hypothesis that amifostine increases polyamine synthesis in these cells, reducing the amounts of L-arginine that can be metabolised by nitric oxide (NO) synthase to NO. It is well known that spermidine does not affect migration, while we have previously shown that decreased levels of NO inhibit HUVEC migration. Therefore, the decrease in migration seems to be due to a decrease in NO production by these cells. Finally, amifostine reduced tyrosine nitration of the cytoskeletal proteins actin and tubulin, in a time dependent manner. This last action could be due to the reduced amounts of NO or to other, not yet identified mechanisms.

Conclusions: Collectively, our results suggest that amifostine acts on endothelial cells through pathways that affect the redox status of the cells, either by producing H_2O_2 or by modulating NO production.

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Microvessel density of bone metastasis is dependent on the cancer type and therapy

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Background: Bone may provide an extremely fertile microenvironment for angiogenesis. Experimental investigations indicate angiogenesis as a major regulator of bone metastasis development. However, no studies have investigated angiogenesis in bone metastases of human cancers.

Methods: We have evaluated microvessel density in bone metastases of various cancer types and compared to their primary tumors in paraffin samples of 39 patients. Microvessel density (MVD) was determined by using the hot spot method and the endothelial marker, CD34. Patients were chemotherapy-naïve except a subgroup of breast cancer cases.

Results: Two patterns of modulation of the angiogenic phenotype in the bone emerged in this study which seem to be cancer type specific: decreased angiogenic potential characterizing 45% of renal cell cancers and breast cancers of high vascularity in their primary, and increased angiogenic potential characterizing 40% of lung adenocarcinomas and breast cancers of low vascularity in their primary lesion. Analysis of the breast cancer cases indicated no differences in VEGF expression, hormone receptor status or histology between the two groups of primary tumors. However, when we have analysed these cases for possible cause for the different angiogenic responses we found that those cases where MVD decreased in bone metastases were all but one have been treated by chemo- or hormone therapy.

Conclusions: Our data demonstrate that 1. the vascularization of cancer metastases is different from that of the primary tumors, 2. patterns are different in the case of various cancer types. Among factors modulating MVD in bone metastases the unique microenvironment as well as the therapeutic interventions both have to be considered.

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1p chromosomal deletion and candidate genes mapping in liver fluke related cholangiocarcinoma.

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Background: We have characterized genetic alteration in the development of liver fluke related cholangiocarcinoma which is commonly found in northeastern region of Thailand. Genomic wide aberration have been previously examined in 30 cases of cholangiocarcinoma patients (Uchida K,et al. unpublished data). They found the most frequent chromosomal loss at 1p36-qter with the frequency of 35%. To identify the possible candidate gene on this region, deletion mapping were investigated in cancerous tissues using quantitative PCR.

Material and methods: Five Sts markers covering 1p36-pter were firstly screened in 23 cancerous tissues using lightcycler- DNA Master SYBR GreenI (Roche). All samples were run in triplicates with an acceptable CV of less than 10%.

Results: Large deletion was spanned between these markers with 48-60% of all 23 cases. Nine out of 23 cases were selected as representatives for further fine mapping study. Gene copy number was quantitated using 6 gene markers designed in accordance with candidate gene present on this region. At least 4 gene markers demonstrated high deletion frequency. The most frequent deletion (7/9cases) was found at p73 locus.

Conclusions; Our data provided deletion information on 1p36-pter in liver fluke related cholangiocarcinoma. The possible candidate gene was represent as potential marker for further investigation. The expression of p73 will be investigated for the involvement in malignant progression of cholangiocarcinoma.

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Gene expression profiling in papillary thyroid carcinoma: Are there different pathways of carcinogenesis?

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The aim of the study was to evaluate the expression profiles in papillary thyroid carcinomas (PTC) by means of high density DNA microarrays. The molecular mechanisms leading to different types of thyroid tumors are not completely understood. RET protooncogene activation, as a consequence of chromosomal rearrangement, is regarded at present as the most important initiating event in the development of papillary carcinomas. However, in those papillary thyroid tumors which are RET-negative the molecular mechanisms of carcinogenesis are unknown. Nine samples of PTC together with the corresponding normal tissues were frozen immediately after excision. Total RNA was isolated using RNeasy Total RNA Midi and Mini Kits. The RET gene rearrangements were found in four cases by RT-PCR. All samples were hybridized to Human Genome U133A arrays as recommended by Affymetrix. Three different approaches have been used to analyze gene expression data. In the first four methods of gene selection and Support Vector Machine technique with a linear kernel for classification were applied. In the second Singular Value Decomposition and hierarchical clustering algorithm and in the third Affymetrix Data Mining Tool software were used. Very similar results were obtained by all three methods giving a clear separation of gene expression profiles in tumors and normal samples. There were 99 genes overexpressed and 93 genes underexpressed in tumor samples, among them genes previously indicated by Huang et al (2001), particularly SCYA21, TFF3, CITED1, FABP4, LAMB3, SCEL, DPP4. Also, other differentially expressed genes, unreported so far, were found: EVA1, LRB1B, CDH3, gastrointestinal tumor-associated antigen GA733-1, prostate differentiation factor, low density lipoprotein receptor-related protein, TMPRSS, CDH16, PCSK2 and solute carrier NaPiIIb. Expression patterns observed in RET-positive and RET-negative tumors exhibited some differences which were related to expression of both thyroid-specific genes (i.e. PDS), cancer-related (i.e. CAXII, PCNA, PICOT) and still unknown genes (i.e. FLJ10044, FLJ10359). This differences may represent distinct pathways of carcinogenesis Our results obtained so far corroborate the rather stable molecular profile of PTC as postulated by Huang and form a starting point for the further studies of molecular markers in RET-negative thyroid cancers.

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The role of XPD exon 10 polymorphism in susceptibility to ovarian and breast cancer

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Background: Breast and ovarian cancer are two neoplasia with important incidence and mortality in women all over the world. The mechanisms involved in the carcinogenesis of these cancers are not well understood. Nucleotide excision repair (NER) is a crucial pathway in the maintenance of genome stability. Variants of several DNA repair genes, including gene *XPD*, have been described. This protein has a dual function, both in nucleotide excision repair and in basal transcription. The *XPD* exon 10 polymorphism is characterized by a G to A change, being responsible for aspartic acid to asparagine amino acid substitution in the coding region of the *XPD* gene.The purpose of this study was to evaluate the role of *XPD* exon 10 polymorphism as genetic indicator of susceptibility to breast and ovarian cancer.

Materials and Methods: We have used a case-control study. We analysed DNA samples from 499 unrelated individuals, 199 breast cancer