Abstracts of Theses from the Nordic Countries

Abstracts of Nordic theses on oncologic subjects are published under this heading. The full theses are as a rule published by the universities or as supplements to different journals. They can usually be obtained after contact with the author.

Role of platelet-derived growth factor in neoplastic transformation

C. BETSHOLTZ

Department of Pathology, University Hospital, S-751 85 Uppsala, Sweden

Simian sarcoma virus (SSV) is an oncogenic primate retrovirus that arose owing to the recombination between the genome of a non-pathogenic virus and a host cellular gene. Its transforming function is provided by the transduced host gene, v-sis. The host gene itself, c-sis, was recently identified as the structural gene for one of the constituent chains of platelet-derived growth factor (PDGF), the B-chain. The product of the simian sarcoma virus (SSV) oncogene, v-sis, was partially purified from the conditioned medium of SSV-transformed marmoset cells and is shown to be immunologically and functionally related to platelet-derived growth factor (PDGF). It binds to and activates PDGF receptors and induces DNA synthesis in cultured human fibroblasts.

SSV-transformed human fibroblasts are morphologically indistinguishable from fibroblasts stimulated with PDGF. The SSV-induced phenotypical transformation is reverted by anti-PDGF antibodies or a non-specific growth factor inhibitor, suramin. Thus, SSV-transformation is likely to be a physiologic, but sustained, response to an endogenous PDGF-like growth factor, probably having the structure of a PDGF B-chain homodimer.

Human tumour cell lines are shown to synthesize and secrete a growth factor with structural and functional resemblance to PDGF. Using mRNA from one of these cell lines, a cDNA library was constructed and screened using synthetic long oligonucleotide probes directed against parts of the known PDGF A-chain sequence. Nucleotide sequence analysis of four positive clones revealed the complete PDGF A-chain precursor primary structure. Using human–mouse cell hybrids the PDGF A-chain gene is shown to be located on human chromosome 7. RNA blot analysis with ^{32}P-labelled A-chain cDNA as probe, shows expression of PDGF A-chain mRNA in a majority of human sarcoma cell lines. Many cell lines express PDGF A-chain but not B-chain mRNA, suggesting that the secreted PDGF-like growth factors in these cases are A-chain homodimers.

Human osteosarcoma cells are shown to coexpress a PDGF-like growth factor with PDGF receptors. An autocrine loop can be envisioned but does not appear to affect cellular proliferation, since this is not affected by anti-PDGF antibodies. The role of PDGF and other growth factors in neoplastic transformation is discussed.

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DNA content in renal cell carcinoma
A clinical study with special reference to tumor heterogeneity and prognosis

B. LJUNGBERG

Department of Urology and Andrology and Department of Pathology, University of Umeå, S-901 85 Umeå, Sweden

The prognosis for patients with renal cell carcinoma is difficult to predict. For other malignant tumors, predictions of prognosis have been facilitated by analysis of tumor DNA content. It seemed therefore important to investigate DNA content and its possible prognostic value in renal cell carcinoma. DNA measurements were performed retrospectively on paraffin sections or aspiration biopsy smears by static cytometry. Paraffin-embedded tissues were also analysed, after enzymatic isolation of nuclei, using flow cytometry. Prospective analyses were performed by flow cytometry of fresh tissues. Four different methods for analysis of DNA content were compared in 30 samples: flow cytometry of fresh and paraffin-embedded tissue and static cytometry on imprints and paraffin sections. Comparable results were obtained for all 4 methods ($r=0.744$–0.970, $p<0.001$). Histopathologic grade correlated with tumor DNA content. All grade 1 and 81% of grade 2 tumors were diploid. Grade 3 tumors were most common and about 50% of these were aneuploid. Eighty-three % of grade 4 tumors had an aneuploid DNA content. By analysis of 8 different samples from each of 25 tumors, a considerable heterogeneity was found in 11 of 13 non-diploid whereas 12 tumors were homogeneously diploid. Fifty-five patients without distant metastases at nephrectomy were grouped with respect to survival time. Patients surviving more than 10 years had nearly all diploid tumors (32/33) whereas all 22 patients surviving less than 4 years had aneuploid tumors. For 32 patients with distant metastases, analyzed retrospectively, the survival time was significantly correlated to the DNA content of the metastases. For their primary tumors no such correlation was found, when only one sample was analysed. In contrast, by prospective analysis of multiple samples from the primary tumors of 23 other patients with distant metastases, the DNA content gave important prognostic information. Thus, analysis of multiple samples improved the prognostic information given by the DNA content in primary tumors. The metastases were more frequently aneuploid, as compared with the primary tumors, indicating higher metastatic ability of aneuploid cell populations. Occasionally, in patients with aneuploid cell clones in the primary tumors, metastases with a diploid DNA content were found. The DNA content of the metastases provided additional prognostic information to that obtained from the primary tumors. In conclusion, tumor DNA content provides valuable prognostic information for patients with renal cell carcinoma. Since heterogeneity is common, it is necessary to analyze multiple samples to obtain the true DNA content of each primary tumor. Knowledge of DNA content in primary tumors as well as metastases provides information valuable for therapy of individual patients with renal cell carcinoma.

