Tumor associated proteases -- prognostic markers of colorectal cancer

Associations between matrix metalloproteinase (MMP) 2, 7, 9, tissue MMP inhibitor TIMP-1 and plasminogen activation system components (uPA, tPA and PAI-1) plasma and/or tumor levels in colorectal cancer (CRC) patients were evaluated in order to reveal their potential clinical implications. Two groups of CRC patients monitored for 5 or 10 years were enclosed in the study. Earlier, corresponding markers’ levels were measured in their plasma and/or tumors by immunoenzymatic techniques. High tumor PAI-1 (≥ 4,0 ng/mg protein) was demonstrated to be a significant, but not independent unfavorable prognostic factor for 5 and 10 years overall survival. Its role was mostly pronounced in stage III patients. High preoperative plasma MMP-7 and TIMP-1 levels (cut-offs -- 4,0 and 347 ng/ml respectively) were shown to be independent unfavorable prognostic factors, and univariate analysis revealed unfavorable prognostic value of high tumor MMP-7 content (≥ 7,8 ng/mg protein) in patients with disseminated process.

Key words: urokinase type plasminogen activator (uPA), tissue type plasminogen activator (tPA), type 1 plasminogen activator inhibitor (PAI-1), matrix metalloproteinase 2, matrix metalloproteinase 7, matrix metalloproteinase 9, tissue matrix metalloproteinase inhibitor 1, colorectal cancer, prognosis

References


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Clinico-morphological analysis of the neuroendocrine neoplasms of the gastroenteropancreatic system

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Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are unusual and rare epithelial tumors for which the diagnosis of the grade of malignancy and prognostic assessment on the basis of histology represent considerable challenges for the pathologist. In this study we conducted a retrospective analysis of the cell proliferation (Ki-67 nuclear antigen) in primary and metastatic GEP NENs of 137 patients as well as the assessment of keratin 19 (CK19) and progesterone receptors (PR) expression in pancreatic NENs of 57 patients. In 19 (27,1%) GEP NEN metastases was found 1,5--4,5-fold increase of Ki-67 index compared with their primaries. Consequently, 6 (21,4%) cases of NET G1 and 4 (7,0%) cases of NET G2 were up-graded. Pancreatic NETs G2 with Ki-67 index >5% were significantly associated with presence of distant metastases.
(p=0.007) and decreased survival (p=0.03). Decreased survival also was found in the group of gastrointestinal NET G2 with Ki-67 index > 15% (p=0.005). Further analysis of immunomorphological features and proliferative activity allowed to separate a rare group of tumors -- "NET G3", characterized by decreased survival comparing to NET G2. Expression of CK19 in pancreatic NETs was significantly associated with higher proliferative activity of primary tumor (p=0.04) and adverse outcome (p=0.003). On other hand, PR expression correlated with lower Ki-67 index (p=0.006), absence of metastases (p=0.004) and favorable outcome (p=0.000). Our results show that Ki67 index is a key parameter of morphological diagnosis of GEP NENs. Thus, the studied markers are important parameters of the morphological diagnostic of GEP NENs, which allow more accurately assess the degree of malignancy, prognosis and treatment of the disease.

**Key words:** neuroendocrine tumor, gastrointestinal tract, pancreas, proliferative activity, grade, prognosis

**References**

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**Tumor-specific blood serum factors as determinants of tumor growth**

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In the present review, we focus on the importance of blood serum factors for tumor growth in vivo. Data from mice experiments indicate the existence of serum factors, which increase the mitotic index of Ehrlich carcinoma cells from 15 to 80%. The impaired production of these factors increases the life span of tumor-bearing animals from 14--20 days to 90 days. Blocking the production of tumor-specific factors causes the complete regression of already developed Ehrlich carcinoma. These serum factors do not affect the malignant carcinoma cells in vitro. We identified serpins as tumor-specific serum factors. Experimental evidence suggests that serpins are not only essential for tumor growth. Serpins are also involved in the regeneration of normal tissues, such as adipose tissue, recurrence after cosmetic operations (liposuction), inhibiting rejection after liver transplantation, protection of parasitic flat worms living in host tissues and organs etc. We conclude that the inhibition of serum factors may represent attractive novel strategies for the prevention and treatment of relapsed cancers.

