with suicide genes will need procedures for therapy planning and monitoring. Finally, new biomolecules will be developed by bioengineering methods which may be used for isotope-based diagnosis and treatment of disease.

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S21. CURRENT STATUS ON MOLECULAR MARKERS AND TARGETS IN PANCREATIC DISEASE

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With an overall 5-year survival rate of approximately 4%, pancreatic ductal adenocarcinoma is one of the most aggressive human malignancies. Studies that aimed at the understanding of this exceptionally aggressive behavior discovered an increasing number of genetic and epigenetic alterations such as deregulated growth factor receptor/ligand systems, oncogenes, tumor suppressors, metastasis suppressors and related signal transduction pathways. Alterations of these genes and their respective proteins may occur throughout pancreatic carcinogenesis suggesting an adenoma-carcinoma model with an increasing number of molecular and cellular alterations. The most commonly mutated oncogene in pancreatic cancer is K-ras which induces cell proliferation via MAPK signaling. On the other hand, mutations in tumor suppressors such as p53, p16 and Smad4 also occur frequently. Besides, there are less common mutations in the tumor suppressor genes STK11, APC, FHIT, DCC, ARP, BRCA2, MKK4, TβR-I and TβR-II. Epigenetic alterations in growth promoting signaling pathways of the EGF, IGF and FGF family as well as autocrine or paracrine effects of their respective ligands have been shown to endow a growth advantage to pancreatic cancer cells. Concomitantly, it was shown that the important growth inhibitory pathway mediated by TGF-beta family members and their intracellular signal transduction molecules is lost in pancreatic cancer. Resistance to apoptotic cell death gives cancer cells a further growth advantage with downregulation of pro-apoptotic factors such as bak and bcl-2 or upregulation of anti-apoptotic bcl-X_L. Furthermore, aberrant expression of genes influencing invasion and metastasis is observed. Among those, heparanase, matrix metalloproteinases and galectins have been shown to mainly influence invasion while decreased expression of the metastasis suppressor KAI1 was associated with worse survival and an increased metastatic potential.

Identified alterations of signal transduction pathways can be used clinically as therapeutic targets, e.g. small-molecule tyrosine kinase inhibitors and other approaches show encouraging results in first clinical trials.

Thus, a translational research approach will be a promising way to slow down tumor progression and improve survival and quality of life of pancreatic cancer patients in the future.

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S22. NEW KEY MARKERS AND THERAPEUTIC SUBGROUPS IN BREAST CANCER RESULTING FROM MOLECULAR STAGING

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In breast cancer, tumor biological markers are urgently needed to individualize clinical decision making, particularly in order to avoid overtreatment in the increasing number of patients with small tumors. Urokinase-type plasminogen activator uPA and its inhibitor PAI-1 are the first novel markers validated at the highest level of evidence for their prognostic and predictive impact by a multicenter therapy trial (Chemo N_0) and a large EORTC-RBG pooled analysis. Their greatest clinical use so far is in node-negative (N_0) breast cancer where the test can be used to avoid adjuvant chemotherapy in patients with non-aggressive disease. In addition, in intermediate-risk patients as defined by the St. Gallen consensus, the test can be used to identify patients who should receive chemotherapy because their tumor has a more aggressive biology than classical pathological factors would otherwise lead to believe. The NNBC3 therapy trial (AGO, GBG, and EORTC PBG), which has already recruited almost 700 patients, compares risk assessment by uPA/PAI-1 to that by established prognostic factors and evaluates optimization of chemotherapy (FEC vs. FEC-DOC) in high-risk N0 patients. Other promising markers include methylation markers such as PITX2 for identification of patients with good outcome under adjuvant endocrine therapy, microarray signatures or multi-gene scores for risk group stratification. In addition to NNBC3, other large international therapy trials in N_0 breast cancer using gene signatures for risk group stratification will soon start recruitment. The current and future challenge is to integrate the most promising tumor biological factors into advanced decision support algorithms.

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S23. DNA-METHYLATION MARKERS AND YB-1 AS INDICATORS OF THERAPY RESPONSE IN BREAST CANCER

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Intrinsic or acquired resistance to chemotherapy is responsible for failure of current treatment regimens in breast cancer. For instance, transcription factor YB-1 regulates expression of P-glycoprotein gene *mdr*1 which plays a major role in the development of a multidrug-resistant tumor phenotype. High YB-1 protein expression in tumor tissue and surrounding benign epithelial cells is significantly associated with poor outcome in patients who received postoperative chemotherapy, indicating clinical drug resistance. Furthermore, in untreated patients, those with low YB-1 protein expression are still free of disease, whereas the 5-year relapse rate in those with elevated YB-1 is 30%.

