

KARL WILHELM VON KUPFFER A HISTORICAL REVIEW ABOUT A GREAT TEACHER AND SCIENTIST

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Karl Wilhelm von Kupffer is best known in medical literature particularly for the discovery of the liver macrophage that bears his name. As frequently happens in medical research, Kupffer did not realized from the early observations which are the functions of the cell he noticed, neither their involvement in the pathology of the liver. At that time, he believed that these cells belong to the vascular wall and represent a subpopulation of perivascular cells with stellate features. In histology, pathology, immunology, and hepatology, we continue to call the liver macrophage as Kupffer cell. It is not clear who named this cell with the name of Kupffer. Anyway, this name lives for more than a century, we have not a better one, and we do not search for another.

Karl Wilhelm Kupffer (later von Kupffer) was born in 1829, as the eldest son of pastor Karl Hermann Kupffer, in Lesten, Tucktum province (at that time in Russian Empire, today in Latvia). After “on site primary education”, in 1848 he passed the admission test at the school of medicine. He graduated medical studies at the University of Dorpat (Imperial University of Dorpat, today University of Tartu, Estonia), and then he returned at home to work as a family physician. Fortunately or not, Karl Wilhelm Kupffer was not satisfied with this job, and he went back to the University of Dorpat where he served for a short while as assistant of anatomy. Here, under the guidance of Professor Bider, he investigated mainly the components of the central nervous system. The title of his dissertation was “The spinal cord of a frog, with special reference to the gray matter” (9). On the same topic, he investigated the development of the spinal cord in different mammals. He described that dorsal-root nerve fibers entered the spinal cord and contributed to the formation of the marginal layer of the white matter, and showed that the ventral root fibers derive from the neurons of the ventral horn (4).

He begun a scientific journey in Europe that lasted for about two years, and worked in Vienna, Berlin, and Göttingen, and finished his PhD Thesis, under

the supervision of Emil DuBois-Reymond, Johannes Peter Müller and Friedrich Bider (1). After he get the PhD title he returned at the University of Dorpat as associate professor of anatomy. Based on his scientific contributions he was than appointed chair of anatomy at the University of Kiel in 1866, and then at the University of Königsberg (today Kaliningrad) as professor of anatomy. During his stay in Kiel he discovered the stellate cells. From 1880 till his retirement (1901), he was the chair of the department of anatomy at the University of Munich. He died in December 1902, at Munich, at the age of 73 years, with stroke complicated with a pneumonia (1).

The scientific contribution of Kupffer covers a broad spectrum of subjects, mainly related to neuroanatomy and embryology, and he is considered a pioneer of comparative embryology. His studies were conducted on the development of the brain, spinal cord, spleen, pancreas, and kidney, and on the innervation of exocrine glands, like the liver and pancreas. During his career in research, he published over 60 original articles, reviews and books. Interestingly, from these papers only two are dedicated to “Sternzellen” (2, 5), so we may think that investigation on the liver cells was just one incident (4).

In 1876, he published the work entitled “On the stellate cell in the liver” (in German), in *Archiv für Mikroskopische Anatomie* (2). Virtually, this was the birth certificate of Kupffer cells. Kupffer believed that these stellate cells belong to pericytes or adventitial group. Moreover, this work opened a new field in hepatology, specifically related to the sinusoid microenvironment. In the end of the XIXth century, the pathologist Tadeusz Browicz from Krakow, correctly identified these cells as macrophages (3). Although very difficult to say nowadays, it is possible that Kupffer observed both liver macrophages and true stellate cells, known today as Ito-Nemoto cells.

