RESEARCH HIGHLIGHTS

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Basic Research

Low-Dose Cyclooxygenase-2 Inhibitor and Fish Oil Component May Reduce Risk of Colon Cancer

Studies have suggested that nonsteroidal anti-inflammatory drugs and diets rich in polyunsaturated fatty acids (PUFAs) can reduce the risk of colorectal cancer. Researchers from the Institute for Cancer Prevention, American Health Foundation–Cancer Center in Valhalla, NY, presented the results of a study of the combined effect of a cyclooxygenase-2 inhibitor, celecoxib, and an n-3 PUFA, docosahexanoic acid (DHA), which is a component of fish oil, on colon cancer cells in a cell culture. The results showed that a high dose of celecoxib (150 mcM) or DHA (300 mcM) induces apoptosis and inhibits cell proliferation. Synergy occurs at lower doses when the two agents are combined, 50–100 mcM celecoxib and 100 mcM DHA. Key molecular targets of celecoxib and DHA were suppressed at these low doses. This work suggests that the combination of celecoxib and DHA warrants further investigation in preclinical studies.

New Gene Is Associated With Breast Cancer

Researchers from the University of Rochester and Vaccinex Inc., both in Rochester, NY, have identified a novel gene, C35, that could become a target for breast cancer therapies. In a study of 35 grade II and III infiltrating ductal carcinomas, 34% expressed the protein encoded by the C35 gene as well as the HER2-neu protein known to be a marker of poor prognosis in breast tumors. Another 31% that did not express HER2-neu did have the C35 protein. All tissues that had the HER2-neu protein also had the C35 protein. When the researchers examined normal tissues, they found that the C35 protein was present at very low levels in normal breast epithelium and in the Leydig cells of the testes. They also found that they could generate specific cytotoxic lymphocytes using C35 peptides. This work suggests that C35 may be a novel target for breast cancer therapy. The cellular immune response may make C35 a suitable target for immunotherapy. Researchers also are working to develop a diagnostic test for C35 protein or antibodies in blood samples.

Clinical Research

Low-Dose Tamoxifen May Enhance Compliance in Treating Breast Cancer

A randomized trial directed by researchers at the Division of Cancer Prevention European Institute of Oncology in Milan, Italy, involved 120 women with estrogen receptor- (ER-) positive breast cancer. The study examined treatment with 1, 5, or 20 mg of tamoxifen daily for four weeks prior to surgery. The results were compared with two nonrandomized control groups: 34 women with ER-negative breast cancer and 29 women with ER-positive breast cancer. Ki-67 levels, a marker for tumor proliferation, were measured before and after tamoxifen treatment. Tamoxifen was shown to significantly reduce Ki-67 levels in the tissues, but no associated drug dose effect existed. Even though more of the drug accumulated in tumors of patients taking 20 mg tamoxifen daily, no correlated reduction in Ki-67 occurred. Because lower doses of tamoxifen are associated with a lower risk for complications such as endometrial cancer, the researchers suggest that patients may achieve maximum benefit from lower doses. On the other hand, researchers found that other disease markers were tamoxifen-dose dependent: insulin-like growth factor-1, cholesterol, triglycerides, and antithrombin III. Lower doses of tamoxifen would reduce the beneficial effects associated with these markers.

Serum Caveolin-1 May Be a Predictor of Prostate Cancer Progression

Caveolin-1 (cav-1) is important in signaling pathways, molecular transport, and cellular proliferation and differentiation. Cav-1 was shown previously to be increased in metastatic prostate cancer and to be a predictor of recurrent disease after radical prostatectomy. Researchers from Baylor College of Medicine in Houston, TX, developed a highly specific and sensitive enzyme-linked immunosorbent assay to measure cav-1 levels in serum. Serum from four groups was analyzed: group one (control) from patients with prostate-specific antigen levels below 1.5 ng/ml for two years (n = 115), group two from patients with clinical benign prostatic hyperplasia (BPH) (n = 149), group three from patients with clinically localized prostate cancer prior to radical prostatectomy (n = 119), and group four from patients with recurrent prostate cancer prior to radical prostatectomy (n = 23). The median serum cav-1 levels for group three (0.429 ng/ml) were statistically higher than those of either group one (0.214 ng/ml, p = 0.267) or group two (0.127 ng/ml, p = 0.175). No statistical difference existed in serum cav-1 levels between groups one and two. The serum cav-1 level also was shown to be a significant predictor of time to recurrence (p = 0.0074, Cox proportional hazard model). The researchers concluded that cav-1 may be an important biomarker to differentiate prostate cancer and BPH. It also may be a significant predictor of disease recurrence.

Serum IGF-1 May Predict Favorable Outcomes for Patients With Renal Cell Carcinoma

Researchers from Umea, Sweden, presented the results of a study of serum leptin, IGF-1, and prealbumin at the time of diagnosis for 256 patients with renal cell carcinoma. IGF-1 and prealbumin levels were inversely proportional to tumor stage and grade. Eighty-six patients were alive at the time of follow-up (median 61.5 months). Tumor stage and IGF-1 levels were shown by multivariate analysis to predict survival. Other variables, such as age, gender, serum leptin, and prealbumin, did not predict survival. IGF-1 levels greater than the median value of 55 ng/ml were correlated with a more favorable outcome compared to lower levels. These data suggest that IGF-1 level may be a useful prognostic indicator.