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Colorectal liver cancer
Resection and regional chemotherapy

H. EKBERG

Department of Surgery, University Hospital, S-221 85 Lund, Sweden

Liver resection and various modes of regional chemotherapy for colorectal liver cancer were studied with respect to survival, complications and prognostic determinants. After liver resection major complications consisted of bleeding, infection and liver failure. The hypoalbuminemia was not treated but caused no problem. The absence of hypoglucemia was attributed to preoperative loading with parenteral glucose. Early hepatic recurrence and short survival was seen in patients with 4 or more colorectal liver metastases, extrahepatic disease, and a tumour-free margin of resection of less than 10 mm. Bilateral as compared with unilateral liver metastases did not have a demonstrable survival influence but had an increased risk of early hepatic recurrence. No factor was of any help in predicting the extrahepatic recurrence seen in half of the patients and in nearly all with recurrent disease after liver resection. In patients receiving hepatic arterial infusion of 5-FU, survival was negatively influenced by a large

liver tumor volume, extrahepatic metastases, especially to the liver hilum, synchronous liver metastases, and single temporary dearterialization. Treatment morbidity was substantial, especially after combination with temporary dearterialization. Continuous intraperitoneal infusion of 5-FU via an implantable portal gave stable blood levels, low morbidity and excellent patient acceptance. These results have implications for selection of patients for liver resection, and help in designing chemotherapy trials in patients with non-resectable or resected colorectal liver secondaries.

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Polycyclic aromatic hydrocarbons in Swedish foods
Aspects on analysis, occurrence and intake

B. LARSSON

The Swedish University of Agricultural Sciences, S-750 07 Uppsala, Sweden

The aim of the present study was to investigate the occurrence of polycyclic aromatic hydrocarbons (PHA) in Swedish foods and, further, to assess the importance of different factors influencing the levels and profiles of PAH in foods. The analytical methodology currently used for the determination of PHA in foods is reviewed. Based on an interlaboratory study on PAH analysis food samples, the relative merits of capillary gas chromatography and high performance liquid chromatography for measuring PAH levels in foods are discussed. Smoked fish samples from traditional kilns showed higher PAH levels than those from modern kilns with external smoke generation. The PAH concentrations in grilled foods were strongly influenced by the mode of cooking and the type of heat source used. Extremely high levels were found in foods grilled over a burning log fire. PAH emissions from automobile traffic and an aluminium smelter were shown to influence the PAH levels and profiles in lettuce grown nearby. Washing the lettuce resulted in a substantial reduction of the PAH content. Vegetable oils not treated with activated carbon during refining showed relatively high levels of high molecular PAHs. The concentrations of PAH found in Swedish foods are generally at the lower end of the ranges reported in foods from other countries. The highest levels occur in grilled food and smoked fish, and in leafy vegetables from areas with dense industry and traffic. The average total intake of the sum of 9 PAHs (most of which are carcinogenic) via the consumption of Swedish foods was estimated to be about 1 mg, per person and year. Cereals contribute the most to the total intake, followed by vegetables and ediable fats and oils. Grilled food and smoked fish make rather small contributions, since they are minor components of the normal Swedish diet.

