Posters

P-257   DIFFERENTIAL EXPRESSION OF EPIGENETIC REGULATORY GENES IN LIVER CANCER

G. Yildiz [1, 2,*], M. Ozturk [1, 2]

[1]Université Joseph Fourrier U823, Institut Albert Bonniot, Grenoble, France, [2]Molecular Biology and Genetics, Bilkent University, Ankara, Turkey

Introduction: Epigenetic mechanisms are involved in the organization of chromatin structure and global regulation of gene expression [1]. Cancer cells display multiple epigenetic changes including aberrations in the methylation of DNA, expression of non-coding RNAs and post-translational modifications of histones [1,2]. Epigenetic changes appear to play a major role in liver cancer [3], one of the rare malignancies that can be induced by dietary restriction of methyl donors. Furthermore, global DNA hypomethylation and selective promoter hypermethylation of a large set of genes affect these cancers. Recently, mutations of ARID1a and ARID2 genes involved in chromatin remodeling have also been reported [4], but a systematic study of the status of epigenetic regulatory genes is lacking. Our aim was to identify epigenetic regulatory genes associated with liver cancer.

Methods: We first established a comprehensive list of well-known and putative epigenetic regulatory genes using data gathered from gene ontology databases and literature. Then, we performed cluster analysis of their expression in different liver diseases, using publicly available whole genome expression datasets. We also produced global gene expression data for a set of cirrhosis and liver cancer samples for validation studies.

Results: We constructed a comprehensive list representing more than 1000 epigenetic regulatory genes. We observed differential expression of many genes in liver cancer as compared to dysplasia, cirrhosis and normal liver samples. A few genes known that involved in liver cancer previously (such as EZH2 and WHSC1) were among them, as expected. Genes involved in histone methylation/demethylation and deacetylation formed the largest set that displayed major expression changes, some upregulated while some others downregulated in liver cancer. Changes in histone variant and DNA methyltransferase gene expression were also observed. Most importantly, we identified more than 20 genes overexpressed in liver cancer.

Conclusion: Our bioinformatic analysis of global gene expression datasets allowed us to demonstrate that epigenetic regulatory genes undergo important expression changes during hepatocellular carcinogenesis. A subset of these genes is upregulated in liver cancer and thus may serve as potential tumor markers and therapeutic targets.

References: 1. Sandoval J, Esteller M. Cancer epigenomics: beyond genomics. Curr. Opin. Genet. Dev.2012. 22(1):50-5.
2. Gilbert S.F., Ageing and Cancer as Disease of Epigenesis. J. Biosci. 2009. 34: 601-604.
3. Kung J.W.C., Currie I.S., Forbes S.J., Ross J.A. Liver Development, Regeneration, and Carcinogenesis. J. Biomed. Biotech.2010. 2010: 1-9.
4. Guichard C. et al. Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. Nat. Genet. 2012. [Epub ahead of print].

Disclosure of Interest: None Declared

P-258   SERUM ALPHAFETOPROTEIN (AFP) CONCENTRATION IN SMALL (<2CM) HEPATOCELLULAR CARCINOMAS

A. Leber [1,*], M. Sherman [1]

[1]Gastroenterology, University Health Network, University of Toronto, Toronto, Canada

Introduction: The value of AFP as a screening tool for hepatocellular carcinoma (HCC) is controversial. Advantages of the test include its low cost, ease of use and its high specificity at values greater than 400 ng/L. However, the sensitivity of AFP in the detection of small tumors is felt to be poor. The size of the tumor at initial detection is fundamentally important as it dictates available treatment options and the possibility for cure. Our objective was to examine the AFP level of tumors detected at a size of <2cm, 2-5cm and >5cm.

Methods: Patients presented at the multidisciplinary hepatoma rounds at the University Health Network (UHN) in Toronto, Canada were reviewed. Only those patients with a first presentation of HCC and those who had a pre-treatment serum AFP and radiological measurement of tumor size were included. Data pertaining to baseline characteristics, treatment modalities and prognosis at 1 year was collected through the electronic patient records.

Results: A total of 2330 patients were reviewed, and 1076 patients were selected based on the inclusion criteria. The mean age was 63 (range 18-94) and 80% of patients were male. The most prevalent liver disease etiologies were hepatitis B, hepatitis C and alcoholic cirrhosis. The AFP value and tumor size are displayed in table 1. Treatment modality varied with size of HCC. RFA was the most common modality used in tumors less than 2cm and TACE was the most common modality used in tumors >5cm. In those with one year follow up data, the one year survival for HCC < 2cm, HCC between 2.1-5cm and HCC >5cm in size was 97%, 94% and 77% respectively. The risk of tumor recurrence at one year was 32% in those with HCCs < 2cm and 76% in those with tumors > 5 cm.

Table 1: AFP value, tumor size and number, treatment modality and prognosis at 1 year

Measurement	<2cm (n=200)	2.1cm-5cm (n=515)	>5cm (n=361)
Mean AFP (ng/L)	115	481	22,526
Median AFP (ng/L)	9	19	145
Range (ng/L)	1-1277	1-98,112	1-957,168
% of patients with AFP <20 (ng/L)	73%	50%	23%
Mean tumour size (cm)	1.6	3.4	8.4
Number of tumours			
1	141	325	234
2	37	71	45
3	16	53	28
multiple	6	66	53

Conclusion: The majority of patients with small HCCs do not have significantly elevated AFP levels. AFP is not a sensitive tumor marker for small HCCs less than 2cm in size.

Disclosure of Interest: None Declared

P-259   PREDICTING THE TREATMENT EFFECT OF SORAFENIB USING PLASMA ANGIOGENESIS MARKERS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

T. Honda [1,*], T. Ichikawa [1], N. Taura [1], H. Miyaaki [1], H. Shibata [1], S. Uchida [1], Y. Kamo [1], T. Seno [1], E. Yoshimura [1], K. Nakao [1]

[1]Department Of Gastroenterology And Hepatology, Nagasaki University School Of Medicine, Nagasaki, Japan

Introduction: Sorafenib, the first agent demonstrated to have efficacy to improve the survival of patients with advanced hepatocellular carcinoma (HCC), is an active multikinase inhibitor affecting angiogenesis and tumor proliferation. We analyzed cytokines related to angiogenesis or cell proliferation, and tried to determine their utility as biomarkers of sorafenib treatment effect for HCC.

Methods: A total of 21 patients with HCC diagnosed between 2009 and 2011 in the Department of Gastroenterology and Hepatology, Nagasaki University Hospital, were recruited for this study. We evaluatedthebiomarkerof all patients in plasma vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), des-gamma-carboxy prothrombin (DCP) and interleukin-8 (IL-8) levels at the start of sorafenib therapy, and examined the association between objective tumor response, progression-free survival and overall survival.

Results: We evaluated patients for Response Evaluation Criteria in Solid Tumors (RECIST), 12 out of 21 patients (57%) achieved disease control. The median progression-free survival day of all patients was 161 days. They were categorized into two groups as follows: 1) 12 were classified as the responder group: partial response (PR) or stable disease (SD), and 2) 9 were put into the non-responder group: progressive disease (PD). There were no significant differences in the VEGF, HGF and DCP levels. However, the plasma IL-8 was significant lower the responder group than the non-responder group (p = 0.014). The progression-free survival of 10 patients with low IL-8 level (<8.0 pg/ml) group was significantly longer than the high IL-8 (=>8.0 pg/ml) gorup patients (P = 0.015).

Conclusion: The plasma level of IL-8 can be a predictive marker to assess the tumor response and progression-free survival to sorafenib therapy.

Disclosure of Interest: None Declared