induced apoptosis for example of endothelial cells or bone marrow stem cells is clinically relevant as initiating step for normal tissue damage after radiotherapy.

We have established several gene-therapeutic approaches to suppress radiation induced apoptosis by overexpression of super-oxide dismutase (SOD) and P-glycoprotein (P-gp) the product of the multi-drug resistance gene (MDR). Clonogenic assays showed that radioresistance can be induced in normal tissue cells (e.g. human primary lung fibroblasts), whereas the survival of human tumor cells (e.g. HeLa) after radiotherapy is not altered. Using differential gene expression analysis and quantitative real-time PCR, we showed up-regulation of detoxification genes and down-regulation of pro-apoptotic genes (e.g. CASP1, CASP4).

Targeting the apoptotic pathway to induce radioresistance in normal tissue cells is a potential strategy to increase the therapeutic index in radiation oncology.

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S42. CHALLENGES IN DEFINING GENETIC RISKS FOR FAMILIAL COLORECTAL CANCER

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Twenty to twenty-five percent of all cases of colorectal cancer (CRC) show some familiarity. Although the role of genes is not yet completely understood, a number of well-defined genetic disease entities is known to contribute to the familiarity: Lynch syndrome (formerly hereditary nonpolyposis colorectal cancer, HNPCC), familial adenomatous polyposis (FAP), MYH-associated polyposis (MAP), juvenile polyposis, Peutz–Jeghers syndrome. The most common genetic form of CRC is Lynch syndrome that is responsible for 2–3% of all cases. The analysis of these diseases led to valuable insights into the disease process also of the sporadic forms of CRC.

We need a filter system within the public health care system that allows the detection of families with an increased genetic risk. Individuals belonging to such families should first undergo genetic counselling. Genetic analysis can largely differentiate between the risks. Persons at increased risk should be included in a risk-adapted screening programme. Only specialized centers for inherited CRC will be able to efficiently organize programs of CRC prevention.

The ongoing collaborative study of the German Cancer Aid will give clear data as to the efficacy of systematic cancer prevention in Lynch syndrome through early detection, particularly through colonoscopy and gynecological examinations.

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S43. MOLECULAR DIAGNOSIS OF HEREDITARY COLORECTAL CANCERS

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Hereditary colorectal cancer accounts for up to 5% of all colorectal cancers. A variety of known and unknown genes are responsible for the two known phenotypes. Familial adenomatous polyposis coli (FAP) is phenotypically characterized by hundreds or even thousands of polyps in the colon and rectum and by a very high incidence of colorectal cancer at young age. FAP is caused by the tumour suppressor gene *APC* and is a highly penetrant autosomal condition, while the phenotypically similar *MUTYH*-associated polyposis is an autosomal recessive disease.

The much more frequent hereditary non-polyposis colorectal cancer syndrome (HNPCC) is caused by mutations in five mismatch repair (MMR) genes. Although no clear-cut genotype/phenotype correlations in pathogenic mutations carriers of the same MMR gene have been identified, distinct phenotypic differences are associated with mutations in different MMR genes. The mode of inheritance of HNPCC is autosomal dominant, yet a small but increasing number of very young patients have been reported as carriers of biallelic MMR gene mutations. Notably, their phenotype is different from the HNPCC phenotype and resembles the phenotype of MMR gene knockout mice. In addition to an incomplete penetrance of about 80% for colorectal cancers, and susceptibility to a wide range of tumours, the age of onset of HNPCC varies widely, ranging from 16 to 90 years. We have identified additional genetic factors located in *p53* and *RNASEL* that influence age of disease onset in HNPCC patients carrying a pathogenic MMR germline mutation.

In conclusion, mutations in a variety of genes can cause hereditary colorectal cancer. In addition to genetic heterogeneity, there is evidence for multiple genetic factors that contribute to the development of disease. Identification of causative genetic and environmental factors may contribute to a more detailed tumour risk assessment in carriers of mutations in MMR genes. Particularly, the knowledge of the age of onset of disease in carriers of pathogenic germline mutations in MMR genes might affect preventive strategies, including age at first surveillance, surveillance intervals, and age at preventive surgery.

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S44. EGFR-SIGNALLING IN COLON CANCER

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Activation of the epidermal growth factor receptor (EGFR) pathway seems to be involved in the regulation of proliferation and invasion in gastrointestinal tumors. In colon cancer increased EGFR levels were reported in advanced and more invasive carcinomas. Recently EGFR-inhibitors are used as a new treatment option in patients not responding to standard chemotherapy. However, EGFR-signalling is dependent on the presence of various EGFR ligands and mechanisms of ligand presentation. In addition several other mechanisms involved in the regulation of EGFR binding have been reported (PKC, Syk, Mig6, SIRPs). Furthermore costimulatory effects between other G-protein coupled receptor (GPCR) were shown to increase tumor cell proliferation.