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%.