(95% CI, 1.53–20.04; $P = 0.009$) for LSM 18.1–23 kPa; and 6.60 (95% CI, 1.83–23.84; $P = 0.004$) for LSM > 23 kPa.
Conclusion: Our data suggest that LSM could be a useful predictor of HCC development in patients with CHB.
Acknowledgement: This study was supported by a grant from the Bilateral International Collaborative R&D Program, Ministry of Knowledge Economy, and by the Good Health R&D Project, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (A050021).

CS14.3 The potential of genetically modified T cells to prevent HBV related HCC

A.J. Gehring*. *Department of Infection and Immunity, Singapore Institute for Clinical Sciences, Agency for Science, Techonlogy and Research (A*STAR), Singapore*

Hepatocellular carcinoma (HCC) that develops in chronic hepatitis B patients can express viral antigens from chromosomally integrated hepatitis B virus (HBV) DNA. Virus-specific T cells that could control HBV and eliminate HCC expressing viral antigen are deleted or dysfunctional in chronic patients. We have used T cell receptor (TCR) gene transfer to reconstitute antiviral T cell immunity in chronic HBV patients with the hope of developing a cell-based therapy to target HBV-HCC and the underlying chronic HBV infection. Using retroviral vectors we can introduce HBV-specific TCRs into chronic HBV patient T cells. We measure TCR expression using HLA-pentamers and transduced T cell function by intracellular cytokine staining, cytotoxicity and using a xenograft model of HCC ((γc)Rag2−/− mice). The introduced TCRs are efficiently expressed on the cell surface and result in polyfunctional T cells (IFN-γ, TNF-α, IL-2, Mip-β, MIP-α, IL-17, GM-CSF, IL-8) that can lyse hepatocyte-like cell lines expressing cognate HBV antigens. Adoptive transfer of TCR-redirected T cells in the xenograft HCC model prevents formation of the transplanted tumors and eliminates established tumors, demonstrating their *in vivo* functionality. Furthermore, HBV-specific TCR-redirected T cells can recognize Hep3B and PLC-PRF5, HCC lines with natural HBV-DNA integration, demonstrating they can respond to tumors expressing viral antigen. Thus, TCR gene transfer can generate large numbers of multifunctional HBV-specific T cells from chronic HBV patient lymphocytes that are capable of recognizing HBV infected hepatocytes and HCC tumor cells expressing viral antigens from naturally integrated HBV genomes. These genetically modified T cells could potentially be used to reconstitute virus-specific T cell immunity for adoptive cell therapy in chronic HBV and target tumors in HBV-related HCC patients.

CS14.4 Reevaluation of the carcinogenic significance of HBV integration in hepatocarcinogenesis

S.Z. Jiang[1,2], Z.W. Yang[1], X.J. Li[1], W.J. Li[1], Y.F. Wang[1], J.B. Zhang[1], J.L. Hou[2], X.M. Chen[1], H. Zhuang[1], F.M. Lu[1]*. [1]*Infection Disease Center & Department of Microbiology, Peking University Health Science Center, Beijing 100191, China,* [2]*Southern Medical University, Guangzhou 510515, China*

Aims: To re-evaluate the carcinogenic significance of hepatitis B virus (HBV) integration in hepatocarcinogenesis.
Methods: Viral host genome junction sequences in both tumor and paired corresponding non-tumor tissues from HCC patients with chronic HBV infection were analyzed using cassette ligation-mediated PCR (LM-PCR) and Alu-PCR and direct sequencing. The integration sites were mapped based on the acquired flank sequence of human genome. The potentially affected genes (interrupted directly by integration or mapped within 100kb up- or downstream of the viral-host junctions) were clustered based on their function via gene ontology (GO) were performed to cluster analysis. The somatic mutation and loss of heterogeneity (LOH) of TP53 were screened by direct sequencing. Array-based comparative genomic hybridization (aCGH) was performed to detect the chromosomal aberrations in tumor tissues.
Results: Collectively, a total of 232 different viral-host sequences were identified in 68% (34/50) of tumor and 70% (35/50) of non-tumor tissues. Among them, chromosomal locations were determined in 87.52% (71/84) of integrations in tumor tissues and 82.43% (122/148) in non-tumor tissues, respectively. The viral-insert sites were evenly distributed in all chromosomes including X and Y. However, 35.71% (30/84) of integrants were found within either exonic or intronic sequences of a host gene in tumor tissues, and 35.13% (52/148) in non-tumor tissues. Further GO annotation revealed that the affected genes were enriched in transcription regulation (9/31) and nucleus (12/31) with statistically significant. Such enrichment was not observed in non-tumor. Of 179 genes in tumor and 313 in non-tumor, which mapped within 100 kb up- or downstream from or interrupted by the HBV integration, GO annotation demonstrated that genes involved in metabolism, transcription, and DNA-binding were more enriched in tumor than in non-tumor. In particular, 23.46% (42/179) genes were related with transcription in tumor, but few genes were discovered in non-tumor. When regarding to the HBV genome, 59.48% (138/232) integrants contained X region sequences, 40.52% (94/232) integrants contained pre C/C region sequences. The break points of the integrants were mainly distributed between the DR1 and DR2 of HBV. The percentages of 3′ deleted X gene caused by integration were 97.96% (48/49) in tumor and 95.51% (85/89) in non-tumor tissues ($p > 0.05$). Further analysis of these integrated 3′ truncated X gene via immunohistochemistry assay detected few expression of HBx in tumor. In addition, data from aCGH study indicated that no direct correlation between chromosome instability and HBV integration, while mutations or LOH of TP53 were found in most tumor tissues with greater chromosome instability.
Conclusions: HBV DNA integration could be observed in both tumor and non-tumor tissues, with similar rates of HBV C or X region integration. A similar frequency of integrated X gene 3′ truncated deletion in tumor and corresponding non-tumor tissues did not support a role in hepatocarcinogenesis. Chromosomal instability (CIN) has no prominent correlation with HBV integration. GO analysis showed that genes located surrounding or interrupted by the HBV integration in tumor tissues were clustered with functions more relevance to transcription, nucleus and so on, indicating that HBV integration affecting the expression of the nearby genes is a previously unrevealed molecular mechanism leading to cell malignant transformation.
Funding: This work was supported by grants from the National S&T Major Project for Infectious Diseases (2008ZX10002–012 and 2009ZX10004–903).