Acta Oncologica 42, *No.* 2, *pp.* 174–175

Abstracts of Theses from the Nordic Countries

Short abstracts of theses on oncologic subjects are published under this heading. The abstract should contain background, problems, results and conclusions and be an independent informative unit that can be read without access to the thesis. It should not contain references to literature, figures or tables in the thesis. A suitable size is about 500 words. The abstract can be sent to Acta Oncologica together with information about department, faculty and university and date of dissertation.

Paracrine and autocrine functions of PDGF in malignant disease

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Growth factors and their receptors are frequently activated by mutations in human cancer. Platelet-derived growth factor (PDGF)-B and its tyrosine kinase receptor, the PDGF β-receptor, have been implicated in autocrine transformation as well as paracrine stimulation of tumor growth. The availability of clinically useful antagonists motivates evaluation of PDGF inhibition in these diseases.

In chronic myelomonocytic leukemia with t(5;12), parts of the transcription factor TEL and the PDGF β-receptor are fused, generating a constitutively signaling protein. Oligomerization and unique phosphorylation pattern of TEL-PDGFβR was demonstrated, as well as the transforming activity of TEL-PDGFβR, which was sensitive to PDGF β-receptor kinase inhibition.

Dermatofibrosarcoma protuberans (DFSP) is characterized by a translocation involving the collagen Iα1 and PDGF B-chain genes. The COLIA1-PDGFB fusion protein was processed to mature PDGF-BB and transformed fibroblasts in culture. The PDGF antagonist STI571 inhibited growth of *COLIA1-PDGFB* transfected cells and primary DFSP cells in vitro and in vivo through induction of apoptosis.

Paracrine effects of PDGF-DD, a ligand for the PDGF β-receptor, were evaluated in a murine model of malignant melanoma. PDGF-DD production accelerated tumor growth and altered the vascular morphology in experimental melanomas.

A validated immunohistochemical procedure for PDGF β-receptor detection was established and applied to normal tissues and more than 280 tumor biopsies. Perivascular and stromal expression was detected in 90% and 50%, respectively, of human tumors.

Recently, non-transformed cells in the tumor microenvironment have emerged as targets in cancer therapy. Selective sensitization of tumor fibroblasts to paclitaxel by STI571 was evaluated in vitro and in a xenograft model. Whereas neither drug alone caused growth inhibition, combination of the two significantly reduced tumor growth, suggesting anti-stromal therapy as a possible treatment modality in solid tumors.

October 2002

Molecular and cytogenetic studies of oncogene alterations in human breast and cervical carcinomas

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Characterization of human tumors with associated genetic changes is of importance for better understanding the tumor's basic biological behavior and of great value for clinical management of cancer patients. We therefore investigated oncogene amplifications in human breast and cervical carcinomas using molecular and cytogenetic methods, especially FISH. Genetic changes of one potential oncogene hTERT and its possible role in deregulation of telomerase activity in human cancers were also studied.

In breast cancer, eight locus markers were analyzed. 17q showed complex rearrangement. Amplification of *ERBB2, CCND1, CSH1(PL)* and *MYC* accounts for nearly 90% of the tumors that exhibit amplified genes with a various frequencies from 14 to 22%. Amplification of 20q13, *MDMX, MDM2* and Xq*21* was detected at a relative low frequency (2–9%). Subsequent analyses showed that gene amplification was significantly correlated with aneuploidy and high proliferative activity. Co-amplification involving two or more genes was exclusively detected in aneuploid tumors with high proliferation rates. A large proportion of tumors also exhibited increased gene copy number. Tumors with gene amplification showed overall more genetic alterations than the tumors without gene amplification. We also observed an association between gene amplification and other prognostic parameters (tumor size, grade lymph node involvement and clinical stage). The data suggests that distinct patterns of gene amplification accompany different subgroups in terms of tumor behavior, which indicates that breast tumors with high malignant potential can be distinguished by detection of global oncogene amplification.

In cervical cancer, low-level amplification with 3–7 copies of six locus markers was detected in 65% of the tumors. *PIK3CA* was altered in 43% of the tumors, followed by *hTERT* (33%), 20q13.2 (30%), *ERBB2* (29%), *C-MYC* (25%) and *CCND1* (12%). Alterations of *PIK3CA* or complex changes involving three or more genes occur more frequently in advanced stage tumors. High-levels of protein expression of c-erbB2 and c-myc were observed predominantly in tumors with the corresponding gene amplified. A general trend was observed with increase of oncogene amplification in tumors with HPV infection, particularly for *C-MYC* and *hTERT*. The data thus indicates that HPV associated cervical carcinomas bear frequent alterations of oncogenes that might be involved in cervical cancer progression.

Activation of hTERT is crucial for telomerase activity in human tumors. Genetic changes of hTERT were thus examined in both tumor cell lines and primary tumors. hTERT was amplified in about 30% of the samples and increased copy number of this gene was also frequently observed. Tumors with amplified hTERT in general showed high expression of its protein and telomerase activity, suggesting a potential role of this gene in up-regulation of telomerase activity. The close association of hTERT amplification with its protein expression and HPV infection suggest an interaction of HPV and hTERT in contributing to the dysregulation of this gene in carcinoma of the uterine cervix.

October 2002

DOI: 10.1080/02841860310005066

Toxicity of smokeless tobacco in human oral epithelium with emphasis on carcinogen metabolism and regulation of programmed cell death

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The oral mucosa is globally a common site for cancer development. Primary risk factors include tobacco smoking and alcohol consumption whereas the contribution from usage of smokeless tobacco remains debated. The susceptibility of the human oral epithelium to carcinogens in tobacco likely depends on the presence of biotransformation enzymes, capable of metabolically activating or detoxifying these agents as well opposing influences from oxidative stress. Induction of programmed cell death (PCD), including function of tumor suppressor p53, may also modulate smokeless tobacco toxicity. On this basis, the purpose of this study was to investigate the expression of biotransformation enzymes as well as the roles of PCD and p53 in smokeless tobacco toxicity in oral epithelium.

