Kenjiro and the Star Cells

EASL International Recognition Award 2017 to Professor Kenjiro Wake

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Hepatology is a science developed by associating clinical manifestations with biochemistry and liver tissue morphology. The EASL Recognition Awards were introduced in 2006 and so far awarded only to clinicians. The EASL International Recognition Award to Professor Kenjiro Wake is therefore characterized by at least two points of originality. First, the award goes for the first time to an anatomist and actually a liver micro-anatomist. Second, a Japanese hepatologist is awarded for the first time. In addition, the award is also motivated by the long standing career (Professor Wake is 84 years old and still active) characterized by hard work, intuition and discoveries, humbleness and great mentorship to Japanese and international hepatologists.

Kenjiro Wake was born in Osaka, Japan, in 1932. He obtained his MD at Osaka City University Medical School in 1958 and his PhD at the same University in 1963. In 1976, after a brilliant career at Osaka City University, he was appointed Professor of Anatomy at the School of Medicine of Tokyo Medical and Dental University. He retired from prime academic activity in 1997 and since then he is Emeritus Professor at Tokyo Medical and Dental University. Since his early academic career, Kenjiro Wake established a strong professional relationship with Europe and Germany in particular. From 1971 to 1973 and in 1983 he was Fellow of the Alexander v. Humboldt Foundation, Department of Anatomy and Cytobiology, Justus-Liebig-

University (Giessen), Germany. During his career, he received important recognition awards including the Osaka City Mayor's Award, the Elvin Stein Award (Federal Repuplic of Germany), the Japan Electron Microscopy Association Award, and the Order of the Sacred Treasure awarded by his majesty the Emperor of Japan.

Undoubtedly, Kenjiro Wake's name is associated with hepatic stellate cells and the definition of their physiological and physiopathological role in liver fibrogenesis. Hepatic stellate cells were firstly described by Carl von Kupffer in 1876 [**1**] using the gold chloride method. These star-shaped cells (*sternzellen*) were located outside of sinusoids. However, after his second paper published in 1899 [**2**] these stellate cells were thought to be liver macrophages, a role that was retained until Kenjiro Wake finally defined their precise phenotype in 1971 [**3,4**]. The work of Kenjiro Wake was based on the observations of another master of Japanese anatomy, Toshio Ito, who, in 1952, found that the cells in the perisinusoidal space contained abundant fat droplets (originally observed by von Kupffer), were distinct from the phagocytosing cells in the sinusoids (now known as Kupffer cells), and called them "fat-storing cells" [**5**]. Accordingly, after 20 years Kenjiro Wake, using gold chloride and silver impregnation technique and vitamin A autofluorescence confirmed that von Kupffer and Ito had described the same cells and further observed that they contained well-developed rough endoplasmic reticulum [**3**]. This observation in 1971 indicated the strong ability of stellate cells to synthesize proteins. In a subsequent study 3 years later, Wake reported presence of cytosolic lipid droplets in stellate cells which were differentiated into two types: Type I droplets were electron dense, variable in size (up to 2 µm in diameter), membrane-bound, and appeared to be derived from multivesicular bodies, whereas Type II droplets were larger and uniform in size [**4**]. Type I lipid droplets were found to accumulate in the cells of animals with hypervitaminosis A in the intermediate and central zones of the liver lobule [**6**, **7**]. The number

of stellate cells containing lipid droplets was estimated to be 25-75% both in rat and human [**7**, **8**]. The lipid droplets in isolated stellate cells contained high concentrations of both retinol and retinyl palmitate [**9**]. The observation of vitamin A stores (lipid droplets) in the 1980s led investigators to refer to stellate cells as fat-storing cells, lipocytes, perisinusoidal cells and Ito cells (after Toshio Ito). Due to potential confusion that may arise from such different nomenclature for this cell, a consensus was reached in 1996 that it should be referred to as hepatic stellate cell (HSC) [**10**]. It is important to appreciate the efforts of von Kupffer in distinguishing these cells with very basic techniques available at that time. Thus it was only a case that hepatic resident macrophages were named "Kupffer cells" in recognition of von Kupffer's original contribution to the field.

Wake's work in the 1970s established that HSCs were the major storage site of vitamin A (nearly 80% of the body's retinoids is stored in these cells). This was confirmed by Knook and co-workers in 1982 [**11,12**]. These findings in the 1980s opened a major area of investigation to determine the role of HSCs in vitamin A homeostasis. In addition, the observation that the loss of intracellular retinoids in HSCs is a key feature of their transformation into a highly proliferative, contractile and fibrogenic myofibroblastic phenotype paved the way for the identification of HSCs as the key effectors of hepatic fibrogenesis following chronic liver damage [**13**].

Besides these key contributions to the identification of the role of HSCs in liver fibrosis, Kenjiro Wake provided other key evidence on the structure of these cells and on that of hepatic sinusoids. Along these lines, Wake demonstrated the 3-D structure of HSCs using Golgi method and SEM. The quiescent HSC consisted of the cell body and some dendritic processes which encompass two or three sinusoids. Thorn-like microprojections, called 'spines', protrude from the surface of the cells. Number of spines of a single HSC is >300, whose tips

make contacts with hepatocytes. A single HSC contact two or three endothelial cells and 20-40 hepatocytes. This cellular complex is called 'the stellate cell unit' or 'the stellon' [**14**]. Importantly, HSC distributed in different zones of the liver lobule appear to be morphologically (and functionally) heterogeneous [**15-19**], thus supporting different strategic roles particularly in the regulation of sinusoidal blood flow.

I have had the pleasure and the honour to meet many times Professor Wake in Japan and elsewhere. I have always admired his passion, deep knowledge and humbleness. I am sure that this admiration is shared by all the colleagues who have dedicated their career to the study of the HSC biology and the mechanisms of liver fibrogenesis. In 2004, he wrote an article celebrating the achievements of Karl von Kupffer [**20**], which was concluded with the statement "A century has passed since then, but his greatly inspiring achievements continue shining on in hepatology still today and, I'm sure, will remain in the memory of the people as ever". I think that there are no better words to conclude this presentation of the EASL International Recognition Award 2017 to Professor Kenjiro Wake to whom the Hepatology community expresses its gratitude.

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