Key words: anti-proteases, Ehrlich carcinoma, proteases, serpins, serum proteins, tumor growth

References

Gene expression of androgen metabolising enzymes in benign prostatic hyperplasia

Benign prostatic hyperplasia is still one of the most important problems of modern urology. We studied the gene expression of androgen metabolic enzymes involved in the synthesis of androgens directly in the target organs in 20 patients using real-time RP-PCR. A significant increase in the mRNA of HSD17B3 ~ 1.7 fold, SRD5A2 ~ 2 fold, HSD3B1 ~ 2 fold, STS ~ 2.3 fold и AR ~ 2.5 fold and reduced HSD17B2 ~ 4 fold in samples of tumor tissue compared with adjacent tissues.

Key words: benign prostatic hyperplasia, androgen receptor, androgen metabolism enzymes

References


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Matrix metalloproteinases and inflammatory cytokines in the oral fluid of patients with chronic generalized periodontitis various structural materials restoration of teeth and dentition

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Results of comparative immunoenzymatic study of matrix metalloprotease (MMP) 2, 8 and 9, interleukins (IL) 1β and 6, tissue MMP inhibitors (TIMP-1 and TIMP-2) and TNF-α in oral fluid of patients with different teeth and denture constructive materials show that MMP-9 content in oral fluid can serve as a marker of chronic generalized periodontitis because it is elevated in all patients irrespective of presence or absence of metallic tooth restorations. MMP-8 level is elevated as compared to control only in periodontitis patients with metallic restorations. The character of correlative relationships between the parameters studied in various patients’ groups demonstrate relative similarity of MMP, IL and TIMP secretion regulation in patients with intact periodontal. In patients with inflammatory destructive periodontal lesions both with and without metallic restorations the correlation data reveal a cascade of biochemical reactions in response to etiologic factors. More pronounced response is observed in periodontitis patients with metallic orthopedic constructions. The presence of chromium-cobalt or chromium-nickel constructions leads to an increase of MMP-2, IL-1β and IL-6 content in oral fluid.

Key words: periodontitis, matrix metalloproteinase 2, 8, 9, IL-1β, IL-6, TNF-α, oral fluid, the materials of construction

References


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**Associations of single nucleotide polymorphisms with malignant and borderline bone tumors**

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Bone neoplasms -- are a rare group of diseases, which etiology and pathogenesis are not fully understood. We have studied 6 single nucleotide polymorphisms rs7921(GH1), rs7956547(IGF1), rs3761243(GNRH2), rs11737764(FGF2), rs6599400(FGFR3), and rs1690916(MDM2) associations with bone tumors. In our work we’ve detected significant associations with some single nucleotide polymorphisms: IGF1.rs7956547, GNRH2.rs3761243 and FGFR3.rs6599400 in patients with malignant and borderline bone tumors.

**Key words:** bone tumors, single nucleotide polymorphisms

**References**


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Expression of molecular markers in low-grade chondrosarcomas and cartilaginous tumors with uncertain differentiation

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Among the wide array of human neoplasms, primary tumors of bone are relatively uncommon and sundry group of solid tumors traditionally categorized according to their presumed mesenchymal differentiation. A locally aggressive or malignant group of cartilaginous matrix-producing neoplasms with diverse morphological features and clinical behavior require additional ancillary studies for prompt diagnosis and appropriate surgical treatment. They are histologically, behaviorally and genetically diverse, their pathogenesis is poorly understood. Moreover, treatment options are limited with surgical resection continuing to provide the only possibility of cure in many cases. However, there has been tremendous progress in the last decade in understanding the molecular pathogenesis of sarcoma, which may ultimately lead to more effective therapy and prognostification for these rare malignancies (1). Atypical cartilaginous tumor/grade 1 chondrosarcomas behave as locally aggressive lesions, and only metastasize in exceptional cases. Only a small percentage of the IDH1 mutations can be identified using the specific IDH1R132H antibody. Histologic grade is the most important predictor of local recurrence and metastasis in chondrosarcoma, commonly patents die from locally recurrent tumor of pelvis or scull, that is difficult to manage surgically. Association between ratio of matrix metalloproteinase-1 and tissue inhibitor of metalloproteinase-1, expression of metalloproteinase-1, -2 and -9, Col-IV, Cox-2, Bcl-2, Bax in context with histological and clinical data could play a significant role in determining prognosis in patients with borderline cartilaginous tumors. The mandatory application of multidisciplinary care in management of atypical cartilaginous tumor/grade 1...
chondrosarcomas with integration of histologic, molecular, radiographic and clinical data is difficult to overestimate.

