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

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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

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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

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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