antigen, staphylococcal enterotoxin A. This agent is capable of inducing exceedingly potent superantigen-dependent cellular cytotoxicity mediated by T-cells. Phase I trials designed to define the optimal dose and schedule of administration are in progress; multiple variables contribute to the identification of the proper dose for each patient. These new strategies are examples of contemporary approaches to antibody-promoted induction of cellular immunity.

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Targeted cytokine delivery with recombinant antibody fusion proteins for therapeutic intervention

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Purpose: A major goal of tumor immunotherapy is a cell-mediated antitumor response effective in eradicating disseminated metastasis followed by a persistent tumor protective immunity. We tested the hypothesis that this can be achieved by targeted cytokine therapy with genetically engineered antibody fusion proteins.

Methods: Syngeneic animal models of murine melanoma, neuroblastoma and colon carcinoma were established and treated with tumor specific recombinant antibody cytokine fusion proteins compared to mixtures of antibody and cytokine at equivalent dose levels.

Results: We demonstrate that the fusion proteins can eradicate experimental and spontaneous metastases and prolong the animals' life span in contrast to equivalent mixtures of antibody and cytokine. Effector mechanisms involved included natural killer cell mediated tumor cell eradication and CD8+ T-cell responses. This was demonstrated in vivo with immunodeficient animals and by depletions of CD8+ T cells or NK cells, followed by anti tumor cytotoxicity assays in vitro with purified T or NK cells.

Conclusion: These data demonstrate that targeted delivery of cytokines to the tumor microenvironement offers a new strategy to elicit an effective cellular immune response against metastasized tumors.

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Radiation induced anomalies in control of signal transduction in Ataxia telangiectasia and Fanconi anemia

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Ataxia telagiectasia (AT) and Fanconi anemia (FA) are recessive genetic diseases featuring increased predisposition to cancer, chromosomal instability and hypersensitivity to DNA damaging agents. In both syndromes, altered induction of the tumor suppressor protein p53 as well as that of p53-target genes (bax, gadd45 and wafl) after gamma-irradiation is observed. Moreover cells from AT and Fa display a deregulation of the apoptotic process spontaneously, after a gamma-rays exposure or following Fas activation. The recently observed alteration of Poly ADP ribose polymerase (PARP) and of DNA-PK cleavage might explain the altered response to ionizing radiations and suggests a deregulation of the ICE-like proteases. Our current investigation of the Bcl-2-like proteins and of the ICE-like proteases should give insights about the functions of the proteins altered in AT and FA. Our results support the contention that a) the AT and FA genes play a major role in regulating apoptosis; b) the hypersensitivity to genetoxic agents is related in both syndromes to necrosis rather than apoptosis.

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Molecular radiation biology at the clinical interface

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The last decade has been characterized by the development of an increased understanding of the role of signal transduction in carcinogenesis. We will review signal transduction models of tumor development with particular emphasis on the role of the ras oncogene in carcinogenesis and its role in signal transduction. We will also discuss the control of the cell cycle and the impact of oncogenes and tumor suppressor genes on the control of the cell cycle. Finally we will review the control of apoptosis and its integration with cell cycle control. This lecture will review the clinical evidence that radiosensitivity is a determinant of outcome in the radiotherapy of cancer and will also examine some of the methods that have been used to try to determine the impact of this factor on cancer management. We will also review the current data on the molecular mechanisms which underlie radioresistance to attempt to define targets for manipulation of radiosensitivity in the clinic. In particular we will show that the ras oncogene can be directly targeted with prenyl transferase inhibitors to sensitize human cell lines carrying naturally occurring ras mutations to the killing effects of ionizing radiation.

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Genetic determinants of radiosensitivity: Potential for therapeutic modulation

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Elucidation of the key components of the signal transduction pathways involved in the cellular response to DNA damage is fundamental to understanding mechanisms of therapeutic resistance. It is also critical to the development of novel strategies for modulation of radiosensitivity, p53 is an inducible regulator of the response to DNA damage; it is activated by DNA strand breaks, inducing G1 arrest via transcriptional regulation of the cyclin kinase inhibitor, p21. We have evaluated the role of p53 in the processing of DNA damage induced by ionising radiation in murine and human cells of defiend p53 status (wild type; knockout p53 −/−, mutant p53 expression systems) using endpoints of clonogenic survival, DNA repair, and mutability at the hprt locus.

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Pathways and time effect of radiation-induced apoptosis

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The dominant cause of radiation-induced cell death is loss of clonogenic capacity due to unrepaired DNA damage. The recent (re)emergence of apoptosis may provide an alternative to this conventional cell kill model. One of the signalling mechanisms initiated by radiation that transduces cell membrane-derived death signals to the nucleus, and does not require DNA damage as a triggering mechanism, is the sphingomyelin (SM) pathway. This pathway is initiated by hydrolysis of the plasma membrane lipid SM, generating ceramide, a potent inducer of apoptosis. We have recently shown that ceramide activates a cascade of kinases that leads to stimulation of *stress-activated protein kinase (SAPK),* a critical event in radiation-induced apoptosis. In bovine aortic endothelial cells (BAEC) radiation induced a biphasic pattern of ceramide generation and SAPK activation. The first, immediate phase of SAPK activation occurred independently of *de novo* protein synthesis, while the second, starting around 4 h, was abolished by cycloheximide. Which of both radiation-induced signals is essential to cause apoptosis, remains to be established. Recent studies have implicated an important role of the interleukin-1β-converting enzyme (ICE)-like proteases in TNF- and Fas-mediated apoptosis. CPP32 has been identified as the protease that cleaves poly (ADP-ribose) polymerase (PARP) during apoptotic DNA degradation. In BAEC, radiation-induced CPP32 cleavage products were identified around 10 h after exposure, but inhibition of this protease by the tetrapeptide DEVD did not affect radiation-induced apoptosis. Currently, studies are conducted to further evaluate the role of the ICE-like protease cascade in radiation-induced apoptosis, and to establish its relation with the ceramide-SAPK signalling pathway.

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Induced radioresistance: Possible mechanisms and impact in the clinic

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Stress responses are upregulated following exposure to radiation and other DNA-damaging agents. Therefore response may be dose-dependent so that small acute radiation exposures, or exposures at very low dose rates, are more effective per unit dose than larger exposures above a threshold where induced radioprotection is triggered. This is termed low-dose hypersensitivity (HRS) and induced radioresistance (IRR) as the dose increases. HRS/IRR has been recorded in studies with yeast, bacteria, protozoa, algae, higher plant cells, insect cells, mammalian and human cells *in vitro*, and in studies on animal models *in vivo*. There is indirect evidence that HRS/IRR in response to single doses is a manifestation of the same underlying mech-