Connective Tissue Vol. 30. 1998

Minireview

Hepatic Stellate Cells

Kenjiro WAKE

Department of Anatomy, School of Medicine, Tokyo Medical and Dental University

Received, 30 April, 1998; accepted, 23 May, 1998.

Abstract: The hepatic stellate cells were first described by Kupffer in 1876, using the gold chloride method. At that time these cells were thought to be perisinusoidal connective tissue cells. However, a misconception by himself in 1898 led to a deep-rooted confusions in liver histology. I rediscovered the original stellate cells by the use of Kupffer's gold method in 1971. These cells are now known as the vitamin A-storing cells which locate perisinusoidally and produce collagens and other extracellular substances. Three-dimensional entire forms of the stellate cells are effectively demonstrated by the Golgi's silver method. Their dendritic processes wrap the endothelium of sinusoids. Numerous spine-like microprojections of the stellate cells make spotty contacts with hepatocytes. The space of Disse is the space between the endothelial cell-stellate cell complex and the hepatocytes, being bridged by the spines. Intralobular heterogeneity of these cells is examined in relation to the microcirculation and the fibrogenesis.

Key words:hepatic stellate cell, Kupffer cell, vitamin A-storing cell

Introduction: A brief history

Hepatic stellate cells were first described by Kupffer in 1876, using the gold chloride method[1,2]. In his preparations, the black-stained star-shaped cells distributed regularly within hepatic lobules. These cells were located outside of sinusoids. He named these cells "Sternzellen der Leber (stellate cells of the liver)". Rothe (1882)[3] observed clear inclusions in the black-stained cytoplasm and thought that they might be small nuclei of the stellate cells. In 1898, Kupffer[4] changed his earlier opinion and concluded that the stellate cells were the special endothelial cells of sinusoids which incorporated India ink injected. Kupffer's renewed concept was widely accepted and since then this designation was given to the phagocytic cells in the liver. On the other hand, investigators reported several perisinusoidal cells independently using different staining methods.

By the use of Kupffer's gold method, I rediscovered the original stellate cells in 1971 [5]. I proved that the inclusion bodies in the cytoplasm reported by Rothe were the lipid droplets containing vitamin A and that the perisinusoidal cells such as Berkley's 'granular cells', Zimmermann's 'pericytes in the liver', Ito's 'fat-storing cells', and Suzuki's 'interstitial cells' were the same cells as the original stellate cells. Since 1996, the term "hepatic stellate cells" [6] has been used widely in referring to this perisinusoidal cell type in the liver, according to the first designation by Kupffer (1876).

Reprint requests to :Dr. Kenjiro Wake Liver Research Unit
Minophagen Pharmaceutical Co. Ltd. No. 3, Tomizawa Bldg. 4F
3-2-7, Yotsuya, Shinjuku-ku, Tokyo 160-0004 Japan
Tel: 81-333-55-6567 Fax: 81-333-411-6160

Structure of the hepatic stellate cells

The Golgi's silver impregnation method, which was first used by Zimmermann in 1923 [7] for liver histology, is only one method to visualize the entire profile of the single stellate cells. The cell consists of an spindle-shaped or angular cell body and long and branching cytoplasmic processes (subendothelial processes), which encompass the endothelial tubes of sinusoids [8]. Some processes penetrate the hepatic cell plates (interhepatocellular processes) to reach the neighboring sinusoids to taper off to several subendothelial processes. Accordingly a single stellate cell wraps two or three, sometimes, four sinusoids with long processes. The total length of sinusoids surrounded by a single cell is 60-140 μm in the rat liver.

The subendothelial processes are flat and have three cell surfaces; inner, outer and lateral. The inner one is smooth and adhere to the upluminal cell surface of the endothelial cells. Between the two cells, the basement membrane-like materials are intercalated. The outer cell surface, facing to the space of Disse, is decorated with short microvillous protrusions. The lateral edges of the subendothelial processes are characteristically studded with numerous spine-like microprojections whose tips make contacts with the microvillous facets of the hepatocytes [9]. Thus these microprojections may be called as 'hepatocyte-contacting processes (HCP)'. The stellate cells adhere to the endothelial cells, and on the other hand, make spotty contacts with hepatocytes.

