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?

Klaus Pantel. *Institut für Tumorbiologie, Universitätsklinikum Hamburg-Eppendorf, Germany.*

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

Mathias Schmidt, Hans-Peter Hofmann, Karl Sanders, Volker Gekeler, Thomas Beckers. *Altana Pharma AG, Therapeutic Area Oncology, Byk-Gulden Str. 1, D-78467 Konstanz, Germany.*

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

Celia Vogel, Christian Hager, Holger Bastians. *Philipps University Marburg, Institute for Molecular Biology and Tumor Research (IMT), Marburg, Germany.*

The concept of "G2 checkpoint abrogation" in combination with various chemotherapeutic drugs is currently successfully explored in clinical trials. The anti-cancer drug UCN-01 allows the entry into mitosis in the presence of DNA damage selectively in p53 defective tumor cells.

We show here that this leads to a mitotic arrest and to the activation of a branch of the mitotic spindle checkpoint that monitors the lack of tension across kinetochores involving the function of Mad2, Bub1, BubR1, Mps1, Aurora B and survivin. Subsequently mitotic cell death, also known as "mitotic catastrophe", is induced, which potentiates the efficacy of standard chemotherapy. Interestingly, mitotic cell death is associated with the activation of the mitochondria associated apoptosis pathway, thus, we refer to it as mitotic apoptosis. Importantly, while the mitotic arrest in response to UCN-01 is dependent on the spindle checkpoint, only the checkpoint component Mad2 is required for the execution of mitotic apoptosis suggesting that Mad2 might have an additional function as a pro-apoptotic protein. Significantly, the mitotic apoptosis is counteracted by a survivin dependent survival pathway. Thus, the mitotic apoptosis is a result of a balance between pro- and anti-apoptotic pathways. Most importantly, pharmacologiocal interference with Aurora B, CDK1 or PI3-kinase modulating the levels of survivin leads to a significant increase of apoptosis in response to UCN-01. Thus, our results suggest a highly improved strategy for anti-cancer treatment using UCN-01 and abrogators of a mitotic survivin dependent survivial pathway without neglecting the selectivity of UCN-01 for p53 defective cancer cells.

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S36. VIRAL ONCOGENES CAUSING HUMAN CANCERS

Harald zur Hausen. *Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany.*

Research of the past 25 years resulted in the identification of a number of infectious agents engaged in the etiology of in part very common human cancers. Among the latter are cervical cancer and hepatocellular carcinomas. Members of several different virus families possess oncogenic potential: these are papillomaviruses (e.g. HPV 16 and 18), herpes group viruses (Epstein-Barr virus and human herpesvirus type 8), Hepatitis B and Hepatitis C virus, Human T-lymphotropic retrovirus type 1 (HTLV-1). Most of these agents contain oncogenes and act as "direct carcinogens". The functions of these oncogenes have been partially characterized and will be discussed. Humans and their cells infected by these viruses are commonly able to cope with these infections by intra- and intercellular surveillance mechanisms or by immunological interference. Cancer development requires a modification of genes within the signalling pathways regulating the intra- and intercellular defense. Part of the modifications of cellular genes is also mediated by viral oncogenes.

Besides direct carcinogenic functions via oncogenes, other agents contribute to human cancer by rather indirect modes. This seems to be the case in hepatitis B and C infections where the induction of oxygen radicals apparently plays a significant role in cancer induction. Human immunodeficiency viruses (HIV) promote cancer induction by other viruses due to the induction of immunosuppression. Possible other mechanisms of indirect carcinogenesis by infectious agents will also be discussed.

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S37. ONCOPROTECTIVE PARVOVIRUSES IN CANCER THERAPY

Jean Rommelaere. *Deutsches Krebsforschungszentrum, Abt. F010 and INSERM U701, Heidelberg, Germany.*

As a result of their oncotropism, oncolytic effect and low inflammatory activity, some autonomous parvoviruses open up new prospects to the fight against cancer and were tested for their safety in pilot phase I clinical trials. Preclinical studies in animal models showed that the parvoviruses H-1PV and MVM are endowed with a genuine oncosuppressive capacity, for which various tumours can be targets. However, the antineoplastic potential of these agents is insufficient, in many instances, for tumours to irreversibly regress. Efforts are thus made to improve the oncosuppressive activity of parvoviruses, using different strategies. On the one hand, discrete modifications are introduced into the parvoviral genome so as to keep its infectiousness while stimulating its antineoplastic properties. Parvovirus mutants were engineered so that their capacity for tumour cell lysis or immune cell activation is enhanced. On the other hand, parvoviruses are used as vectors to generate recombinants that are able to deliver therapeutic transgenes in target cells. MVM and H-1PV-based vectors transducing and expressing anti-angiogenic and/or immunomodulating factors were more particularly produced. Appropriate combinations of these recombinant vectors were found to efficiently suppress highly vascularised tumours, e.g. gliomas, in animal models. On the basis of these data, the promise of the application of parvoviruses to cancer viro- and gene therapy will be discussed.

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S38. PROPHYLACTIC VACCINES AGAINST CERVICAL CANCER

Lutz Gissmann. *DKFZ, Heidelberg, Germany.*

Since several years it has been accepted that persistent infection with certain (so called-high risk: HR) types of Human papillomaviruses (HPV) represents a strong risk factor for cervical cancer. The most frequent HR HPV types 16 and 18 account for about 70% of this tumour, which is the second most frequent malignancy in women worldwide. Several studies in animal papillomavirus models revealed that protection against infection is conferred by neutralizing antibodies directed against conformational epitopes of the major structural protein L1. Such antibodies can most efficiently be induced by immunization with virus-like particles (VLP) that assemble spontaneously following expression of L1 in recombinant vectors. Large-scale production of HPV 16 and 18 VLPs proved to be successful facilitating, a few