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.

Therefore, EGFR signalling in colon cancer is modulated at the level of receptor capacity, receptor heterodimerization, regulation of intracellular tyrosine kinase activity, ligand presentation and by other costimulatory receptor pathways. These mechanisms have to be considered when therapeutic strategies using EGFR-inhibition are evaluated.

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S45. THERAPEUTIC DECISIONS FROM MOLECULAR STAGING IN COLORECTAL CANCER

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Colorectal cancer is one of the most prevalent cancers worldwide. Whereas surgery is the basis of therapy, chemo- and/or radiotherapy are used frequently to reduce local and distant recurrences. Many prognostic factors have been defined, with only the UICC classification being relevant for therapeutic decisions at present. The prognosis for an individual patient, however, still cannot be sufficiently predicted. Therefore, many patients will receive radio-/chemotherapy that do not benefit from this treatment. Other patients might not receive radio-/chemotherapy as they are judged to be at a low risk for recurrence, but will develop recurrent disease. Better prognostic factors are therefore needed, in order to individualize the therapeutic strategy. As recurrences after complete tumor removal are most likely caused by disseminated tumor cells, it seems to be a logical approach to develop methods to detect these cells. Ideally, patients in whom tumor cells can be detected should have a worse prognosis and should therefore benefit from adjuvant therapeutic strategies. The effect of this therapy should then become apparent by a reduced detection rate of disseminated tumor cells. Even though some studies demonstrate a prognostic relevance of disseminated tumor cells, the prognostic relevance of these cells is not generally accepted. Due to the heterogeneity of disseminated tumor cells, demonstration of the mere presence of these cells will most likely not be an adequate basis for therapeutic decisions. Molecular characterization of disseminated tumor cells and/or of the primary tumor might be a more successful approach in this respect. The clinical relevance of molecular staging for therapeutic decisions, however, has still to be proven in well designed clinical trials.

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S46. ANTI-TUMOUR POTENTIAL OF ZOLEDRONIC ACID (Zometa®)

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Bisphosphonates have been used extensively for more than 3 decades to inhibit osteoclastic activity in a variety of benign and malignant diseases characterized by increased bone resorption. Due to the bisphosphonate moiety, these compounds bind avidly to bone mineral and accumulate at sites of active bone turnover. During bone resorption they are released and ingested by osteoclasts via fluid-phase endocytosis. The nitrogen-containing bisphosphonates (N-BPs) inhibit a key intracellular enzyme in the mevalonate pathway, farnesyl pyrophosphate synthase, thereby reducing prenylation of small GTPase signalling proteins that are essential for osteoclast function and survival. Consequently, bone resorption is impaired and osteoclast apoptosis is induced.

Zoledronic acid (Zometa®) is a novel compound which retains the bisphosphonate "bone hook" and possesses a heterocyclic imidazole substituent containing 2 nitrogen atoms. X-ray crystallography studies with human farnesyl pyrophosphate synthase have shown that the zoledronic acid molecule binds with high affinity to the active site of the enzyme and induces an irreversible conformational change that prevents further access of substrate. Structure-activity studies with more than 300 novel compounds identified zoledronic acid as the lead candidate for clinical development due to its outstanding potency as an inhibitor of osteoclastic bone resorption both in vitro and in vivo, and its excellent in vivo tolerability.

In animal models of breast cancer, prostate cancer, osteosarcoma and haematological malignancies such as multiple myeloma and leukaemia, low doses of zoledronic acid markedly inhibit osteoclastic activity and thus reduce tumour-induced osteolysis and hypercalcaemia. Bone is a rich source of growth factors which are released during bone resorption and can stimulate tumour cell proliferation. By inhibiting osteoclastic activity, zoledronic acid reduces the release of tumour growth factors from bone and thus interrupts this stimulatory cycle. Furthermore, the high local concentration of bisphosphonate at an osteolytic site may exert direct cytostatic and apoptotic effects on the tumour cells in a bone metastasis. Extensive in vitro data show that zoledronic acid is cytostatic and pro-apoptotic against a variety of human tumour cell lines. Interestingly, zoledronic acid enhances the efficacy of some cytotoxic drugs in a synergistic manner, especially when the drugs are administered sequentially rather than concomitantly. Apart from these direct effects on tumour cell proliferation and viability, N-BPs also impair the metastatic behaviour of tumour cells and modulate the host's response to neoplastic disease. In vitro, zoledronic acid potently inhibits tumour cell invasion through extracellular matrix, decreases cell adhesion to both mineralized and non-mineralized matrices, and disrupts soft tissue angiogenesis. Preclinical data from a variety of animal tumour models demonstrate that, in vivo, these effects translate into reduced tumour load, increased tumour cell apoptosis, and in some cases delayed disease progression with a corresponding survival benefit. Although these effects have been predominantly observed in models of bone metastases in nude mice, emerging data indicate that zoledronic acid can also inhibit the growth of primary soft tissue tumours in transgenic animals by a mechanism that apparently involves inhibition of angiogenesis and disrupted macrophage function.

Recently, another intriguing facet has been added to the pharmacological profile of the N-BPs. It has been known for many years that these compounds interact with the immune system to produce an acute phase response in a significant proportion of patients, especially when administered intravenously, but the molecular mechanism remained elusive. It is now known that this effect is caused by inhibition of farnesyl pyrophosphate synthase in monocytes, leading to accumulation of upstream metab-