processing and cell surface expression. Since development and progression of tumors is not only dependent on cancer cells themselves but also on the active contribution of the stromal cells, e.g. by secreting growth supporting factors, enzymes degrading the extracellular matrix or angiogenic factors, the tumor stroma may also serve as a target for immune intervention. To this end several antigens have been identified which are induced or upregulated on the tumor stroma. Tumor stroma-associated antigens are characterized by an otherwise restricted expression pattern, particularly with respect to differentiated tissues, and they have been successfully targeted by passive and active immunotherapy in preclinical models. Moreover, some of these strategies have already been translated into clinical trials.

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S33. MOLECULAR PHENOTYPING OF MINIMAL RESIDUAL DISEASE IN SOLID CANCER – DEFINING THE MARKERS FOR TUMOR PROGRESSION?

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Metastasis is the major cause of deaths in patients with solid tumors. Occult micrometastatic spread of tumor cells might be the seed for the occurrence of overt metastases in distant organs within the years following successful surgical resection of the primary tumor. The two major approaches to detect such "minimal residual disease" are immunocytochemical staining and polymerase chain reaction analysis. These assays are sensitive enough to detect a single disseminated tumor cell (DTC) in the background of millions of normal cells [Pantel and Brakenhoff. *Nat Rev Cancer* 2004;**4**:1–9]. For epithelial tumors, cytokeratins have become the best marker for the immunocytochemical detection of DTCs in blood, lymph nodes and bone marrow (BM).

Micrometastatic cells in BM can be easily collected from the iliac crest, and BM seems to be a common homing organ for DTCs derived from various types of malignant epithelial tumors (e.g., breast, lung, prostate or colorectal cancer). DTCs are present in BM samples of 20–40% of patients even in the absence of lymph node metastases (stage N0) or clinical signs of overt distant metastases (stage M0). A pooled analysis on 4703 breast cancer patients [Braun et al., *NEJM* 2005;**353**:793–802] has shown that the detection of DTC in BM is a marker for an increased risk to develop metastatic relapse. The molecular and biochemical characterization of DTCs helps to identify progression markers towards overt metastases and new therapeutic targets for therapies that are specifically directed against minimal residual disease. This information may refine the current DTC detection approaches, which the major goal of the EU-funded consortium "DISMAL" coordinated by K.P.

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S34. TARGETING Plk1 FOR CANCER THERAPY

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A stringent control of mitosis is mandatory to warrant the accurate segregation of sister chromatids in dividing cells. Eukaryotic cells have evolved sophisticated mechanisms to monitor faithful progression through each phase of mitosis in order to prevent the occurrence of aneuploid daughter cells. Polo like kinase 1 (Plk1) has been identified to be a key player for G2-M transition and mitotic progression in both, normal and tumor cells. Multiple essential roles have been assigned to Plk1 at the entry into M-phase, mitotic spindle formation, condensation and separation of chromosomes, exit from mitosis by activation of the anaphase-promoting complex and in cytokinesis.

We have employed chimeric antisense oligonucleotides and siRNA to investigate the molecular alterations after targeted interference with Plk1 in a multitude of human cancer cells. Suppression of Plk1 mRNA inevitably resulted in a dramatic increase of the mitotic index followed by the onset of apoptosis. Mitotically arrested cells displayed randomly separated condensed chromosomes and the occurrence of multiple spindle poles with well-formed asters. Induction of apoptosis was strictly dependent on cell cycle progression: Genetically engineered RKO human colon adenocarcinoma cells with inducible expression of the cdk inhibitor p27Kip1 were completely refractory to Plk1 depletion-induced apoptosis when they were arrested in the G1 phase of the cell cycle. Various mitotic markers including MPM-2, cdc25c, cyclinB1, or phospho-histone H3 were investigated to explore the molecular consequences of Plk1 depletion. While most marker proteins only showed alterations typical for mitosis, modifications of cdc25c allowed distinction between mitotic targeting via Plk1 or via other mechanisms, such as microtubule inhibitors. cdc25c was fully phosphorylated solely in paclitaxel-treated cells, while it was only partially phosphorylated in Plk1 depleted cells despite the fact that both treatments caused a profound mitotic arrest. This differential phosphorylation of cdc25c was used to test whether a pharmacological inhibitor of Plk1 kinase activity would exert the same cellular effects as interference with Plk1 on an mRNA level. In deed, pharmacological intervention with Plk1 using a specific Plk1 kinase inhibitor induced exactly the same molecular alterations and displayed the cell cycle-dependent cytotoxicity as Plk1 interference on an mRNA level. Taken together, these data substantiate the attractiveness of Plk1 as candidate for mitotic targeting of cancers.

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S35. REGULATION OF UCN-01 INDUCED MITOTIC CELL DEATH BY PRO- AND ANTI-APOPTOTIC PATHWAYS

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