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Radiation responses of cells and tissues: from local events to systemic effects with emphasis on preclinical animal models of radiation therapy and response

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Increasing genomic instability during cancer therapy in a patient with Li-Fraumeni syndrome

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Introduction: Li-Fraumeni Syndrome (LFS) is a rare familial cancer predisposition syndrome with germline mutations in the TP53 tumor-suppressor gene that codes for the p53 protein. The activation of the transcription factor p53 stimulates protective cellular processes including cell cycle arrest and apoptosis and thus is termed "guardian of the genome". A broad range of tumors affect individuals with LFS from childhood through adulthood, and are characterized by their significantly early age of onset. Choroid plexus carcinomas (CPCs) are rare neoplasms of the brain that are associated with LFS. Here, we report on a 3-year-old child with LFS who developed progressive genomic instability during fractionated radiotherapy (RT) of the craniospinal axis for metastatic CPC.

Methods: To test radiosensitivity, DSB repair capacity of the LFS patient was analysed by DNA-damage foci approach. Before RT, blood lymphocytes were irradiated *ex-vivo* with 2Gy to determine induction at 15 min and to capture foci loss within 8h and 24h after exposure. Subsequently, foci levels in blood lymphocytes of the LFS patient were measured during and after completion of RT in comparison to an aged-matched tumour-child with wild-type p53 protein receiving craniospinal irradiation for medulloblastoma. Blood samples were analysed directly after the first fraction (induction), as well as 24h after 1x, 5x, 10x, 15x and 20x fractions. To evaluate the long-term effects of DNA-damaging irradiation foci levels were also measured 1, 2, 3 and 4 months after the completion of RT. To analyze G1 arrest and apoptosis following radiation-induced DNA damage p53-deficient lymphocytes from the LFS patient were analyzed by FACs after *ex-vivo* irradiation with 2Gy. To investigate the role of TP53 status on radiation-induced genomic instability, chromosome aberrations were studied by mFISH 6 months after RT in comparison to his non-irradiated sister (TP53 mutation carrier).

Results: Although, the DNA repair capacity was not impaired, blood lymphocytes of the LFS patient revealed a significant accumulation of persisting DNA damage foci during and even several months after RT. For the LFS patient the frequency of chromosome aberrations was about 80% with high amounts of complex rearrangements. But also the p53-deficient sister, not exposed to DNA damaging cancer treatment, revealed a remarkable amount of spontaneous chromosomal imbalances compared to healthy individuals.

Conclusion: Functional p53 is well known to induce cell cycle arrest and apoptosis to block aberrant cell growth. Our results indicate that individuals with altered TP53 status develop progressive genomic instability during fractionated RT, due to the failure of radiation-induced DNA damage to trigger apoptosis or permanent cell cycle arrest during hematopoiesis. This extreme sensitivity of p53-deficient cells to DNA damage should be considered for the cancer treatment of LFS patients, to reduce the risk of secondary radiation-induced malignancies.

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