Pathology and molecular diagnosis of early hepatocarcinogenesis

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Pathological and molecular biological analyses have shown two patterns of cancer development: de novo carcinogenesis and multistep carcinogenesis. Evidences are accumulating that indicate the multistep development of human hepatocellular carcinomas (HCCs) associated with chronic hepatitis or cirrhosis.\(^1\)\(^3\) It has been shown that small nodular hypercellular lesions known as adenomatous hyperplasia or dysplastic nodule appear in damaged liver infected with hepatitis virus B or C. These lesions develop into early HCC, which corresponds to in situ or microinvasive carcinoma, in which the portal tracts within the nodule are preserved. Early HCC then develops into progressed HCC through the stage of “nodule-in-nodule”-type HCC (progressed HCC within early HCC), which indicates a transition from early to progressed HCC. These pathological findings are also supported by clinical and radiological findings.\(^4\)\(^7\) On the basis of this current knowledge of multistage hepatocarcinogenesis, high-risk patients are closely followed up, and increasing numbers of small equivocal lesions are detected by imaging diagnosis. Ultrasound-guided needle biopsy is performed on such lesions, and if they are diagnosed histologically as cancer they are treated. However, as is the case with other early cancers, such as those of the lung, stomach, and colon, early HCC shows minimum atypia, and lacks definite invasive or destructive growth. Therefore, it is often difficult even for the hepatopathologist to distinguish regenerative nodules, precancerous lesions, and early HCC. For these reasons, the discovery of an objective molecular marker that will help to standardize histological diagnosis of early HCC and lead to appropriate treatment is eagerly anticipated. In addition to this diagnostic problem, the molecular mechanisms of hepatocarcinogenesis are far from clear. Though some oncogenes and tumor suppressor genes have been revealed to be mutated in early stage carcinogenesis of colon, pancreas etc., the molecular changes that occur in early HCC are not well understood. Our unpublished observations indicated that histologically evident multistep hepatocarcinogenesis is most frequent in cases with HCV infection. However carcinogenic potential of
HCV and how HCV triggers carcinogenic process is not clearly explained. A molecular understanding of multistep hepatocarcinogenesis is an important step toward the identification of additional biomarkers and new therapeutic targets with increased specificity for HCC development. The establishment of microarray methods for large-scale analysis of gene expression has made it possible to seek molecular markers for cancer classification and outcome prediction, and to identify molecules involved in carcinogenesis in a variety of tumor types.\textsuperscript{8} We compared expression profiles among 7 early components and 7 progressed components of "nodule-in-nodular"-type HCCs and their corresponding noncancerous liver tissues using oligonucleotide array.\textsuperscript{9} Of the approximately 12600 genes that were analyzed, a set of 95 genes provided a molecular signature that distinguished between early HCC components and their non-cancerous liver tissues, and a set of 92 genes distinguished between progressed and early HCC components. Of these genes, the most abundantly upregulated gene in early HCC components \( (P < 0.001) \) was heat-shock protein 70 (HSP70). Real-time quantitative reverse transcription polymerase chain reaction confirmed this finding. Further immunohistochemical examination of HSP70 using mouse monoclonal antibodies for HSP70 (SC-24; Santa Cruz Biotechnology, Santa Cruz, CA) at a dilution of 1:500 revealed its significant overexpression in early HCC compared with precancerous lesions \( (P < 0.001) \), and in progressed HCC compared with early HCC \( (P = 0.0011) \). At present, it is not clear why HSP70 expression increases in early HCC and progressed HCC. One possibility is that HSP70 expression increases as a result of a stressful environment in early HCC such as oxidative stress and hypoxia. It is also expected that HSP70 plays some role in carcinogenesis. It has been reported that the HSP family of proteins is involved in stabilization of telomerase, and that HSP70 inhibits apoptosis by negative regulation of Apaf-1 apoptosome. In addition to HSP70, other candidate genes involved in multistep hepatocarcinogenesis are now under investigation. Finally human HCC is an excellent model to study multistep process of carcinogenesis, and further efforts are expected to overcome this highly malignant cancer.

REFERENCES


Education
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