Estrogen Receptor Alpha Levels in Prostate Tissue Differ Among Men According to Ethnicity

Hispanic and Asian American men have a lower incidence and mortality rate for prostate cancer compared to African American men. The molecular mechanisms underlying this difference may involve estrogen receptor alpha. Researchers from Baylor College of Medicine in Houston, TX, and the University of California, San Francisco, used cDNA microarrays, quantitative polymerase chain reaction, and immunohistochemistry

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technologies to examine estrogen receptor alpha levels in normal prostate tissues from 200 men. Microarray analysis demonstrated the highest levels in Hispanic men, with progressively lower levels in Asian Americans, Caucasians, and African Americans. These results showed statistical significance at $p < 0.002$. The results support the hypothesis that activity of estrogen receptor alpha may be involved in reducing the prostate cancer risk in certain ethnic groups.

p300 May Be a Biomarker for Prostate Cancer Progression

Prostate tumors frequently become androgen independent, and this progression is thought to involve the androgen receptor. The transcriptional coactivator p300 interacts with the androgen receptor in androgen-dependent and androgen-independent (via interleukin-6) mechanisms. Researchers from the Mayo Clinic in Rochester, MN, showed that androgen-positive cell lines can be stimulated to proliferate by interleukin-6 and that this proliferation was halted by silencing p300. They hypothesized that prostate cancer progression may be correlated with increased levels of p300 in prostate tumor tissues. Biopsy specimens from 72 patients who subsequently received radical retropubic prostatectomy were examined for p300 expression. Cancer progression was defined as postoperative prostate-specific antigen levels greater than 0.4 ng/ml, local recurrence, or systemic progression. The mean follow-up period was 4.8 years. Increased levels of p300 were found to correlate with cancer progression following radical retropubic prostatectomy (Cox proportional hazard model, risk ratio: 1.06, $p = 0.008$). These results suggest that p300 expression may be important as a target for prostate cancer therapies and also may prove to be a marker for disease progression. A larger study with samples from 454 patients currently is under way.

Clinical Proteomics May Be Used to Monitor Drug Treatment Effects

Specific protein levels or the proteomic profile of patient tissues may permit tailoring therapies to patient tumors. Researchers from the National Cancer Institute in Bethesda, MD, presented a study of key signaling proteins (ERK, pERK, AKT, pAKT, BAD) and apoptotic proteins (caspases 2, 3, 7, and 9) in cell samples from various time points during and after treatment of patients with metastatic breast or ovarian cancer in phase II trials using Herceptin® (Genentech Inc., South San Francisco, CA), Iressa® (AstraZeneca, Wilmington, DE), or Gleevec® (Novartis, East Hanover, NJ). Laser capture microdissection was used to isolate malignant, premalignant, and normal cells from needle biopsy specimens. These were analyzed using array technology to quantify protein levels. The relative abundance of pAKT (phosphorylated) compared to AKT (unphosphorylated) was found to correlate with poor clinical outcomes. In addition, following treatment, significant differences in proteins involved in apoptosis were noted. This technology is hoped to permit early identification of responders and nonresponders and the individualization of therapies.

Epidemiologic Research

Nonsteroidal Anti-Inflammatory Drugs May Protect Against Breast Cancer

An analysis of data from the National Cancer Institute (NCI) Women's Health Initiative (WHI) Observational Study indicated that regular weekly doses of nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of breast cancer, according to researchers from Ohio State University in Columbus. The study involved 80,741 postmenopausal women, aged 50–79, with no reported history of cancer other than nonmelanoma skin cancer. Data were collected by personal interview using questions to assess the individual risk of developing breast cancer, including the use of NSAIDs such as ibuprofen or aspirin. Women taking two or more NSAIDs per week for five to nine years had a 21% reduction in risk of breast cancer. Those taking NSAIDs for more than 10 years had a 28% reduction in risk. The incidence of breast cancer in the WHI participants was similar to the risk for women over the age of 50 reported in the 1998 NCI Surveillance, Epidemiology, and End Results data (478 per 100,000).

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Clinical Research

Soy Extract May Reduce Prostate-Specific Antigen Levels in Patients With Untreated Prostate Cancer

Researchers at the University of California, Davis, Cancer Center in Sacramento studied the effects of a dietary supplement containing genistein, a soy extract, for patients with prostate cancer. Genistein is an isoflavone, a phytoestrogen or plant-derived agent that mimics estrogen effects. In this study, 62 men with biopsy-proven prostate cancer and elevated prostate-specific antigen (PSA) levels received 5 g per day of genistein-concentrated polysaccharide for six months. Sixteen of these patients were undergoing "watchful waiting," and the remaining 46 had received treatment with surgery, radiation, or hormone therapy. Watchful waiting may be recommended for men whose prostate cancer is asymptomatic. Of those undergoing watchful waiting, three stopped taking genistein because they experienced diarrhea and 13 completed the study. Of these 13 patients, 8 (62%) experienced a decline in PSA levels that averaged 3%–61%. The remaining 5 patients (38%) undergoing watchful waiting had increased PSA levels. This is compared to the men who received treatment for their prostate cancer, of whom 98% had an increase in PSA levels over the course of the study. The researchers noted that this was a small study; however, the results do suggest that a larger, placebo-controlled study may be warranted.

Basic Research

Overexpression of Id-1 Is Associated With Androgen-Independent Prostate Tumor Growth

Treatment of prostate cancer often involves androgen suppression therapy to reduce male hormone levels and shrink prostate tumors or slow their growth. Eventually, hormone suppression fails and tumors become androgen independent. The molecular mechanisms involved in the development of androgen independence must be understood to design successful therapies. Researchers in the School of Medicine at the University of California, Davis, in Sacramento used microarray technology, screening more than 12,000 genes, to identify those that may be involved in these processes. They first found 21 genes of interest in cells that also had specific mutations in p53, known to be associated with androgen independence in prostate cells. From these 21 genes, they singled out the *Id-1* gene. Additional analysis revealed that *Id-1* suppresses cell aging and promotes tumor aggressiveness.