Junction between Kupffer Cells and Hepatic Sinusoidal Endothelium. A Review

By

TOSHIO ITO, YUTAKA TANUMA and SUSUMU SHIBASAKI*

Department of Anatomy, Teikyo University School of Medicine, Tokyo 173 and
(*)Department of Anatomy, Gunma University School of Medicine,
Maebashi 371, Japan

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Summary. In this review, the junctions between Kupffer and sinusoidal endothelial cells previously revealed by the present authors under the transmission electron microscope in both normal human and bat livers has been discussed and compared with stereo-images of the connections between the two cell types reported by other authors in scanning electron microscopic studies. It is concluded that Kupffer cells lie on the gap or opening of the endothelial lining of the sinusoid, that part of the perisinusoidal surface of the cell body which is applied to the opening directly faces the perisinusoidal space, and that the margin of this part of the perisinusoidal surface of the Kupffer cell and the margin of the endothelial opening are circularly bound by means of a peculiar close junctional area identical in structure and appearance with the so-called "junctional complex" (Wisse) between endothelial cells. The two junctional areas between the Kupffer cell and the endothelial sheet which are found in a pair in transmission electron microscopic preparations on two diametrical parts of the perisinusoidal surface of the Kupffer cell, should be derived from the perpendicular section of such a circular margin of the endothelial opening attached to the Kupffer cell body. Thus, the integrity of the lining of the sinusoid is maintained and Kupffer cells are immovably fixed to the sinusoidal lining resisting the drag induced by the blood flow in the sinusoid.

This short review was prepared on the basis of transmission electron microscopic findings for the junction between Kupffer and sinusoidal endothelial cells in normal human livers (Ito and Shibasaki, 1968; Ito, 1973) and in normal as well as excess vitamin A-administered bat livers (Tanuma and Ito, 1978), and gives a critical appraisal of scanning electron microscopic stereoimages of Kupffer cells and their connections with sinusoidal endothelial cells.

Recently, using the scanning electron microscope, many investigators have observed the sinusoidal surface of the hepatic sinusoidal wall in an attempt to clarify the stereostructures of Kupffer and endothelial cells. As a result, several topographical relationships between these morphologically distinct cell types have been elucidated to some extent (Itoshima et al., 1974; Motta and Porter, 1974; Muto, 1975; Motta, 1977; Vonnahme, 1977; etc.). Some of the scanning electron
microscopic findings reported by the above authors, especially concerning the relations between Kupffer and endothelial cells, seemed to require further precise reexamination with reference to those obtained by transmission electron microscopy. The scanning electron microscopic images often indicated that filopodia and lamellipodia projecting from the surface of the Kupffer cell body might spread towards the endothelial wall to be attached to or overlap the latter, or that in some cases they might communicate with adjacent Kupffer cells across the sinusoidal lumen (Muto, 1975; Vonnahme, 1977; Motta, 1977). The above findings, however, were only rarely confirmed in transmission electron microscopic images (Fig. 1). It was also the case in transmission electron microscopy that filopodia penetrated through endothelial gaps (Fig. 2). However, filopodial communication between adjacent Kupffer cells has never been demonstrated by transmission electron microscopy.

The Kupffer cells are fixed macrophages of the liver; they are anchored on the hepatic sinusoidal wall bulging into the sinusoidal lumen and are provided with an irregular and changeable rough sinusoidal surface which projects temporal ruffles, microvillous processes, filo- and lamellipodia as seen under the scanning electron microscope. Recently, Carr (1977) humorously conjectured on the immobility of Kupffer cells as follows: “they don’t move and if they don’t move, the drag of the sinusoidal blood on their irregular surfaces must be considerable. Their contacts with adjacent cells do not involve the formation of elaborate desmosome. So we don’t really understand how they resist the temptation to move, sitting like spinsters continually saying no”. To be immovably anchored to the hepatic sinusoidal wall resisting the blood flow in the sinusoid, the Kupffer cell body must be bound to the sinusoidal endothelial lining by means of a definite junctional structure. This was first demonstrated by Ito and Shibasaki (1968) with the transmission electron microscope in normal human livers and then confirmed by Tanuma and Ito (1978) in bat livers. According to Ito and Shibasaki, a finger-shaped end part of the cytoplasmic sheet of the endothelial cell came in contact with the marginal portion of the perisinusoidal surface of the Kupffer cell. At the contact site, a minute slit about 250 Å in width was recognized between juxtaposed plasma membranes of the two cell types (Figs. 3, 4). In these junctional areas, a density increase in the plasma membranes and adjacent cytoplasm was observed, and in the slit a slightly electron dense material was demonstrated. However, no fusion line of the outer leaflets of the plasma membranes as seen in the tight junction was noted, so that the Kupffer-endothelial junctions were identified with neither the tight junction nor desmosome. They represented a peculiar junctional pattern different from a simple membrane apposition. As shown in Figure 4, two junctional areas were often found in a pair on two diametrical marginal regions of the perisinusoidal surface of the Kupffer cell.

