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.