

Mucositis represents a potential risk for astronauts on extended space flights*

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Radiation-induced mucositis is a severe complication of heavy ion radiotherapy [1] and may also represent a health risk during extended space flights [2].

To evaluate the risk of developing a radiation-induced mucositis through highly energetic heavy ions in space, a three-dimensional organotypic oral mucosa model of immortalized human keratinocytes and fibroblasts was irradiated with ¹²C particles (150 MeV/u) at the SIS accelerator at GSI. The focus of this study was on immediate and early effects after irradiation, where NFκB activation and increased expression of the cytokines are precursors of oral mucositis. 3D cultures were irradiated with 2 or 4 Gy and NFκB activation as well as IL6/IL8 expression was analyzed 4, 8, 24 and 48 h after treatment. In order to study NFκB activation NFκB p50 was immunofluorescence stained in cryosections of irradiated 3D cultures. This revealed a translocation of NFκB p50 from the cytoplasm to the nucleus after irradiation. The nuclear NFκB p50 signal was quantified and normalized against the nuclear DAPI signal. The relative change of the NFκB p50 amount in the nucleus upon irradiation is shown in Figure 1. In cultures exposed to 2 Gy ¹²C heavy ions we observed a translocation of the transcription factor to the nucleus 24 h and 48 h after treatment. 4 Gy of ¹²C irradiation caused a nuclear increase of NFκB p50 already after 4 h; this localization could still be seen after 8 h, 24 h and 48 h.

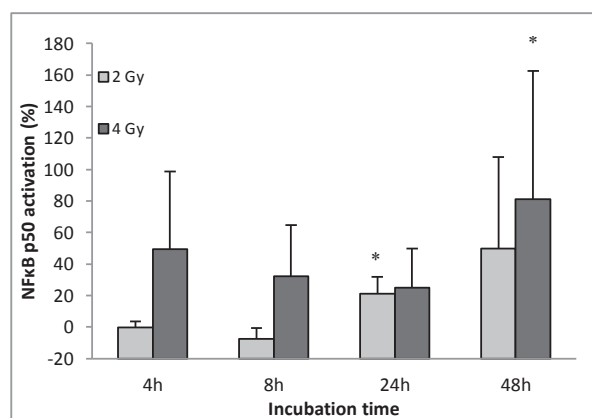


Figure 1: The percentage change of the NFκB p50 amount in cell nuclei upon ¹²C irradiation. Cryosections of 3D cultures were immunofluorescence stained against NFκB p50. Only nuclear NFκB p50 stained areas were related to whole DAPI stained areas (n=4, mean ± sd);

*p < 0,02 with reference to not irradiated cultures).

The pro-inflammatory cytokines IL6 and IL8 were analyzed in the culture's supernatants in four independent

experiments (Figure 2). In general, a tendency of dose-dependent increase of IL6 and IL8 could be detected for up to 24 h after irradiation. 48 h after irradiation the IL6 and IL8 level was back to the initial value.

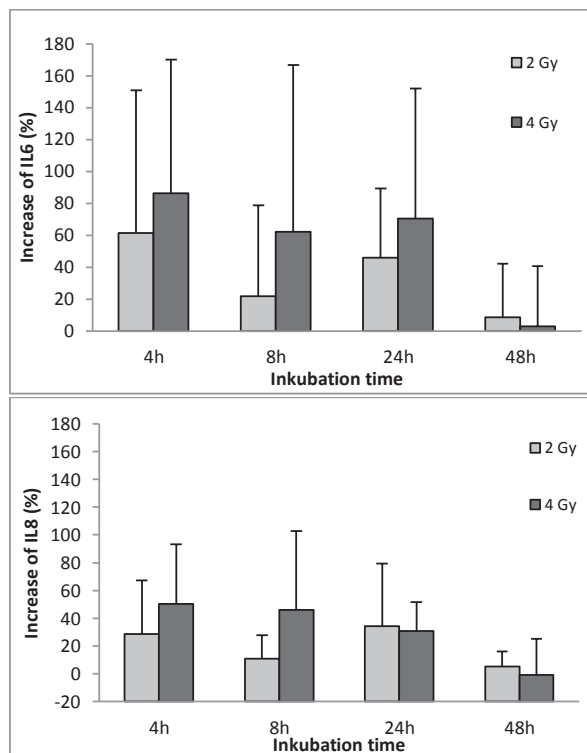


Figure 2: ELISA analyzes of cytokines IL6 and IL8 from supernatants of organotypic cultures. The relative increase compared to the control level (untreated) in IL6 or IL8 is shown. (n=4, mean ± sd)

Taken together, inflammatory responses as a sign of the initiation stage of oral mucositis could be detected in organotypic mucosa models exposed to highly energetic carbon ions. This suggests that mucositis indeed poses a risk for astronauts on extended space flights.

References

- [1] Schultz-Ertner, D et al., (2002). Radiotherapy and Oncology 64; 189–195.
- [2] Gonda, TA et al., (2009). Cell Cycle 8:13:2005-2013.

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