The above transmission electron microscopic findings for junctional areas between the Kupffer cell body and endothelial sheet were confirmed later by Tanuma and Ito in their bat liver study. In the bat livers examined, junctional areas between Kupffer and endothelial cells were frequently encountered, often in a pair on two diametrical parts of the perisinusoidal surface of the Kupffer cell body with a more of less wide gap in the endothelial sheet in between (Figs. 5, 6), although it remained unknown whether such a gap was intracellular or intercellular. High power views of such junctional
areas between the Kupffer cell body and "cytoplasmic process" of the endothelial sheet are shown in Figures 7 and 8. Density increases in the juxtaposed plasma membranes and adjacent cytoplasm as well as slightly electron opaque material filling up the minute slits of about 200 Å in width between apposed plasma membranes, were apparent. As Tanuma and Ito (1978) pointed out, the junctions between the Kupffer cell body and cytoplasmic process of the sinusoidal endothelium were identical in structure and appearance with the so-called "junctional complex" (Wisse, 1970, 1972) between the margins of the "cytoplasmic processes" of neighboring endothelial cells. It is of great interest that two cell types which composed the hepatic sinusoidal wall were bound by means of an identical peculiar close junction different in fine structure from the tight junction and desmosome. Wisse (1974) considered the contacts between Kupffer and endothelial cells as simple appositions of cell membranes with some electron dense material present in which, according to his own description, he could not detect the exact fine structure, probably because he failed to demonstrate the trilaminar aspect of plasma membranes. Kurtz (1964) had already described the presence, between the endothelial cytoplasmic process and Kupffer cell body, of a similar membrane apposition across a 300 Å slit containing electron dense material.

Concerning the relationship between the Kupffer cell and the sinusoidal endothelial lining, Tamaru (1979) recently stated that the former was either incorporated in or attached to the latter. At their contact site, the juxtaposed plasma membranes were characterized, similarly to the junction between neighboring endothelial cells, by the presence of electron dense material without, however, forming a peculiar junctional structure as proposed by Wisse (1974).

In his transmission electron microscopic studies on the rat hepatic sinusoidal wall, Wisse (1970, 1972, 1974) noted that Kupffer cell bodies were incorporated into the sinusoidal wall, which remained intact as a whole, because of the contact between endothelial cell processes and the surface of the Kupffer cells and because the endothelial lining might be replaced by insertions of Kupffer cell cytoplasm of varying dimensions.

In his scanning microscopic observations on Kupffer cells in monkey liver, Vonnahme (1977) noted that they generally lay on the endothelial lining, overlapping it, whereas in rat sinusoids their cell body filled the gaps between adjacent endothelial cells. The latter description agrees with the scanning electron microscopic studies of Muto (1975) on the rat liver sinusoid in which he reported that the Kupffer cell generally lay on a large endothelial opening and was anchored to its margin by filopodia to be incorporated in the formation of the sinusoidal wall.

