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Basic Research

Reduced Expression of Survivin May Enhance Antitumor Therapies

Researchers from Eli Lilly and Company in Indianapolis, IN, and ISIS Pharmaceuticals in Carlsbad, CA, presented a study involving downregulation of survivin in human cancer cells. Survivin is an antiapoptosis protein found in most human cancers but not in normal adult tissues. In this study, a survivin antisense oligonucleotide (LY2181308) that inhibited production of the protein was found in lung, colon, pancreas, breast, prostate, ovary, cervix, skin, and brain cancer cells using quantitative reverse transcriptase polymerase chain reaction and Western blot analysis. It also was shown to induce caspase-3–dependent apoptosis, G2/M cell cycle arrest, and multinucleated cells. LY2181308 sensitized tumor cells to chemotherapeutic agents. In a xenograft human tumor model, it showed significant antitumor activity that was associated with inhibition of survivin expression. The researchers concluded that the preclinical data support clinical development of LY2181308 as an anticancer agent.

Inhibitor of Vascular Endothelial Growth Factor Receptor 2 Shows Antitumor Activity in Mouse Model

Many central nervous system tumors demonstrate increased activity of vascular endothelial growth factor receptor and ErbB family proteins. Therapies that target these proteins have been shown to inhibit new blood vessel formation and tumor growth. Researchers from Duke University Medical Center in Durham, NC, and AstraZeneca Pharmaceuticals, LP, in Wilmington, DE, investigated the activity of ZD6472, an orally active inhibitor of vascular endothelial growth factor receptor 2 tyrosine kinase, in athymic nude mice bearing glioblastomas, medulloblastomas, or ependymomas. Significant inhibition of tumor growth was found in all cases compared to the controls. The growth delay ranged from 10.4–25.4 days. In addition, most xenografts showed 10%–100% regression. Mild weight loss occurred. The tumors showed a decrease in the number of blood vessels, suggesting that ZD6472 had an antiangiogenic effect. The researchers concluded that ZD6472 has therapeutic potential that warrants clinical investigation.

Tumor Cell Circadian Clock Genes May Be New Therapeutic Targets

Circadian coordination of cells within organisms is regulated, in part, by the expression of a series of circadian clock genes. Optimal circadian drug delivery has been shown to possibly improve outcomes for patients with ovarian cancer, acute childhood leukemia, and metastatic colorectal cancer. Researchers from the University of South Carolina in Columbia investigated the influence of tumor cell circadian clock gene expression on cancer cell functions essential for tumor growth. In their study, 30 female C3H/FeJ/HBe mice were kept on a 12-hour light and 12-hour dark schedule. The mice were injected with syngeneic mammary tumor cells at a single time of day, and minimally invasive measurements of the tumor growth rate were made over many days. The tumor growth rate was nearly doubled during the daily activity/dark circadian phase compared to the sleep/night phase. Mice were euthanized during the diestrous or late follicular phase of their estrous cycles at one of six equispaced circadian stages (5 mice per group). Livers and tumors were examined for RNA expression of circadian clock genes. The results showed that normal liver tissue and tumor tissue from tumor-bearing mice retained circadian clock gene expression. The circadian clock gene expression pattern was similar to that in the nontumor-bearing mice. The researchers suggested that circadian clock genes may be novel anticancer targets.

Clinical Research

Molecular Marker Phenotype May Be a Prognostic Factor for Head and Neck Cancer

Researchers from the Gray Cancer Institute, Mount Vernon Hospital, and University College London, all in London, England, and the Barbara Ann Karmanos Cancer Institute in Detroit, MI, presented the results of a study examining molecular markers in head and neck squamous cell carcinomas. Patients (N = 402) were randomized into study arms receiving continuous hyperfractionated accelerated radiation therapy (CHART) or conventionally fractionated radiation therapy (CRT). Patient survival, distant metastases, local tumor control, and nodal recurrence were examined. Immunohistochemistry was used to examine tissues for the presence of Ki-67 (a marker of cell proliferation), p53 (a tumor suppressor protein), and bcl-2 (a protein involved in apoptotic pathways). In this study, cluster and Cox survival analysis permitted identification of groups of patients who responded differentially to the treatment arms. Patients with tumors that showed mostly organized Ki-67 staining, absent p53 staining, and negative bcl-2 staining had local control and survival benefit from CHART. Those who had tumors that highly expressed Ki-67 with a random pattern, absent p53 staining, and negative bcl-2 staining did not benefit from CHART. Significantly better than average response to CHART and CRT was found for patients with bcl-2–positive tumors. These patients demonstrated 67% and 68% local control, 75% and 82% metastasis-free disease, and 56% and 67% five-year survival for the CHART and CRT arms, respectively. The researchers concluded that molecular phenotypes may be useful for determining appropriate treatment for patients with head and neck cancers.

[F-18]-Fluoroestradiol Positron Emission Tomography May Predict Breast Tumor Response to Therapy

Researchers from the University of Washington in Seattle presented the results of a study of [F-18]-fluoroestradiol (FES) uptake measured by positron emission tomography (PET) for patients with recurrent or metastatic breast cancer from estrogen receptor (ER)–positive primary tumors treated with hormonal therapy. Breast tumors with high levels of ER respond to hormonal therapy, and those with low levels do not. Furthermore, recurrent tumors may have low levels of ER even though the initial tumor had high expression. Data were analyzed for 34 patients. Of these, more than 50% had received prior tamoxifen therapy. All patients had discontinued therapy for more than two months prior to the study. The participants first underwent FES PET and then were treated with hormonal therapy, primarily aromatase inhibi...