Various qualitative and quantitative analyses of oral tissue specimens and normal, immortalized and malignant oral keratinocytes indicated presence of multiple biotransformation enzymes. Several cytochrome P450 (CYP) transcripts were demonstrated including 1A1, 1A2, 2C, 2D6, 2E1, 3A4/7 and 3A5. Typical CYP substrates, including ethoxyresorufin, methoxyresorufin and chlorzoxazone, were detectably oxidized in vitro and metabolism of the tobacco-specific N-nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and aflatoxin B_1 (AFB_1) resulted in covalently bound adducts. Moreover, normal keratinocytes and SV40T antigen-immortalized keratinocytes (SVpgC2a) were shown to express enzymes catalyzing conjugation reactions and detoxification of reactive oxygen. Notably, SVpgC2a showed higher expression levels than normal keratinocytes of some enzymes, e.g. CYP1B1. By RT-PCR, the CYPs were generally shown to be expressed at levels < 50 molecules, the conjugation enzymes at levels between 50–1000 molecules and the enzymes involved in detoxification of reactive oxygen at levels > 1000 molecules, using 10^6 molecules of β-actin as reference. Microarray analysis confirmed expression of these enzymes at levels > 300 molecules per 10^6 molecules of β-actin. The results indicated presence of several biotransformation enzymes in oral buccal mucosa in vivo and in vitro indicating the usefulness of oral keratinocyte cell lines for studies of both single agents and complex mixtures in human oral epithelium.

Studies of smokeless tobacco toxicity involved cultured oral keratinocyte cell lines and oral tissue specimens obtained from healthy controls, snuff users (SDL) and patients diagnosed for lichen planus (OLP). Assessments of net growth rates, apoptosis, necrosis and terminal differentiation in vitro showed, that aqueous smokeless tobacco extract prepared from 'Ettans snus' (STE) primarily caused necrotic death without substantial involvement of PCD. Carcinoma cells (SqCC/Y1) were more resistant to necrosis from STE as compared to normal cells. Extract prepared from 'Kentucky standard reference tobacco' caused similar toxicity as STE. The latter extract induced increases in p53 content that did not associate to increased apoptosis, whereas in contrast, the DNA damaging agent mitomycin C (MMC) increased both p53-content and apoptosis. STE and nicotine separately, significantly inhibited apoptosis induced by various regimens. Slight increases in bcl-2 transcripts in STE-exposed keratinocytes indicated the involvement of this gene. Analysis of Jurkat cells implied that reactive smokeless tobacco chemicals might also block apoptosis by inhibiting caspase activity. Oral tissue analysis agreed with the concept that smokeless tobacco may inhibit apoptosis, i.e. increased mitosis in SDL (relative to normal controls) was not associated with increased apoptosis, whereas OLP exhibited increases in both mitosis and apoptosis. Finally, expression of the p53 and Bcl-2 proteins was noted in SDL whereas OLP expressed p53 but not bcl-2.

In summary, the analysis of the expression of biotransformation enzymes and smokeless tobacco toxicity generally demonstrated similar results in tissue and cultured cell lines implying the usefulness of cell culture technology in the investigation of mechanisms underlying carcinogenesis and other oral disease processes. Thus, keratinocytes actively expressing multiple biotransformation enzymes were susceptible to smokeless tobacco toxicity. The toxicity mechanism of smokeless tobacco likely involves metabolism of carcinogenic agents, including N-nitrosamines, and inhibition of p53-mediated apoptosis. Thus, this study suggests several mechanisms whereby smokeless tobacco usage may contribute to adverse health effects including those associated with cancer development in the oral epithelium.

October 2002

ACTA ONCOLOGICA

Acta Oncologica is the scientific periodical for the Danish Society of Oncology, Finnish Society of Oncology, Icelandic Society of Oncology, Norwegian Society of Oncology, Swedish Society of Oncology, and Scandinavian Breast Group. The journal is owned by the Foundation Acta Oncologica which is responsible for its scientific editing and economy.

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Publication Information

Acta Oncologica (ISSN (print) 0284-186, (online) 1651-226X) is published eight time a year by Taylor & Francis, Rankine Road, Basingstoke, RG24 8PR, Hampshire, United Kingdom. Annual subscription rate for volume 42 (2003) is USA 495.-, including supplements (ISSN (print) 1100-1704, (online) 1651-2499), postage and online access to be paid in advance. Airspeeded to subscribers worldwide.

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Air freight and mailing in the USA by Publications Expediting Inc., 200 Meacham Ave., Elmont, NY 11003. Periodicals postage is paid at Jamaica, NY 11431. U.S. POSTMASTERS: Send address changes to Taylor & Francis, Journals Customer Services, 325 Chestnut Street, 8th floor, Philadelphia, PA 19106, USA, fax +1 215 625 29 40, e-mail: info@taylorandfrancis.com

Indexed/abstracted in:

Biological Abstracts; CINAHL; Clinical Nuclear Medicine; Current Clinical Cancer; Current Contents/Life Sciences; Elsevier BIOBASE/Current Awareness in Biological Sciences; EMBASE/Excerpta Medica; Index Medicus/MEDLINE; INSPEC; Medical Documentation Service; PESTDOC; Reference Update; Research Alert; Science Citation Index; SciSearch.

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Typeset by Datapage International Ltd., Dublin, Ireland, and printed by Hobbs the Printers, Totton, Hampshire, United Kingdom.