DNA methylation in the promoter regions of genes is a prominent epigenetic gene silencing mechanism associated with resistance to endocrine therapy in patients with recurrent breast cancer. We have employed a microarray-based technology to investigate the promoter DNA methylation status of 117 candidate genes in tumors of breast cancer patients who received tamoxifen as first-line endocrine treatment for recurrent breast cancer. Of the genes analyzed, phosphoserine aminotransferase (PSA-T1) emerged as the strongest marker to predict progression-free survival. Among the 117 candidate genes, DNA-methylation markers associated with breast cancer patient outcome after adjuvant endocrine therapy were also identified and validated in independent groups of patients. DNA-methylation status of PITX2 showed the strongest correlation with disease recurrence. These results provide validated high-level evidence that DNA-methylation status allows clinically relevant risk assessment in tamoxifen-treated breast cancer, both in the adjuvant and palliative setting.

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S24. MOLECULAR PATHOGENESIS OF PAPILLOMA VIRUS ASSOCIATED CANCERS

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A number of human cancers are caused by persistent infections with high risk human papilloma viruses (HR-HPV), among them about 100% of cervical cancers, many anogenital cancers, some head and neck cancers, and a subset of skin cancers. HPVs infect basal epithelial cells via microlesions and usually replicate in differentiated superficial epithelial cells. Two HPV oncogenes, E6 and E7, interfere with the hosts cell cycle and apoptosis regulation. Most importantly, E7 disrupts the binding of pRb and E2F and induces continuous cell cycle activation. E6 triggers degradation of p53 and thus abrogates apopotosis. Local immune defense mechanisms lead to spontaneous clearance of HPV infections in the majority of cases. In few infections, however, deregulated expression of E6 and E7 in basal epithelial cells induces major chromosomal instability and can initiate epithelial transformation. Several characteristic changes have been identified in epithelial cells transformed by HPV: Strong p16INK4a expression was found in medium to high grade premalignant lesions as well as in cervical cancer indicating the functional inactivation of pRb. Proliferation associated markers like ki67, telomerase, MCM5 and CDC6 are expressed at various levels in premalignant lesions and invasive cancer. In advanced lesions, high levels of chromosomal imbalances can be observed, a very specific alteration is the gain of 3q. Integration of HPV DNA into the host cell genome specifically indicates advanced lesions with a high probability of progression and is frequently found in cervical cancer. Several biomarkers, especially the detection of HR-HPV DNA and p16INK4a protein, are currently being evaluated in order to improve existing cervical cancer screening procedures.

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S25. DEVELOPING STRATEGIES FOR TUMOR VACCINATION

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Vaccination against cancer has had a variable history, with claims of success often fading into disappointment. The reasons for this include poor vaccine design, inadequate understanding of the nature of the immune response, and a lack of objective measures to evaluate performance. The characterization of tumor-associated antigens (TAAs) recognized by human T lymphocytes in a MHC-restricted fashion has opened new possibilities for specific vaccine approaches to the treatment of human cancers. Recent findings include vaccine formulation, relevant knowledge concerning mechanisms of induction of effective immunity from preclinical models, and translation into clinical trials. We now have novel vaccine strategies to activate specific attack on tumor cells and we understand more about activation and regulation of immunity against cancer (co-stimulation versus co-inhibition, regulatory T cells). We also have modern assays using surrogate markers (MHC multimer analysis, IFN-γ Elispot assay) to correlate with clinical effects. Although early clinical vaccine trials based on synthetic peptides, proteins, 'naked' DNA, tumor-RNA, dendritic cells, and recombinant vaccinia viruses indicate that vaccines can induce immune responses and tumor regression in some cancer patients, careful study design and use of standardized clinical and immunological criteria are needed. Basic principles of tumor vaccination and clinical trials will be discussed.

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S26. TARGETING MUC1 WITH LIPOSOMAL BLP25

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MUC1 is a mucin glycoprotein expressed by both normal cells and a wide variety of epithelial carcinomas. Mucins expressed by cancer cells have abnormal glycosylation that results in shorter and simpler carbohydrate chains as well as exposure of normally hidden (cryptic) epitopes on the protein backbone. These changes result in unique antigenicity of cancer cell mucins relative to their normal cell counterparts and make MUC1 an ideal candidate antigen for immunotherapy.

L-BLP25 vaccine is an investigational therapeutic cancer vaccine being studied for the treatment of epithelial carcinomas. L-BLP25 vaccine incorporates a synthetic lipopeptide sequence identical to a portion of the protein backbone of MUC1. The vaccine is a liposomal formulation that consists of the synthetic MUC1 lipopeptide, an immunoadjuvant [monophosphoryl lipid A (MPL)], and three lipids: cholesterol, dimyristoyl phosphatidylglycerol (DMPG) and dipalmitoyl phosphatidylcholine (DPPC). The BLP25 lipopeptide provides the antigenic specificity for a T-cell immune response, while the adjuvant serves to TLR4 to activate APCs. The liposomal delivery system is thought to ensure delivery of peptide antigen and adjuvant to the exact same cell as well as facilitate access to the intracellular antigen presenting machinery of a cell.