2nd Human Physiology Workshop
Saturday, 9th of December 2017
(Deadline no later than 1st October 2017)
Abstract to be send to humanphysiologie-ws@dlr.de

Finding NEMO – radiation induced bystander effects elicit NF-κB-dependent survival

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Introduction:
Radiation-induced bystander effects (RIBE) are an acknowledged issue of radiation therapy. Irradiation of tumor tissue has been shown to affect non-irradiated neighboring cells in a paracrine and endocrine manner. Transduction of bystander signaling though remains to be investigated in detail. A part of the transduction is the receptor-initiated activation of signaling pathways by secreted factors of the irradiated cell during irradiation damage response. This work focusses on the activation of the transcription factor Nuclear Factor κB (NF-κB) in bystander cells after irradiation. NF-κB is a well-known contributor to inflammatory processes by e.g. cyto- / chemokine production as well as to stress reactions such as the DNA damage response and cell cycle regulation.

Methods:
Murine embryonic fibroblasts (MEF) with an intact NF-κB signaling pathway (wildtype, wt) or with a knock-out of NF-κB essential modulator (NEMO ko) were used. Clonogenic survival and cell cycle distribution were determined in directly irradiated cells and in cells incubated with conditioned medium from X-irradiated cells (bystander treatment).

Results:
Directly irradiated NEMO ko cells, plated for clonogenic survival immediately after X-irradiation, display the same dose-effect curve as the wildtype (wt). But when allowed to recover for 24 h, the wt cells show a broader shoulder in the curve, indicating better repair of sublethal damage and a role of the NF-κB pathway in the repair of radiation induced DNA damages. Looking into the survival of bystander cells, the slope of the survival curves is significantly different, with NEMO ko cells surviving better than wt cells ($S_{16\,Gy}$: NEMO ko = 1.66 vs wt = 0.83). The different behavior may correlate with NF-κB dependent DNA repair in bystander cells for NEMO ko and wt cells. Cell cycle analysis revealed an arrest in G2/M phase that was delayed by 6 hours in directly irradiated NEMO ko cells compared to wt cells. This indicates that NF-κB regulated DNA repair pathways are important for recovery from radiation induced damages. Bystander NEMO ko show an even further delayed arrest at 48 h, while wt bystander cells show no G2/M arrest at all. This supports the assumption that damages have to exceed a certain threshold to be recognized as repair-worthy. As NF-κB has been reported to be involved in homologous recombination, cells with impairment in the NF-κB pathway, such as NEMO ko, register damages caused by bystander treatment differently compared to wt cells. This leads to G2/M arrest extending the time for repair in NEMO ko bystander cells.