Understanding the mechanisms of this interesting phenomenon is of importance in itself and even more so in view of the possibility that these mechanisms may eventually suggest modalities for age- adjusted anti-tumoral therapy. We have shown that one such mechanism is increased tumor cell apoptosis in the old animals (1).

In the present study we attempted to verify whether the aging microenvironment affects differently primary and metastatic tumors of the AKR lymphoma.

Materials and Methods: We compared the tendency to apoptosis of primary and metastatic AKR lymphoma cells from young and aged AKR/J mice, according to various cellular (Apoptag staining, DNA flow cytometry) and molecular (ladder type DNA fragmentation, Bcl-2, Fas receptor and caspase expression) characteristics of apoptotic cells.

Results: We found that tumor cell apoptosis was increased in tumors of old as compared to those of young mice in both primary and metastatic growths of the lymphoma. However, the age- related induced apoptosis was more pronounced in primary than in metastatic tumors.

Conclusions: It appears that the apoptosis- inducing effect of the aging microenvironment depends on the tendency to apoptosis of the tumor. We have previously shown that primary tumors of AKR lymphoma are more prone to apoptosis than those of metastatic tumors (2). It is therefore expected that inducing tumor cell apoptosis as a therapeutic modality in the old (1) can be more effective at early stages of tumor development than at late ones.

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Expression of platelet-derived growth factor (PDGF)-B and PDGF-receptor β is associated with lymphatic metastasis in gastric carcinoma

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Background & Aims: Lymphatic metastasis is closely related to clinical outcome in patients with gastric carcinoma. Recent research regarding lymphangiogenesis focused on two members of the vascular endothelial growth factor (VEGF) family, VEGF-C and VEGF-D. However, recent studies have revealed that platelet-derived growth factor (PDGF) also plays a direct role in promoting lymphangiogenesis and metastatic spread to lymph nodes in murine fibrosarcoma. The purpose of this study was to examine the relation between PDGF and PDGF receptor (PDFGF-R) expression and lymphatic metastasis in human gastric carcinoma. Methods: We examined the expression of PDGF-B and PDGF-Rβ in five human gastric carcinoma cell lines (TMK-1, MKN-1, MKN-28, MKN-45, and KKLS) and in 38 surgical specimens of gastric carcinoma by real-time quantitative PCR, ELISA, and western blotting. Immunofluorescence was performed to examine PDGF-B and PDGF-Rβ expression in surgical specimens and in human gastric carcinoma cells (TMK-1) implanted orthotopic ally in nude mice. Results: PDGF-B and PDGF-Rβ mRNA expression was significantly higher in patients with lymph node metastasis than in those without (P=0.03 and P<0.001, respectively) and was also significantly higher in diffuse-type carcinoma than in intestinal-type carcinoma (P=0.02 and P=0.01, respectively). In most surgical specimens, tumor cells expressed PDGF-B, but PDGF-Rβ was expressed predominantly by stromal cells. Under culture conditions, expression of PDGF-B mRNA was found in all of the gastric cell lines except KKLS. Two of the five gastric carcinoma cell lines (KKLS and MKN-1) expressed low PDGF-Rβ mRNA levels. In orthotopic TMK-1 tumors, cancer cells expressed PDGF-B but not PDGF-Rβ. PDGF-Rβ was expressed by stromal cells, including lymphatic endothelial cells. Conclusions: These data indicate that PDGF-B secreted by tumor cells and PDGF-Rβ expressed by tumor-associated stromal cells are associated with lymphatic metastasis in gastric carcinoma.

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Stem cell factor expression at perinecrotic tumor sites is associated with a high microvessel density and endothelial cell KIT expression in human cancer

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Background: A few studies suggest that KIT receptor tyrosine kinase may be involved with tumor angiogenesis. We investigated association of KIT and stem cell factor (SCF) expression with tumor angiogenesis in human cancer.

Materials and methods: KIT and SCF expression was assessed from 248 human tumors consisting of 15 different histological types of cancer using immunohistochemistry. The results were correlated with tumor microvessel density counted from tissue sections stained with an anti-CD31 antibody.

Results: In general, SCF expression was elevated in perinecrotic tumor regions. SCF expression at perinecrotic tumor sites was associated with a high tumor microvessel density (P=. 0004) and with marked KIT expression in tumor endothelial cells (P=. 0005). Endothelial cell KIT expression was most prominent in glioblastoma (58%), testicular teratocarcinoma (33%), renal cell carcinoma (29%), and melanoma (20%).

Conclusions: The results lend further support to the hypothesis that SCF and KIT are important players in tumor angiogenesis. Perinectotic tumor tissue SCF expression is associated with a high microvessel density. Inhibition of SCF/KIT signalling might be a target for anti-angiogenic therapies.

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Snail is overexpressed in human lung cancer and tumor associated stroma

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Purpose: The acquisition of migratory and invasive capabilities by tumor cells recapitulates a developmental process known as epithelial-mesenchymal transition (EMT).A hallmark during this process is the loss of E-cadherin.Snail is considered to be one of the transcription facors responsible for E-cadherin repression.Here, we evaluate the role of E-cadherin and Snail expression in lung cancer and tumor associated stroma.

Experimental procedure: 74 lung cancers were examined immuno-histochemically for the expression of Snail and E-cadherin proteins.The associations between these proteins and clinico-pathological parameters were also analysed.

Results:Positive Snail expression (nuclear) and impaired E-cadherin expression (reduced membranous/no-membranous) were found in 95,9% and 91,5%, respectively.The impaired E-cadherin expression was significantly associated with tumor grade (p<0,001) and tumor size (p=0,026).Snail expression did not correlate significantly with E-cadherin expression or other clinico-pathological parameters.Tumor associated stromal cells, including myofibroblast-like cells, lymphocytes and macrophages were positive for Snail expression in 94,6%, 87,6% and 79,7%, respectively.Snail expression in myofibroblast-like cells was significantly associated with tumor size (p=0,024) and lymph node status (p=0,042).

Conclusions:Our results demonstrate that Snail,a master regulator of EMT, is overexpressed in human lung cancer cells and tumor stromal cells in vivo but is not associated with E-cadherin down-regulation.

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Regulation of TNF-superfamily members by erythropoietin, in breast cancer

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Background: APRIL (CD256), a Tumor Necrosis Family (TNF) ligand has gained increasing interest in view of cell homeostasis. Although well described in haemopoietic malignancies, its role and regulation in solid tumors remain to be elucidated. Indeed, breast cancer promotion integrates a complex interplay between hormones and cytokines, mediated, among others, through cross-link of membrane initiated steroid signaling with growth factors. Materials and methods: We assayed 52 human breast cancer biopsies by immunohistochemistry for the expression of APRIL as well as its cognitive receptors (BCMA and TACI) and correlated our findings with clinicopathological data and the evolution of the disease. Moreover, utilizing three breast cancer cell lines (MDA-MB-231, T47D and MCF-7) with different phenotypes, we approached by RT-PCR the gene expression profile of this TNF member in breast cancer and the possible transcriptional regulation by membrane androgen and estrogen agonists. Results: APRIL immunoreactive expression was higher in non-malignant than neoplastic breast structures, in contrast to findings in other solid tumors. APRIL expression was associated with more aggressive and undifferentiated phenotypes, correlating with lymph node metastases. Moreover,