Oncogenes, Suppressor Genes and Growth Factors

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THE PARTICIPATION OF p 53 ONCOGENE IN CERVICAL CARCINOGENESIS

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Human cancer is a multistep process in which genetic damage to key regulatory genes known as oncogenes and tumour- supressor genes is accumulated. Among tumour-supressor genes the p53 gene has been extensively studied.
The aim of the project was the observation of the expression of p53 protein in cervical neoplasias, the presence of HPV in p53-positive and negative lesions, proliferative activity and differentiation of neoplastic cells in p53-positive and negative lesions.
The first part of the study is the methodological approach to the p53 detection in paraffin-embedded specimens of cervical cones. p53 was detected using several monoclonal and polyclonal antibodies (Bártek, Lane, Vojtěšek).
In normal cervical tissues no p53 positivity was recorded, while scattered nuclei in the lower part of the ectocervical epithelium was found in CIN and CIN II. The concentration of p53 positive nuclei was convincingly elevated in microinvasive and invasive cancer. In the vicinity of cancer foci, however, a scattered positive reactivity was observed in some nuclei of a normal cervical epithelium.

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PHYSIOPATHOLOGY, CLINICAL AND MOLECULAR ONCOLOGY INTEREST FOR SEVERAL LOCI ON HUMAN CHROMOSOME 8P.

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Heterogeneity of growing subpopulations in human cancers remain a severe obstacle to molecular biology understanding (Growth and Cell Cycle , Differentiation , Genetic and Phenotypic Changes) and anticancer therapy (Dose, Intensity, Resistances , Toxicity). Combined old and new methods in molecular cancer cytogenetics as FISH (Fluorescent in situ hybridization) and flow-sorting, PCR/SSCP , SCE (sister chromatid exchanges) and RFLP (restriction lengh polymorphism) are new promising tools to express structural changes , amplifications, breakpoints and loss of heterozygosity (LOH) . Specific primer sequences , probes and DNA microsatellites permit to evaluate the physiopathologic role of specific genes, their regulation , and their specific alignment (physical and genetic mapping) on human chromosomes. We focused our work on short arm of human chromosome 8 (8p) in order to evaluate these bioinformatives molecules.

On Chromosome 8p specific genes are involved in process of growth control (FGF1 gene) , cell cycle (DNA polymerase ß gene for transcription and chromatin repair, Ankirin1) , hormonal regulation with pituitary and extrapituitary effects (LHRH gene), differentiation (Tissue Plasminogen Activator TPA , NDF Heregulin coligand of erb-2 , Ankirin , Clusterin , Corticostatin , HP4 Defensin precursor genes) and aging (Werner's Syndrome gene) . Deletion (LOH , loss of heterozygosity) on this band 8p1and 8p2 is correlated to cancer specimen and clinical status , almost in prostate 8p22 (+60%), familial breast (30%), colon 8p22-p21.3 (25%), lung cancer and hepatocarcinoma 8p21.3-p22. (Mapping on poster).We suspect a putative suppressor gene on 8p.
In a previous clinical trial (TRIP concept), for example , the LOH of the location of LHRH gene on 8p12 is a useful bioinformation to correlate clinical status , prognosis factors and treatment with analogs of LHRH (Decapeptyl) in breast and prostate cancer. Others genes ,cytogenetics changes and clinical implications will be presented.

Key Words: Molecular Cytogenetics Methods, Chromosome 8, Cancer.

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BREAST CANCER, DESMOID TUMOURS AND FAMILIAL ADENOMATOUS POLYPOSIS COLI - A UNIFYING HYPOTHESIS.

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Evidence exists for an active role of mesenchymal elements in both induction and maintenance of the transformed state. A unifying hypothesis is proposed whereby potential mesenchymal determinants are invoked to account for disparate clinical observations which include a) results of clinical trials revealing efficacy of adjuvant tamoxifen in early breast cancer to be partially independent of oestrogen receptor status and b) the association between gastro-intestinal polyps/cancer in familial adenomatous polyposis (FAP) and desmoids. These may represent epiphenomena resulting from a basic inherited mesenchymal defect, possibly involving the 5q21 locus. Such a defect would impart an abnormal, foetal-like phenotype to fibroblasts with deficient production of the negative paracrine growth modulator transforming growth factor ß (TGFß) as a primary fault. We have previously demonstrated the induction of TGFß in foetal fibroblasts in vitro, and in ER positive and ER negative breast cancer patients in vivo in response to tamoxifen treatment. More recently, the secretion of this growth factor by breast and desmoid fibroblasts in vitro has been confirmed. This mesenchymal defect could produce a local imbalance of growth factors, which in conjunction with putative foetal-like characteristics would lead to a) promotion of fibroblast activity, encouraging desmoid formation b) disturbance of stromal-epithelial interactions with reduction of negative stromal paracrine influences resulting in excessive epithelial proliferative activity of both gastrointestinal mucosa and breast tissue. Predisposition to both desmoids and GI polyps would arise from a mesenchymal defect affecting one of a pair of alleles in proximity to the 5q locus. A further somatic mutation of the homologous allele on the cognate chromosome of colonic epithelial cells would trigger actual malignant transformation. Any imbalance of growth factors could be counteracted by therapeutic agents aimed at modulation of stromal behaviour, and education of these 'immature' fibroblasts by pharmacological manipulation may be a strategy for both prevention and treatment of early breast cancer.

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CHARACTERIZATION OF EGF RECEPTORS (EGFR) IN PRIMARY BRAIN TUMORS OF ADULTS AND CHILDREN.

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Epidermal growth factor (EGF) is a polypeptide growth factor whose receptor (EGFR) has a proven prognostic role in certain malignant tumors, but data on its significance in brain tumors remains incomplete and sometimes contradictory. In this study of 47 patients with a brain tumor, a biopsy sample was obtained prior to any treatment. Histological examination of another sample obtained at the same time revealed 41 glial tumors (including 37 malignant gliomas: grade III and IV astrocytomas and glioblastomas), 2 ependymomas, 2 benign meningiomas, 1 medulloblastoma, and 1 malignant schwannoma. In 38/47 cases, the size of the biopsy material allowed Scatchard graphic representation with a single class of high affinity sites; a simplified binding technique with a single ^{125}I EGF concentration was used for the remaining 9 small biopsy samples. In 18 cases, the labelling index (LI) was measured in parallel by radioimmunolabelling with tritiated thymidine. The EGFR level (fmol/mg) in all of the gliomas was significantly correlated with the histologic grade (mean EGFR: grade II 1377; grade III 416; grade IV 1981; glioblastoma 3550 fmol/mg; $p < 0.05$). For the 27 grade IV astrocytomas and glioblastomas, no significant correlation was found between EGFR and overall survival, patient age, sex, tumor extent, or LI; the same was true for all of the gliomas, and for the entire study population. It was not possible to determine whether a correlation existed between EGFR and relapse-free survival in this patient population. While these preliminary results reveal the presence of EGFR in primary brain tumors, with very elevated levels in high grade gliomas, its exact prognostic significance in these pathologies requires further investigation, and in particular determinationof its independent or dependent nature in multivariate analysis.