Sir,

We have reported two patients with hepatocellular carcinoma (HCC) and type 2 diabetes mellitus (T2DM), who showed abundant glycogen in their liver parenchyma but a marked reduction of glycogen content in HCC.[1] It was suggested that the latter was associated with appearance of a Warburg type glycolysis[1] and discussed in some detail.[2]

Cytokeratins (CKs), the intermediate filament (IF) proteins of epithelia, are sub-divided into type I (CK9-20) and type II (CK1-8) and expressed as type I/II pairs in a cell differentiation manner. In adult liver, hepatocyte IF comprise only CK8/18.[3] CK8/18 expression in normal and diseased liver has been reported, including positive expression in alcoholic steatohepatitis (ASH) and/or non-alcoholic steatohepatitis (NASH) and HCC.[3]

We examined the expression of CK8/18 in the liver to investigate cytoskeletal alterations in hepatocytes, possibly related to changes in hepatocellular glycogen content during hepatocarcinogenesis. Our studies revealed that immunoreactivity for CK8/18 was reduced or frequently even negative in glycogen-rich hepatocytes of background liver [Figure 1b and d], but moderately positive in normal hepatocytes and glycogen-poor cells in HCC [Figure 1a, c, e and f]. Overexpression of CK8/18, as Malory Denk bodies, which are hallmark lesions in ASH and NASH,[4] was not detected [Figure 1b and d]. The results provide evidence for reduced to negative CK8/18 expression in glycogen-rich hepatocytes.

The mechanism of alteration of CK8/18 expression in glycogen-rich hepatocytes has not been elucidated. Su et al.[4] demonstrated that CK8/18 expression was reduced in excessively glycogen-storing (glycogenotic) clear hepatocytes, which also showed a relative reduction of cytoplasmic organelles as demonstrated by electron-microscopic studies. Given simple CK8/18 expression patterns, hepatocytes are sensitive to alterations of cytokeratin architecture.[3] Using hepatic cell culture systems, Mathew et al.[5] reported recently that CK8/18 is involved in the interplay between glucose utilization and insulin signaling. The authors demonstrated that insulin stimulates glucose uptake, glucose-6-phosphatase formation, lactate release, and glycogen formation in hepatocytes via the PI-3 kinase dependent signaling pathway, and that CK8/18 IF loss makes them more efficient glycogen producers.[5] This is in line with the notion that an insulinomimetic effect of oncogenic agents is responsible for the preneoplastic hepatocellular glycogenesis,[6] which is associated with a reduced or negative expression of CK 8/18 in glycogenotic clear cells appearing in chronic human and woodchuck hepadnaviral infection.[6] CK8/18 immunohistochemistry may allow distinct recognition of the glycogen-rich hepatocytes as shown in glycogenotic clear cells under various conditions.[6]
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Conflicts of interest
There are no conflicts of interest.

REFERENCES


