From Micron to Nano: Beyond Light Microscopy- Electron Microscopy Identifies Potentially Predictive Morphological Changes for Hepatocellular Carcinoma

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Abstract

Electron microscopy (EM) has become a vital instrument in scientific research to add or improve knowledge. In this presentation, I highlight how EM enabled key findings from the microscale of light microscopy to the EM nanoscale and its continuing value in scientific discovery.

Screening of hepatic nodules by radiological imaging techniques between 0.5 and 1.5 cm are rarely diagnosed, and they are usually biopsied. Meanwhile, no specific histopathological criteria were postulated by the published studies as a predictor of malignancy.

The present study incorporates transmission electron microscopy (TEM) techniques with light microscopy to explore structural and morphological details that were otherwise inaccessible.

63 liver biopsies were studied via light and EM. They consisted of 14 biopsies from surgically resected HCC over existing HCV and 12 biopsies from experimentally gradually induced HCC in mice with hepatocarcinogenic dimethylnitrosamine (DEN) sacrificed at the intervals of 4, 8, and 16 weeks. Lesion progress up to the onset of HCC was inspected grossly and microscopically.

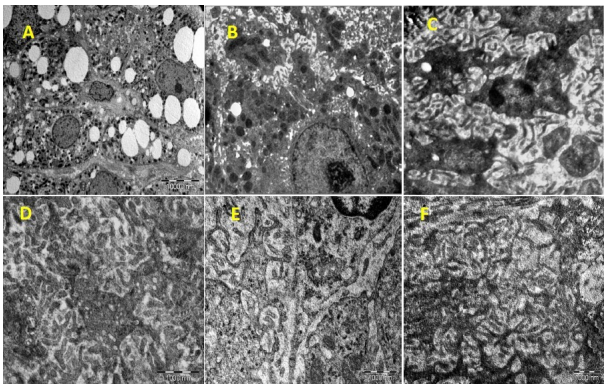
These were compared to premalignant hepatic lesions consisted of: 14 biopsies from corresponding safety tumor resection margin; 20 biopsies of ultrasound guided liver core biopsies from HCV positive patients for serum HCV RNA, including 7 cirrhosis / 5 regenerative nodules stage F4 compensating hepatic cirrhosis; and 3 control normal mice.

This study was done in an attempt to depict cellular criteria denoting or signaling premalignant transformation, to identify the patients at risk who should have a closer follow-up, and to guarantee early diagnosis of malignancy with a more promising curative rate.

Liver Morphological Predictors of malignant transformation proposed in this study include: alternating electron-dense and electron-lucent hepatocytes; Biliary tree changes in the form of bile canaliculi bordered by > 3 hepatocytes with increased junctional complexes, Detection of bile ductules among hepatocytes trabeculae, frequently detected Hering canal, hepatic progenitor cells and dividing intermediate hepatocytes like cell. The most relevant criteria are the detection of star shape cytoplasmic masses detached from progenitor cells or hepatocytes. The fragmented portions derived from the mother cell may contain electron dense mitochondria and form small cytoplasmic processes that could facilitate mobility. These cytoplasmic masses were seen in regenerative nodule, free tumor margin, 16-week induced HCC in mice and in HCC samples. This finding may suggest disruption of normal regenerative process, resulting in reliance on alternative cellular replication mechanisms. Notably, hepatocyte fragmentation or splitting may represent a primitive regenerative form of division, comparable to the division mechanism reported in starfish.

It is recommended that post-resection HCC patients and those with cirrhosis exhibiting regenerative nodules should be enrolled in an appropriate surveillance program.

Research using electron microscopy is mainly for exploring the unknown or for improving the present. Electron microscopy should not be used just to confirm what is already known, as it will not add further scientific value. Instead, it is a tool for discovering the unknown and building upon existing knowledge.



Electron Micrograph of mixed nodular cirrhotic liver(A); Electron Micrographs showing Detached star shape structure from hepatic cells seen in cirrhotic liver with regenerative nodule (B and C) ; 16-week induced HCC in mice (D) ; surgically resected HCC (E); Free tumor resection margin(F)