# Does Monoclonality Mean Malignancy?

## To the Editor:

Kawai et al. reported monoclonality of hepatocellular carcinoma (HCC) using the method based on methylation pattern of polymorphic X-chromosome–linked phosphoglycerate kinase (PGK) gene in females, and they stated that it would be helpful for the diagnosis of HCC in certain cases because of polyclonality of the adjacent cirrhotic liver as well as adenomatous hyperplasia (AH).[1] We would like to notify problems involved in this report. First, regenerative nodules in cirrhosis, even though they are microscopically non-neoplastic, have been shown to be frequently composed of monoclonal cell expansion of hepatocytes using the method based on integration of hepatitis B virus (HBV) DNA into the cellular genome by Yasui et al.[2] and using the PGK-gene–based method by us.[3] Yasui et al.[2] and we[3] could show that 31% and 43% of regenerative nodules analyzed were monoclonal, respectively. Secondly, AH is classified into two groups, i.e., AH with non-neoplastic nature (ordinary AH or type I macroregenerative nodule) and AH with neoplastic nature (atypical AH or type II macroregenerative nodule).[4,5] The authors showed polyclonality of ordinary AH, but it is not ordinary AH but atypical AH that is often difficult to be differentiated from well differentiated small HCC by histological examination of the needle biopsy or surgically resected specimens. Atypical AH, like HCC, was previously reported to have monoclonal origin.[6] High frequency of monoclonal regenerative nodules in cirrhotic liver as well as monoclonality of atypical AH seems to suggest that clonal analysis is unlikely to play a significant role in the differential diagnosis of HCC from other benign lesions.

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## Reply:

Aihara et al. should read our paper more carefully. We stated ". . . Analysis of the methylation pattern of the PGK gene may be helpful on rare occasions in elucidating the nature of liver tumors, but must in fact be used in conjunction with histological appearances to avoid errors secondary to inflammatory infiltrates" and did not claim that we could differentiate HCC from AH by the analysis of clonality alone.[1] We consider that HCC is monoclonal in its origin. However, monoclonality alone does not establish the malignant nature of the nodule. Further study is required to determine whether the nodules having monoclonality becomes HCC later on.

In their report published in *Gastroenterology*, Aihara et al. stated that "these monoclonal nodules are speculated to arise from accumulation of certain genetic alterations that are required for carcinogenesis, thus they can be considered as precancerous lesions, although histological examination fails to identify them."[2] So, they themselves jump to the conclusion that monoclonality means the premalignant nature of the nodules.

Regarding the differentiation between HCC and AH, we have objection to their comment. The borderline between HCC and AH is sometimes obscure, especially in biopsy materials we have examined. If we mistakenly identify a nodule with malignant nature as benign, the results must be disastrous. Therefore, precise differentiation should be made between benign and cancerous/precancerous tissues from the clinical point of view. Tsuda et al. examined the clonality of an atypical AH surrounding HCC and reported that the AH had monoclonal nature as well as HCC and that the HCC might be developed from the atypical AH.[3] So, atypical AH might later develop cancer. Thus, we believe the AH, which should be differentiated from HCC is ordinary AH and not atypical AH. In this sense, we believe a nodule in which monoclonality is observed should be cautiously followed to determine whether HCC develops later on.

Whether these nodules with monoclonal nature develop HCC later on can only be determined by a prospective study.

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