Like many other discoveries in medicine, the

description of stellate cells has its own story. Kupffer investigated the presence of nerve fibers in the parenchyma of the mammal liver, using the Gerlach's gold chloride method. He did not succeed to show nerve fibers, but he noticed by chance stellate cells, stained in black with gold chloride (2). The first known report of the discovery has been written as a letter to Professor Waldeyer in 1876 (2). One of his students in the laboratory of Munich, Paul Rothe, using the same method, confirmed the presence of these cells not only in mammals but also in the chick liver (10). After the seminal observation, Kupffer conducted some investigations based on experimental models, using a vital dye, India ink, injected intravenously to the rabbit. He compared results with data found on preparations stained with gold chloride, and concluded that stellate cells have the ability to uptake foreign particles (5). These findings have been presented during the Anatomical Congress at Kiel (1898), and published one year later. Since then a lot of scientists confirmed the unique morphology and functions of Kupffer cells in both normal and pathological conditions (6, 7, 8).

The distinction between different cells of the sinusoid wall was not easy, and gave rise to many controversial discussions. They came to an end in 1970, when Eddie Wisse in Leiden, using electron microscopy, clearly discriminate between liver macrophages, endothelial cells, and fat storing cells (11). Based on all these observations, soon it was born the theory and concept of the mononuclear phagocyte system, which is well documented nowadays.

Wilhelm Karl von Kupffer clearly pointed out that the stellate cells exist in the liver tissue. His analysis strongly contributed to link the hepatic stellate cells to a pivotal role in liver fibrosis and cirrhosis. Together with Rothe, he stimulated research that lead to the concept of fat-storing stellate cells system, and in 1956, Ito and Nemoto published the characterization of a specific cell type in the liver (12), although its presence was suspected more than fifty years before. After a hundred of years from Kupffer cell discovery, the first conference on cells of the hepatic sinusoid has been held in Noordwijkhout, The Netherlands, in 1977 (4). Currently, we know now a lot of things about Kupffer cells: specific and less specific markers, main and secondary functions, synthesis of many cytokines including interleukins, involvement as pathogenic and prognostic elements in different diseases of the liver, in vitro behaviour, and implications in systemic diseases of the organism. Nevertheless, the story of Kupffer cell continues.

REFERENCES

1. https://en.wikipedia.org/wiki/Karl_Wilhelm_von_Kupffer
2. von Kupffer C. Ueber Sternzellen der Leber. Briefliche Mitteilung an Prof. Waldyer. Arch mikr Anat. 1876; 12:353-358.
3. Browicz T. 1898. cited from Browicz. Ueber intravasculare Zellen in den Blutcapillaren der Leberacini. Arch mikr Anat. 1900; 55:420-426.
4. Wake K. Karl Wilhelm Kupffer and his contributions to modern hepatology. Comp Hepatol. 2004; 3(Suppl 1): S2.
5. von Kupffer C. Ueber die sogenannten Sternzellen der S-ugethierleber. Arch mikr Anat. 1899; 54:254-288.
6. Nicolescu P, Rouiller C. Beziehungen zwischen den Endothelzellen der Lebersinusoide und den von Kupfferschen Sternzellen. Z Zellforsch. 1967; 76:313-338.
7. Wake K, Motomatsu K, Senoo H, Masuda A, Adachi E. Improved Kupffer's gold chloride method for the demonstration of the stellate cells storing retinol (vitamin A) in the liver and extrahepatic organs of vertebrates. Stain Technol. 1986; 61:193-200.
8. Wake K. Liver perivascular cells revealed by gold and silver impregnation methods and electron microscopy. In: Motta PM, editor. Biopathology of the Liver. An Ultrastructural Approach. Dordrecht, Kluwer Acad Publ; 1988.
9. von Kupffer C. De medullae spinalis textura in ranis ratione imprimis habita indolis substantiae cinerae. Diss inaug Dorpati, 1854 (cited from Wake, 2004).
10. Rothe P. Ueber die Sternzellen der Leber. Inaug-Dissert, Munchen. 1882 (cited from Wake, 2004).
11. Wisse E. An electron microscopic study of the fenestrated endothelial lining of rat liver sinusoids. J Ultrastruct Res. 1970; 31:125-150.
12. Ito T, Nemoto M. Morphological studies of the fat storage cells of the liver in various vertebrates. I. Fat storage cells of hoofed animals. Okajimas Folia Anat Jpn, 1956; 28(1-6):521-542.