulated after exposure to X-rays and neon ions (LET 92 keV/µm). After heavy ion exposures, it was noted that the expression of NF-κB target genes such as chemokines and CD83 was highest at an LET value that coincided with the LET resulting in maximal NF-κB activation, whereas expression of the NF-κB inhibitory gene NFKBIA was induced transiently by all radiation qualities investigated.

Conclusion
Taken together, this study clearly demonstrates that NF-κB activation and NF-κB-dependent gene expression by heavy ions are highest in the LET range of ~50-200 keV/µm. The up-regulated chemokines and cytokines (CXCL1, CXCL2, CXCL10, CXCL8/IL-8 and TNF) could be understood to be important for cell-cell communication among hit as well as unhit

cells (bystander effect). The gene expression profile will be further evaluated as possible biomarker for exposure to different radiation qualities.

References:
Hellweg CE (2015) Cancer Letters, 368, 275-289
Hellweg CE, Baumstark-Khan C, Schmitz C, Lau P, Meier MM, Testard I, Berger T, Reitz G (2011) *Int J Radiat Biol* 87, 954-963.
Hellweg CE, Baumstark-Khan C, and Horneck G (2003) *J Biomol Screen*. 8: 511-521.

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