COLLAGEN RESORPTION BY MACROPHAGES AND FIBROBLASTS IN CIRRHOSIS OF THE LIVER

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Phagocytosis and intracellular resorption of collagen by fibroblasts have been demonstrated by many investigations conducted on different models [1, 2, 4, 6, 7, 14, 15]. Macrophages also can ingest collagen and subject it to intracellular lysis [3, 9-11, 13]. However, it is not yet reliably known whether phagocytosis of collagen fibrils by macrophages and (or) fibroblasts takes place in the cirrhotic liver. There is only one study in which fragments of collagen fibers were observed in vacuoles of a macrophage during regression of fibrosis of the liver [8]. It is essential to know whether macrophages and fibroblasts undertake collagen resorption in this process in order to understand the mechanisms of destruction of fibrous tissue in the liver.

In the investigation described below methods of electron microscopy and electron histochemistry were used to study the role of macrophages and fibroblasts, and also of their lysosomal apparatus, in collagen resorption in cirrhosis of the liver and during its regression.

EXPERIMENTAL METHOD

Cirrhosis of the liver was induced by subcutaneous injection of 0.2 ml of a 40% solution of CCl_4 in olive oil into noninbred male albino mice once a week for 5 months. To stimulate regeneration, the left lobe of the liver was resected in all the animals 10 days after the last injection of CCl_4. Material for investigation was taken during resection and also 5, 10, and 15 days thereafter. Material for histological investigation was fixed in 10% neutral formalin, and that for electron microscopy in glutaraldehyde, then postfixed in OsO_4, dehydrated, and embedded in Epon. Some of the material was treated histochemically to detect acid phosphatase [5]. Ultrathin sections were examined in the ÉVM-100L electron microscope.

EXPERIMENTAL RESULTS

Electron-microscopic investigation of the resected material revealed many fibroblasts, macrophages, lymphocytes, polymorphonuclear leukocytes, eosinophile, plasma cells, and Ito's cells in the widened Disse's spaces. The fibroblasts were most frequently surrounded by newly formed collagen. The nuclei of the fibroblasts were large, and hypertrophy and hyperplasia of the rough endoplasmic reticulum and lamellar complex were observed in the cytoplasm. During regeneration of the liver the number of fibroblasts and the quantity of newly formed collagen decreased.

At all stages of the process single fibroblasts containing vacuoles with collagen fibers in their cytoplasm were found (Fig. 1). In their ultrastructure these cells were quite indistinguishable from the remaining fibroblasts.

Macrophages in the resected material and in the early stages of regression of cirrhosis were large and contained many secondary lysosomes, many vacuoles with varied contents, and lipid inclusions. Sometimes phagocytosed platelets were seen in the cytoplasm of these cells. In some macrophages (stellate reticuloendotheliocytes), just as in fibroblasts, vacuoles with phagocytosed collagen fibers were found at different stages of the investigation. Macrophages

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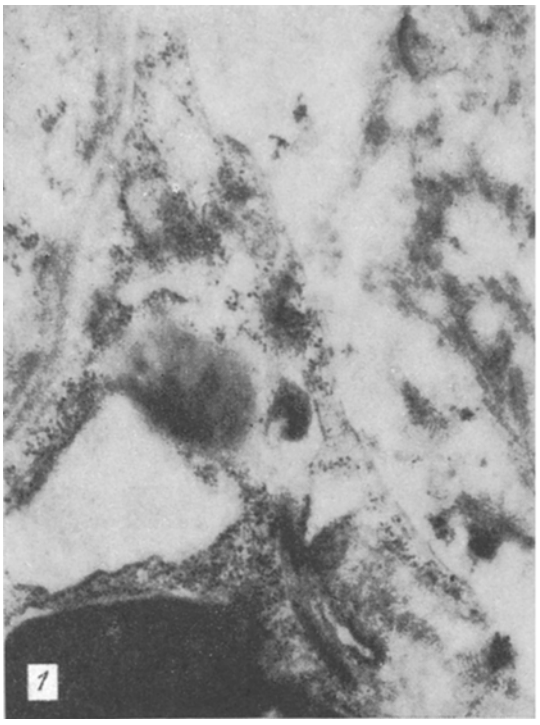