The conspicuous feature of the stellate cells is the occur-

rence of lipid droplets containing vitamin A [2,10]. Two types of lipid droplets are discriminated; membrane-bound (Type I) and non-membrane bound (Type II). Type I is smaller than the Type II and develop from the multivesicular bodies (MVB). Senoo et al. [11] demonstrated that retinol-binding protein is incorporated to MVB of the stellate cells via coated vesicles. The mechanism of development of both types of vitamin A-containing lipid droplets in the stellate cells is not known.

Intralobular heterogeneity of the stellate cells

The stellate cells in the centrilobular zone were conspicuously dendritic with long processes studded with spines in comparison to those emitted by periportal elements [12]. Desmin and vitamin A-storage in the cytoplasm are more prominent in the periportal zone in the pig liver. Within the single zone, vitamin A-containing lipid droplets are larger at periportal than midseptal regions [13]. Numbers of inlet venules of the portal vein are much less in the midseptum than portal regions and vitamin A-low territory is compatible with sites of fibrogenetic propensity during the hepatic fibrosis and cirrhosis.

References

1) von Kupffer, C. (1876) Ueber Sternzellen der Leber, Briefliche Mitteilung an Prof. Waldeyer. Arch. Mikr. Anat. **12**: 353-358
2) Wake, K. (1980) Perisinusoidal stellate cells (fat-storing cells, interstitial cells, lipocytes), their related structrure in and around the liver sinusoids, and vitamin A-storing cells in extrahepatic organs. In: Boune, G.H., Danielli, J.F. (eds) Int. Rev. Cytol. Vol. 66, Academic Press, New York, p. 303-353
3) Rothe, P. (1882) Ueber die Sternzellen der Leber. Inaug-Dissertation, Munich University
4) von Kupffer, C. (1898) Ueber Sternzellen der Leber. Verh. Anat. Ges. 12 Versammlung in Kiel, p.80-86
5) Wake, K. (1971) 'Sternzellen' in the liver: Perisinusoidal cells with special reference to storage of vitamin A. Am. J. Anat. **132**: 429-462
6) Hepatic stellate cell nomenclature [letter] (1996) Hepatology **23**: 193
7) Zimmermann, K.W. (1923) Der feinere Bau der Blutcapillaren. A. f. d. ges. Anat. **63:** 29-109
8) Wake, K. (1988) Liver perivascular cells revealed by gold and silver impregnation methods and electron microscopy. In: Motta, P.M. (Ed) Biopathology of the Liver. An Ultrastructural Approach. Kluwer Acad. Publ, Dordrecht, p. 23-36
9) Wake K. (1995) Structure of the sinusoidal wall in the liver. In: Wisse E, Knook, D.L., Wake, K. (Eds) Cells of the Hepatic Sinusoid. Vol. 5. Kupffer Cell Foundation, Leiden, The Netherlands, p. 241-337
10) Wake K. (1974) Development of vitamin A-rich lipid droplets in multivesicular bodies of rat liver stellate cells. J. Cell Biol. **63**: 683-691
11) Senoo, H., Sato, H., Imai , K. (1997) Hepatic stellate cells-From the viewpoint of retinoid handling and function of the extracellular matrix. Acta Anat. Nippon **72**: 79-94.
12) Wake K., Sato, T. (1993) Intralobular heterogeneity of perisinusoidal stellate cells in porcine liver. Cell Tiss. Res. **273**: 227-237
13) Zou, Z., Ekataksin, W., Wake, K. (1998) Zonal and regional differences identified from precision mapping of the hepatic stellate clls in pig liver: A novel concept of addressing the intralobular area of heterogeneity. Hepatology **27**: 1098-1108