Chromosomal Common Genetic Alterations in and Their Possible Sequences in the Liver Carcinogenesis

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Chronic infection of hepatitis B or C virus and certain environmental toxins as the important risk factors for HCC development have been clearly documented. However, the oncogenic pathways leading to malignant transformation of liver cells remains obscure. As in other human cancers, the development of HCC has been proposed to be a multi-step evolution involving many important and stage-wise genetic changes. The differential involvement of the p53 tumor-suppressor gene in HCC associated with various risk factors has been largely clarified. Evidence for a crucial role of the reactivation of the beta-catenin pathway, through mutations in the beta-catenin and auxin genes, represents a major breakthrough [36]. Beta-catenin mutation may play an important role in the carcinogenesis of a subset of HCC with good prognosis, and mutant and wild-type nuclear beta-catenin proteins may not function equivalent. However, unlike the well-characterized sequential genetic changes of colorectal cancers, most of those in hepatocarcinogenesis remain unknown.

Current cytogenetic and molecular genetic studies have shown interesting findings, including amplification or overexpression of known proto-oncogenes and frequent allelic loss on chromosomes 1p (1p35–36), 4q (4q12–23) or 16q (16q22–23). Recent extensive allelotype studies and genome-wide analysis of HCC chromosomes by using comparative genomic hybridization (CGH), loss of heterozygosity (LOH) or spectral karyotyping (SKY) have resulted in a comprehensive overview of the main genetic abnormalities in HCC, including DNA copy gains and losses. By using CGH, the genetic similarities between HBV- and HCV-related HCC was documented [43], with
frequent deletions of 1p (24%), 4q (39%), 6q (41%), 8p (44%), 9p (24%), 11q (24%), 12q (22%), and 13q (39%), as well as common gains of 1q (46%), 6p+ (20%), 8q+ (41%), 11q (27%), and 17q+ (37%). We recently just finished a high resolution LOH mapping, using 400 microsatellite markers to scan the chromosomes of 40 HCCs. The detailed mapping narrowed down many the smallest common LOH regions that are useful for further positional cloning. The mapping also revealed no significant difference in the number and type of chromosomal LOH between HCV− and HBV−infected tumors. These data suggested that both HBV and HCV cause cancer through non−specific inflammatory and regenerative processes.

Nevertheless, among many most frequently altered chromosomal regions it is not clear which one to be critical and early genetic mutations that should be present not only in neoplastic (cancer) but also in preneoplastic lesions. Therefore the genetic profile and chromosomal allelic imbalances in cirrhotic nodules that are well−recognized preneoplastic stage of HCC are investigated. In one of our studies, we microdissected 180 cirrhotic nodules from 7 female HCC patients to study their clonality nature first by examining the X chromosome methylation pattern. The allelic imbalance in monoclonal cirrhotic nodules and the corresponding HCCs were further analyzed with microsatellite polymorphic markers. Nearly half of the cirrhotic nodules were monoclonal and already had chromosome aberrations. In addition, the allelic imbalance on 4q, 8p, and Xq may be the earlier mutations, whereas the allelic imbalance on 1p, 13q, 16q and 17p are late ones, in hepatocarcinogenesis. Thus it is important to look for putative tumor suppressor genes in chromosome 4q, 8p and even Xq, which can be the causes of liver cancer.

Finally, the extensive alterations in the chromosomes of HCC become a unique signature for individual HCC. Such a signature or fingerprinting can be used in clinical application. In the situation of HCC recurrence after surgical treatment, it is difficult to discriminate whether the recurrent HCC is from the previous one or from a de novo HCC. To address this, we collected 31 pairs of primary HCC and recurrent HCC from the same patient and then compared the CGH profiles of two HCCs resected from the same individual. CGH gave a fingerprinting of chromosomal
alterations for each HCC. By this, we could reliably tells about 30% of the primary and recurrent HCC are identical (shared the same CGH pattern) thus represented a true relapse. About 50% were different in their CGH profiles, thus represented as de novo HCC. These results resolved an important clinical question and might help to understand the cause of recurrence in post-operative HCC and even the plan for further treatment.

In conclusion, molecular genetic study of HCC is just beginning. Many important, common chromosomal regions with alterations are identified but the target genes are not yet cloned. The advent of human genome sequence will enhance the discovery of implicated tumor suppressor or proto-oncogenes. A better understanding of the sequential genetic mutations during carcinogenesis may pave the way for more reliable diagnosis of minute or well-differentiated HCCs. It also opens a possible targets for chemo-prevention during the carcinogenesis or for novel gene therapy in the future.
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Research Interest:  
1) Molecular Virology of Hepatitis Viruses (HDV, HBV and HCV): Major in Hepatitis D Virus  
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   Hepatitis delta antigen posttranslational modifications  
   Biochemistry and biology  
2) Molecular Genetics of Liver Cancer  
3) Clinical Studies of Chronic Hepatitis and Liver Cancer

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Research Interest:  
1) Molecular Mechanism of Angiogenesis of Hepatocellular