Key words: atypical cartilaginous tumor, metalloproteinase, immunohistochemistry

References


survival) of typical osteosarcoma patients depended on tumor malignancy grade (determined by the criterion G). Baseline serum VEGF, its soluble receptors and angiogenin concentrations had no predictive value.

Key words: bone tumors, VEGF, VEGF-R1, VEGF-R, angiogenin

References


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Deregulation of signaling pathways involved in sorafenib resistance of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common neoplasms worldwide. Hepatocarcinogenesis is associated with deregulation of the cell signaling thus targeted therapy can decelerate HCC progression by specific inhibition of alternated signaling cascades. Sorafenib is the only multitarget drug approved for HCC treatment that blocks several crucial oncogenic signaling pathways thus suppressing tumor growth, metastasis and providing survival benefit for subset of patients sensitive to sorafenib. Compensatory activation of other tumorigenic mechanisms may lead to decrease of HCC sensitivity to sorafenib. HCC are heterogenic tumors of epithelial origin, and presence of low-differentiated subpopulations of cancer stem
cells or dedifferentiated fibroblastoid cells, that are less sensitive to sorafenib due to resistance to growth-inhibitory action of the drug, promotes HCC resistance to sorafenib. Analysis of the expression profile of genes encoding tissue-specific proteins, components of cell junctions, stem cell and mesenchymal markers can reveal sorafenib-resistant populations in HCC and identify signaling pathways that reduce response to sorafenib. Identification of individual sorafenib resistance mechanisms may be useful for rational choice of an appropriate combination of targeted drugs for retardation of HCC progression and improving the efficacy of therapy.

Key words: hepatocellular carcinoma; sorfenib; multitargeted therapy; sorafenib sensitivity; sorafenib resistance; signaling pathways, differentiation

References
β-catenin signaling pathway and the tolerance of breast cancer cells to hypoxic conditions

We have previously shown that Snail, a regulator of epithelial-mesenchymal transition, is activated in the hypoxia-resistant breast cancer cell line HBL-100. The purpose of this study was to evaluate the role of β-catennin signaling pathway in the maintenance of breast cancer cells' tolerance to hypoxia. The breast cancer cell lines MCF-7 and HBL-100 were used in this study; HBL-100 cells were characterized by increased resistance to hypoxia.
We have demonstrated that the transcription factor β-catenin is activated in hypoxic conditions and the β-catenin activity is supported by Snail, a regulator of epithelial-mesenchymal transition. The activated β-catenin regulates the expression of genes of the cell response to hypoxia and thus, it maintains the growth of breast cancer in the reduced oxygen conditions. The coordinated activation of Snail/β-catenin/HIF-1α proteins in cell may be considered as an important factor of tumor resistance to hypoxia.

**Key words:** epithelial-mesenchymal transition, breast cancer, β-catenin, hypoxia, HIF-1α

**References**


The paper presents the results of neurospecific proteins S-100 and glial fibrillary acidic protein (GFAP) determination in blood serum samples of 145 neuro-oncology patients and 69 healthy people. The significant elevation of S-100 and GFAP was revealed in glioblastoma (G IV) patients compare to the patients with anaplastic astrocytoma (G III), benign meningioma (G I), cerebral metastasis and healthy controls. The concentration of S-100 in blood serum of patients with anaplastic astrocytoma, benign meningioma, and cerebral metastasis did not significantly differ among themselves, and in relation to the control group there was a significantly increase only in patients with cerebral metastasis. GFAP was characterized by high frequency of its detection in patients with glioblastoma (83%) compare to other groups of patients and healthy donors, in which it was practically undetectable. These data suggest the possibility of using GFAP as a marker of glioblastoma and S-100 -- as an additional biochemical criteria of cerebral lesions in oncology patients.

**Key words:** S-100, GFAP, blood serum, brain tumors

**References**