As mentioned above, the transmission electron microscopic studies on the normal human and bat sinusoidal wall often revealed two junctional areas between the Kupffer cell body and endothelial processes in a pair on two diametrical margins of the perisinusoidal surface of the Kupffer cell. This suggests that the Kupffer cell body might have lain on a large endothelial gap or opening as shown by scanning electron microscopy and that the distance between the two junctional areas might correspond to the diameter of the gap. The margin of the gap and that of the perisinusoidal surface of the Kupffer cell were bound by the so-called "junctional complex" to maintain the integrity of the sinusoidal lining. Such a junction between the margin of the gap in the endothelial lining and that of the Kupffer cell body could not be demon-
As mentioned above, Muto (1975) noted in his scanning electron microscopic study that the Kupffer cell lying on a large endothelial opening was anchored to its margin by filopodia. Transmission electron microscopic findings, however, have never been suggestive of such a filopodial anchorage of the Kupffer cell to the margin of the endothelial gap.

References


PLATES
Explanation of Figures

Plate I

Fig. 1. Junction between the Kupffer cell (KU) and the sinusoidal endothelial lining (EL). Two junctional areas (arrows) are seen in two diametrical marginal regions of the perisinusoidal surface of the Kupffer cell body which faces the perisinusoidal space (PS) containing abundant microvilli of the hepatocyte (H). From the sinusoidal surface, a number of filopodia project into the sinusoidal lumen (SN), one of which extends across the sinusoid to anchor with its swollen end to the endothelial sheet. Bat liver. ×8,000

Fig. 2. Unnucleated portion (KU) of a Kupffer cell which lies on the endothelial lining (EL) of the sinusoid (SN) with two junctional areas (arrows). A filopodium protruding from its sinusoidal surface extends straight towards the fenestrated endothelial lining and penetrates through a fenestrum into the perisinusoidal space (PS). H hepatocyte, W worm-like structure, X process of the fat-storing cell. Bat liver. ×12,000
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Plate II

Fig. 3. Two junctional areas (arrows) between the Kupffer cell body (KU) and the endothelial lining (EL) of the sinusoid. At the junctional areas, the juxtaposed plasma membranes and the adjacent cytoplasm of the two cell types show a conspicuous density increase and are apposed in parallel across an approximately 250 Å wide slit filled with slightly electron dense material. C long centriole within the Golgi complex (G), F collagen fiber, H hepatocyte, NB nuclear body in the Kupffer cell nucleus, L lymphocyte in the sinusoid, X fat-storing cell processes in the perisinusoidal space. Normal human liver. ×16,000

Fig. 4. Junction between the Kupffer cell (KU) and the sinusoidal endothelial lining (EL). Two junctional areas (arrows) are seen in a pair on two diametrical margins of the perisinusoidal surface of the Kupffer cell body. F collagen fibers in the perisinusoidal space (PS), H hepatocytes, SN sinusoid, X fat-storing cell processes in the perisinusoidal space. Normal human liver. ×11,000
Plate III

Fig. 5. Junction between the Kupffer cell body (KU) and the endothelial lining (EL) of the sinusoid (SN). Two junctional areas (arrows) are seen in a pair on two diametrical margins of the perisinusoidal surface of the Kupffer cell body. C centriole within the Golgi complex (G), H hepatocytes, PS perisinusoidal space, X fat-storing cell process. Normal bat liver. ×17,400

Fig. 6. Junction between a Kupffer cell body (KU) containing worm-like structures (W) as well as an ingested erythrocyte (ER) and the endothelial lining (EL) of the sinusoid (SN). Two junctional areas (arrows) are seen in a pair on two diametrical margins of the perisinusoidal surface of the Kupffer cell body. H hepatocytes, PS perisinusoidal space. Normal bat liver. ×8,100
Plate IV

Figs. 7 and 8. High power views of junctional areas (arrows) between the marginal portion of the perisinusoidal surface of the Kupffer cell body (KU) and the endothelial lining (EL) of the sinusoid. Parallel juxtaposed plasma membranes of the two cell types and their adjacent cytoplasm are characterized by a conspicuous density increase, and a 200Å wide slit between the juxtaposed plasma membranes contains a slightly electron opaque material. In Fig. 7, the junctional area is divided into two areas by an interruption. H hepatocyte, PS perisinusoidal space containing hepatocytic microvilli. Normal bat liver. ca. ×48,000