Radiation Biology and DNA Repair - Löbrich Laboratory

The main focus of our current and intended research projects is on the elucidation of the mechanisms of DNA double-strand break (DSB) repair following ionising irradiation. We employ cellular and molecular approaches to identify factors and pathways involved in the sensing and processing of DSBs induced by ionising radiation and other destructive agents. The work is important for the application of radiation and chemical compounds in the clinic for treating malignant diseases as well as for estimating the risk of radiation exposure in natural settings and in the clinic. Mechanistic studies of DNA repair processes have, of course, implications which go beyond radiobiological questions and lie at the heart of cancer research. In particular the elucidation of the cellular and molecular pathways responding to DNA breaks will help to understand the process of carcinogenesis.

Studies on the biological effectivness of space radiation in low earth orbit

The mechanisms underlying the carcinogenic risk of low doses of ionising radiation are poorly understood. Moreover, the quantitative risk level associated with exposure to space radiation is insufficiently defined. The objectives of this research project involve an assessment of the effects of space radiation by analysing the induction and repair of DSBs, genetic lesions believed to represent the most critical damages generated by ionising radiation.

The repair of DSBs after high-LET exposure

The aim of this project is to investigate the repair of DSBs induced by high-LET radiation in human cells. The experiments are performed at the GSI facilities in Darmstadt. It has been known for several years that high-LET-induced DSBs are generally more slowly repaired than breaks induced by X- or γ-rays. Moreover, the level of residual DSBs after prolonged repair incubation appears to correlate with the cell killing capacity of a given radiation quality over a substantial LET range. It is, therefore, important to understand the basis of the compromised DSB repair kinetics of high-LET radiations.

Mechanisms involved in the response to DSBs

We were recently able to quantify the contribution of homologous recombination and non-homologous end joining for the repair of DSBs in defined cell cycle phases, and thereby provided a quantitative evaluation of the two major repair pathways for the repair of individual breaks that are produced in mammalian cells by DNA-damaging agents. We have also recently shown that cells from individuals with the neuro-degenerative and cancer-prone disease ataxia telangiectasia (AT) have a DSB rejoining defect after low doses used to monitor survival, and we have provided evidence that this DSB repair defect underlies the radiosensitivity of AT cells and cells from other patients with chromosomal instability syndromes. The current focus of this research direction lies in the molecular characterisation of the DSB repair defect in AT cells.

Clinical applications of the knowledge gained from DSB response studies

While DSB repair studies have hitherto been restricted to human cells in culture, immuno fluorescence microscopy offers the intriguing possibility to follow the repair process in humans. We have extended the methodological approach from cell culture systems to peripheral blood lymphocytes and were able to detect DSBs in humans that were exposed to diagnostic and therapeutic X-ray doses. This approach has allowed us to assess the extent of DNA damage after various time points following radiation exposure of individuals and, therefore, to quantify DSB repair processes in vivo.