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Regulation of protein metabolism in tumor-host livers

M. TERNELL

The Surgical Metabolic Research Laboratory, Department of Surgery I, Sahlgrenska Sjukhuset, University of Gothenburg, S-413 45 Gothenburg, Sweden

Anorexia and increased energy expenditure both contribute to negative energy and nitrogen balance in cancer disease. In contrast to the overall catabolic state of the tumor-bearing host, the liver seems to present an anabolic condition in the sense that it remains in protein balance. This study has evaluated whether such an indication of hepatic protein balance is unique to a tumor-bearing state or rather represents a generalized response to a paraneoplastic condition, for example inflammation, possibly mediated by the release of monokines. Inbred, adult mice with a methylcholanthrene-induced sarcoma (MCG 101) were used. Hepatic transcriptional activity was measured as the maximum (Vmax) activity of DNA-dependent RNA-polymerase in isolated hepatocyte nuclei. Protein synthesis was measured by labelling of hepatic and plasma proteins following the injection of a large dose of a radioactive amino acid (flooding technique). The flooding technique has been validated in terms of quantification of the specific activities of amino acids in different pools of amino acids, including the tRNA pool for protein synthesis. The pattern of plasma protein synthesis among animal groups was determined by applying various electrophoretic techniques. RNA-polymerase activity was significantly increased in tumor-bearing animals compared with freely food controls. Hepatic protein synthesis rate in sarcoma-bearing mice was unproportionately high accounting for the degree of anorexia and malnutrition. The increased protein synthesis was in part explained by an increased synthesis of hepatic secretory proteins. Plasma protein synthesis in tumor-bearing animals was similar in magnitude and pattern to the synthesis seen in animals suffering from an acute inflammation or after administration of interleukin 1 and tumor necrosis factor. It is concluded that the alterations in plasma protein synthesis in tumor-bearing animals may reflect a generalized response to inflammation, possibly mediated by interleukin 1 and tumor necrosis factor. Increased hepatic transcriptional activity to support protein synthesis in tumor-bearing hosts may indicate a compensatory state against attenuating factors such as a declining food intake.

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ABH blood group isoantigens as tumor markers in transitional call bladder carcinoma
An experimental and clinical study

E. BORGSTRÖM

Department of Urology, Karolinska Sjukhuset, S-104 01 Stockholm, and Department of Virology, National Bacteriological Laboratory, S-105 21 Stockholm, Sweden

The purpose of this investigation was to study aspects of ABH isoantigen expression in single cell populations and on tissue sections from patients with transitional cell bladder carcinoma. Cytologic specimens from bladder carcinoma patients were stained for the blood group isoantigens by fluorescence techniques. Polyclonal blood typing sera identified the A and B isoantigens; fluorinated plant lectin from Ulex Europaeus was used in detection of the H isoantigen. The highest isoantigen concentration was found in peripheral parts of the urothelial cell. Microfluorometric measurements of stained specimens correlated well with the subjective assessment of deletion vs. normal isoantigen expression. The expression/deletion of the ABH isoantigens showed statistically significant correlations with tumor size, benign/malignant cytology and diploidy/aneuploidy. Deletion of blood group expression was, however, not a reliable predictor of short term tumor recurrence. Compared with synchronously stained single cells, histologic specimens stained for the isoantigens yielded information that correlated better with tumor parameters. Serial determination of blood group isoantigens did not add to the prognostic information obtained from the primary tumor. As an early sign of malignant change, isoantigen deletion could be found in biopsy specimens of normal looking urothelium. The malignant field surrounding a tumor was also more extensive as assessed by blood group isoantigens than by histology or DNA modal number. ABH isoantigen deletion could occur prior to DNA changes as recorded by cytoflow techniques. Tumor specimens stained for isoantigens gave as much prognostic information as did cytoflow ploidy determination. Deletion was related to subsequent cancer death.

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