関係論文

①Differential gene expression profiling in blood from patients with digestive system cancers.

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Abstract

To develop a non-invasive and sensitive diagnostic test for cancer using peripheral blood, we evaluated gene expression profiling of blood obtained from patients with cancer of the digestive system and normal subjects. The expression profiles of blood-derived total RNA obtained from 39 cancer patients (11 colon cancer, 14 gastric cancer, and 14 pancreatic cancer) was clearly different from those obtained from 15 normal subjects. By comparing the gene expression profiles of cancer patients and normal subjects, 25 cancer-differentiating genes ($p<5.0 \times 10(-6)$ and fold differences >3) were identified and an "expression index" deduced from the expression values of these genes differentiated the validation cohort (11 colon cancer, 8 gastric cancer, 18 pancreatic cancer, and 15 normal subjects) into cancer patients and normal subjects with 100% (37/37) and 87% (13/15) accuracy, respectively. Although, the expression profiles were not clearly different between the cancer patients, some characteristic genes were identified according to the stage and species of the cancer. Interestingly, many immune-related genes such as antigen presenting, cell cycle accelerating, and apoptosis- and stress-inducing genes were up-regulated in cancer patients, reflecting the active turnover of immune regulatory cells in cancer patients. These results showed the potential relevance of peripheral blood gene expression profiling for the development of new diagnostic examination tools for cancer patients

②Common transcriptional signature of tumor-infiltrating mononuclear inflammatory cells and peripheral blood mononuclear cells in hepatocellular carcinoma patients. Cancer Res. 2008 Dec 15;68(24):10267-79.

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Abstract
Hepatocellular carcinoma (HCC) is frequently associated with infiltrating mononuclear inflammatory cells. We performed laser capture microdissection of HCC-infiltrating and noncancerous liver-infiltrating mononuclear inflammatory cells in patients with chronic hepatitis C (CH-C) and examined gene expression profiles. HCC-infiltrating mononuclear inflammatory cells had an expression profile distinct from noncancerous liver-infiltrating mononuclear inflammatory cells; they differed with regard to genes involved in biological processes, such as antigen presentation, ubiquitin-proteasomal proteolysis, and responses to hypoxia and oxidative stress. Immunohistochemical analysis and gene expression databases suggested that the up-regulated genes involved macrophages and Th1 and Th2 CD4 cells. We next examined the gene expression profile of peripheral blood mononuclear cells (PBMC) obtained from CH-C patients with or without HCC. The expression profiles of PBMCs from patients with HCC differed significantly from those of patients without HCC ($P < 0.0005$). Many of the up-regulated genes in HCC-infiltrating mononuclear inflammatory cells were also differentially expressed by PBMCs of HCC patients. Analysis of the commonly up-regulated or down-regulated genes in HCC-infiltrating mononuclear inflammatory cells and PBMCs of HCC patients showed networks of nucleophosmin, SMAD3, and proliferating cell nuclear antigen that are involved with redox status, the cell cycle, and the proteasome system, along with immunologic genes, suggesting regulation of anticancer immunity. Thus, exploring the gene expression profile of PBMCs may be a surrogate approach for the assessment of local HCC-infiltrating mononuclear inflammatory cells.

③Differential microRNA expression between hepatitis B and hepatitis C leading disease progression to hepatocellular carcinoma.
Hepatology. 2009 Apr;49(4):1098-112.

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Abstract
MicroRNA (miRNA) plays an important role in the pathology of various diseases, including infection and cancer. Using real-time polymerase chain reaction, we measured the expression of 188 miRNAs in liver tissues obtained from 12 patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) and 14 patients with hepatitis C virus (HCV)-related HCC, including background liver tissues and normal liver tissues obtained from nine patients. Global gene expression in the same tissues was analyzed via complementary DNA microarray to examine whether the differentially expressed miRNAs could regulate their target genes. Detailed analysis of the differentially expressed miRNA revealed two types of miRNA, one associated with HBV and HCV infections (n = 19), the other with the stage of liver disease (n = 31). Pathway analysis of targeted genes using infection-associated miRNAs revealed that the pathways related to cell death, DNA damage, recombination, and signal transduction were activated in HBV-infected liver, and those related to immune response, antigen presentation, cell cycle, proteasome, and lipid metabolism were activated in HCV-infected liver. The differences in the expression of infection-associated miRNAs in the liver correlated significantly with those observed in Huh7.5 cells in which infectious HBV or HCV clones replicated. Out of the 31 miRNAs associated with disease state, 17 were down-regulated in HCC, which up-regulated cancer-associated pathways such as cell cycle, adhesion, proteolysis, transcription, and translation; 6 miRNAs were up-regulated in HCC, which down-regulated anti-tumor immune response. CONCLUSION: miRNAs are important mediators of HBV and HCV infection as well as liver disease progression, and therefore could be potential therapeutic target molecules.

④ Identification of novel candidate tumour marker genes for intrahepatic cholangiocarcinoma.
J Hepatol. 2008 Aug;49(2):207-16. Epub 2008 May 5.

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Abstract
BACKGROUND/AIMS: Specific markers are required for early detection and diagnosis of intrahepatic cholangiocarcinoma (ICC); however, the tumour markers currently in use are not specific for ICC.

METHODS: We compared an ICC cDNA library with that of hepatocellular carcinoma (HCC) by serial analysis of gene expression (SAGE). The expression patterns in each were confirmed by quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR), immunoblotting and immunohistochemical analysis of 74 samples including 16 ICC samples.

RESULTS: A comparison of the two libraries revealed distinct gene expression patterns for each type of liver cancer. In addition to the known tumour markers, we detected nine novel genes associated with ICC. By comparing the mean transcript abundance in the ICC library with those in other libraries, including gastric, colon, prostate and breast cancer, together with our RT-PCR results, we identified three genes as specific markers of ICC: biglycan, insulin-like growth factor-binding protein 5 and claudin-4. Immunoblotting and immunohistochemical analyses showed that claudin-4 was highly expressed in ICC. Moreover, discrimination analysis revealed that a combination of these genes could be used to distinguish ICC from HCC or metastatic adenocarcinoma.

CONCLUSIONS: We identified novel marker genes of ICC that are potentially useful for the diagnosis of liver cancer.

⑤Serial analysis of gene expression in chronic hepatitis C and hepatocellular carcinoma.

Biochem Biophys Res Commun. 2001 Mar 30;282(2):647-54.

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Abstract

Hepatitis C virus (HCV) causes chronic hepatitis C (CH-C) and is epidemiologically linked with the occurrence of hepatocellular carcinoma (HCC). To elucidate the comprehensive gene expression profiles of CH-C and HCC, serial analysis of gene expression (SAGE) libraries were made from CH-C and HCC tissues of a patient, and compared with a reported SAGE library of a normal liver (NL). Scatter plots of the distribution of tags from the HCC library exhibited the existence of many differentially expressed genes compared with those from the CH-C and NL libraries. Up-regulation of IFN-gamma inducible genes and oxidative stress-inducible genes were identified in both the CH-C and HCC libraries, and some unpublished new genes were specifically up- or down-regulated in the HCC library. This genome-wide scanning study discloses the molecular portraits of CH-C and HCC, and provides novel candidate genes that should help clarify the mechanism of hepatocarcinogenesis in the chronically HCV-infected liver.