Chapter 3
Ultrastructure of Hepatocellular Carcinoma

The ultrastructural features of HCC vary according to the degree of differentiation [94, 95]. When HCC is less differentiated, the nuclei increase in size and nuclear irregularity becomes more evident. Ultrastructurally, moderately or well-differentiated HCC can be distinguished from the poorly differentiated type by differences in the development of cellular organelles, the number of bile canaliculi, and the cellular attachment. In moderately to well-differentiated HCC, mitochondria and rough endoplasmic reticulum (rER) are well developed; the well-developed rER is believed to be evidence of the production of secretory proteins such as albumin. The Golgi apparatus and peroxisomes are evident, but remarkably decrease in number. In accordance with these findings, the smooth endoplasmic reticulum (sER) is also poorly developed. The formation of bile canaliculi and bile production are of value in the diagnosis of moderately to well-differentiated HCC, but it is occasionally difficult to diagnose poorly differentiated HCC ultrastructurally because of the sparse formation of bile canaliculi.

Trabecular HCC

In a normal liver, the cells occur in one-cell-thick plates, which are arranged in a radiating fashion from the central vein to Glisson’s capsule, while two- to three-cell-thick plates are seen in a cirrhotic liver. In trabecular HCC, a structure reminiscent of normal liver cell cords is seen, but the plates vary irregularly in thickness, forming thin to thick trabeculae (Figs. 3.1-12).

The relationship between the blood space and the trabecular tumor nest is similar to that between the sinusoid and liver cell cords in a normal liver. Isomura and Nakashima [95], however, distinguished the blood space from the normal sinusoid by the sparsity of pores in the endothelial cells, the presence of intercellular junctions between the endothelial cells, and the existence of a basement membrane-like substance, in the subendothelial space of the blood space, which is seen as an either continuous or discontinuous membrane of up to several layers in thickness. The appearance of the basement membrane-like substance in HCC corresponds to capillarization of sinusoids in chronic hepatic lesions or liver cirrhosis [96]. Microvilli formation on the free surface in the subendothelial space becomes prominent when the HCC is well differentiated. The microvilli are, however, partly dependent on the amount of collagen in the subendothelial space. The number of microvilli is reduced in the collagen-rich space, which indicates that the exchange of material in
the blood space in HCC may depend not only on the degree of differentiation of the tumor, but also on the amount of collagen in the blood space.

**Pseudoglandular HCC**

In pseudoglandular HCC (Figs. 3.13–16), the tumor forms a tubular structure to varying degrees. The tubules with microvilli on the free surface of the lumen are similar to normal bile canaliculi or bile canaliculi between tumor cells. In addition, the tubules occasionally contain an electron-dense substance, presumably bile, in the lumen. Thus, some of the tubules can be considered dilated bile canaliculi. The degree of development of microvilli varies, possibly according to the differentiation of the tumor. The microvilli vary in size, but we were unable to find any blebs, as seen in obstructive jaundice. The microfilaments are well developed in some tubules, but are sparse in others. In the lumen of the latter, myelin figures are evident, suggesting that such figures are formed by degeneration of the tumor cells.

**Compact HCC**

In compact HCC, the nucleus/cytoplasm ratio is high, the development of organelles is poor, cellular attachment is poor, and bile canaliculi are sparse. All these electron-microscopic findings suggest that tumors of the compact type are poorly differentiated. In general, compact HCC lacks the histological characteristics of HCC. The structure of the blood space between tumor cells, however, is similar to that seen in trabecular HCC. Therefore, the presence of a blood space-like structure may play an important role in electron-microscopic diagnosis.

**Clear Cell HCC**

Although Anthony [97] and Cameron [98] classified clear cell HCC as a specific type, it is not uncommon to encounter HCC consisting of clear cells in varying degrees. Ultrastructurally, HCC cells of the clear cell type contain abundant glycogen granules in their cytoplasm, or fat droplets in some cases (Figs. 3.17, 18).

**Mallory Bodies in HCC Cells**

Ultrastructurally, Yokoo et al. [99] classified alcoholic hyalins into three distinct morphological forms: *type I*, bundles of filaments in parallel arrays; *type II*, clusters of randomly oriented fibrils; *type III*, granular or amorphous substance containing only scattered remains of fibrils.

In HCC, globular hyalins are observed as either type I or type II inclusions (Fig. 3.19), and reticular hyalins are seen as type III inclusions accompanying type I inclusions in their periphery (Fig. 3.20). Tomimatsu [87] suggested that peroxisomes might be related to the formation of type I and type II inclusions, according to the evidence that they surrounded type I or type II inclusions in some cases (Fig. 3.19).