Fig. 1

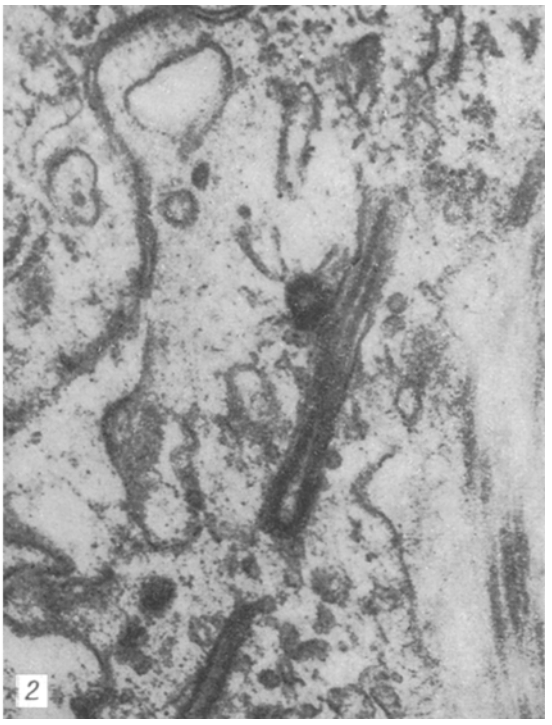

Fig. 2

Fig. 1. Fibroblast from resected material. Vacuole with collagen fiber, preserving cross-striation, present in cytoplasm (arrow).* N) Nucleus, RER) greatly widened rough endoplasmic reticulum, LI) lipid inclusion, C) extracellular collagen. 30,000×.

Fig. 2. Fragment of cytoplasm of macrophage 15 days after recection. Arrows indicate vacuoles with collagen fibers preserving cross-striation. C) Extracellular collagen. 70,000×.

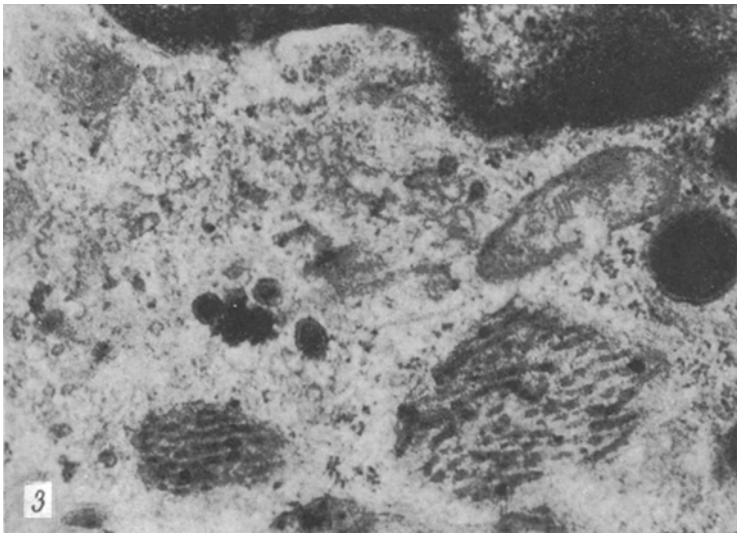

Fig. 3. Macrophage 10 days after resection. Two vacuoles in cytoplasm contain bundles of obliquely cut collagen fibers. Arrows indicate product of reaction for acid phosphatase. N) Nucleus, Cl) cytolemma. 30,000×.

containing vacuoles with collagen in their cytoplasm were found rather more frequently than fibroblasts with phagocytosed collagen.

* Abbreviations missing from Figs. 1-3 in Russian original .

Some degree of hyperplasia of the rough endoplasmic reticulum was observed in macrophages containing vacuoles with collagen fibers; together with the large number of lysosomes, this most probably indicates increased synthesis of protein and, in particular, of lysosomal glycosidases, which participate directly in collagen resorption [12].

In vacuoles containing collagen in macrophages and fibroblasts both single fibers and also bundles of collagen fibers were observed. Several vacuoles containing collagen also were found in the same cell. During involution of the cirrhotic changes, macrophages and fibroblasts carrying out phagocytosis of collagen were more frequently found than at the height of development of cirrhosis.

Reaction product was found in vacuoles containing collagen fibers in material tested for acid phosphatase, evidence of activity of this enzyme in these cells (Fig. 3). The electrohistochemical data confirm the phagocytic nature of the vacuoles with collagen and indicate an active role for lysosomes in the intracellular lysis of collagen by macrophages and by fibroblasts in cirrhosis of the liver.

Thus in cirrhosis of the liver and also during its regression phagocytosis and intracellular resorption of collagen by macrophages (stellate reticuloendotheliocytes) and fibroblasts thus take place. Intracellular destruction of collagen in these cells occurs with the active participation of lysosomal enzymes.

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