The past and the future of Japanese glia research

Yoshihisa Kudo

(An adviser for the present project)

Emeritus professor; Tokyo University of Pharmacy and Life Sciences

The big development of the glia study in the field of brain science from the end of 20th century to the present is miraculous. Now, we have recognized that the glial cell is not a simple supporter for neurons and their network but would be a sophisticated element contributing to the information processing in the brain. We become to believe that the glia study is indispensable for elucidation of the brain function. PubMed Search using a keyword of "glia" identifies less than 1,000 research papers until 1987. However, the number of hits increases approximately linearly or even exponentially after the year, and reached more than 4,000/year in 2013. This trend applies to glia research in Japan. Namely, glia-related papers published per year were not significant before 1987, but it skyrocketed after 1987. The papers from Japan reached to approximately 10% of the total publications by 2000. Thereafter, approximately 300 papers have been published every year. Although the number of glia-related papers from U.S.A. and China increased recently, we believe that the publications from Japan would be one of the core achievements to highlight the glial cell as an important element contributing to higher-order brain functions.

Of course, since the majority of neuroscientists are neuron-centric both in Japan and other countries, early glia research in Japan experienced a hard time in its recognition. However, leading figures in glial cell research in Japan encouraged us to develop the research by showing their excellent accomplishments. Some examples will be described briefly.

Setsuya Fujita, a well-known researcher in developmental biology, published an important paper to demonstrate by his outstanding methods that the origin of neuron and glia is the same matrix cell (Fujita, 1960). However, scientists in other countries tended to believe that glial progenitor and neuronal progenitor were sharply separated from the beginning of the neurogenesis based upon the concept inherited from Wilhelm His (1889). Fujita's theory was criticized and rejected "officially" by the developmental biology committee (Boulder Committee, 1969). After a long period of negation, new technologies in developmental

neurobiology confirmed the presence of common progenitor cells in the developing brain. Fujita's theory is finally accepted as a truth.

In the field of neuropathology, Fusahiro Ikuta published important papers to show the dynamic features of astrocytes during and after the brain injury. He demonstrated the importance of mitosis and migration of astrocytes in the brain indispensable for the normal brain development and also processes for recovering from injury (Ikuta et al 1979).

In the field of ultrastructure study of glial cell, Kiyoshi Hama has examined the features of protoplasmic astrocytes in the brain by using high-voltage electron microscopes (HVEM) since 1970s. He applied HVEM to 5 μm-thick sections of Golgi-impregnated materials, and observed the three-dimensional structural details of astrocyte processes (1986). His efforts on searching the patterns, shapes, and types of the glial cells continue until now. The images of the cells shown by him deeply impressed and made us confirm the importance of these cells in the brain.

Moreover, I should introduce here, Mizuho Nakata (1893-1975), a prominent neurosurgeon and neuroscientist who suggested the importance of glial cells in the brain function. He published a science essay titled "Neuro-Gliology" as early as 1971 (Niigata Medical Journal 85; 667-668 in Japanese). In this essay, he described as; "The brain research should not be slanted to only neurology or gliology, but it should be neuro-gliology that deals with neurons and glial cells as the equal elements for composing brain function". He might foresee the recent development of glial researches more than 40 years ago.

The glial cell researches were performed from biochemical and morphological points of view in the field of neurochemistry from the end of 1960s to 1980s. I have a book titled "Neuroglia - approach to its total feature" published in 1977 (Ed.Yoshimitsu Tsujiyama. Igakushoin in Japanese). This book may be the first specific book for glial cell research in Japan. This book involves the chapters of the structural, biochemical and physiological interactions between neurons and astrocytes, the dynamic features of glia cell in the degenerating brain and also the electrophysiological profiles of astrocytes. The chapter for detailed methods of glial cells culture is also provided, and the importance of the nerve growth factor (NGF) was also discussed here. The glial cell research might be one of the most important targets for the field of the neurochemistry in those days. Since the sources of the cytokines and growth factors such as NGF and BDNF, were found to be in glial cells, some of glia cell researchers started to prove the active roles of glial cells in the maintenance and repair of the brain function. However, those studies were still minor in the field of neuroscience. From the point of view of research funding, attempts to organize a big glial cell research project funded by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) were not successful in 1970s and 1980s.

As it is well known, the most striking impact for the glial research was the measurement of intracellular Ca^{2+} dynamics, which became available owing to an invitation of the intracellularly loadable fluorescence Ca^{2+} indicator (Tsien, 1982). We invented a conventional device to measure the Ca^{2+} concentration dynamics in individual cells by using a fluorescence microscope and a high sensitive video camera. The first experiment was the detection of serotonin induced Ca^{2+} increase in C6Bu1 cell, a clone cell derived from rat C6 glioma cells (Kudo et al, 1986). The most important finding for glia researches was the oscillatory Ca2+ changes in cultured astrocytes induced by glutamate, an excitatory neurotransmitter (Cornell-Bell et al,1990). Thereafter many scientists including us found the characteristic oscillatory Ca^{2+} changes in cultured astrocytes induced by various neurotransmitters. Since almost all neuroscientists had believed that the glial cell was "inactive" from the electrophysiological point of view, they overlooked the

participation of glial cells in the brain function. However, once they recognized the dynamic features of glial cells, they were pressed to reconsider the importance of the cells as one of the leading elements in the brain. When we watched brain functions according to the new profile of glial cells, we could recognize that normal and also abnormal brain functions are tightly related to the activity of the cells.

By taking many scientific evidences as our research background, we applied the project titled "Elucidation of glial cell-mediated control mechanisms in synaptic transmission" (Chief organizer: Kazuhiro Ikenaka). This project was accepted by MEXT as a middle sized group for glial cell research in 1998. This project lasted until 2001. In these four years, we made many important achievements which gave strong impact on neuroscientists in Japan and let them convince the necessity of glial research to elucidate the brain functions. One year after the end of the project (2003), a much bigger project for glial cell research was accepted by MEXT. The title of the project was "Elucidation of information processing mechanisms by neuron-glia networks" (Chief organizer: Yoshihisa Kudo) which lasted until 2007. The project consisted of three groups; (1) The mechanisms for mutual interaction between glia and neuron mediated by neurotransmitters (five subgroups), (2) The mechanisms for functional molecule expression for mutual recognition between glia and neuron (five subgroups) and (3) The mechanisms for expression of brain function and its abnormality through the glia-neuron interaction (four groups). Besides these main groups, we invited collaborators who would participate in one of three groups. As the first invitation for two years collaboration (2004-2005), we selected 32 researchers in total. As the collaborators for the next two years (2006-2007), we invited 26 researchers in total. During these five years we published more than 700 original papers. We organized three international symposiums and Japan-US joint symposium, and also offered many organized symposiums for domestic and international meetings. We believe that this project would contribute to the development of glial research not only domestically, but also internationally.

Unfortunately since Japanese financial condition for the basic science was not satisfactory because of the social condition and a terrible disaster, we could not organize a new project for five years. However, in 2013 owing to great efforts of Kazuhiro Ikenaka and collaborators, the third project for the glia research was accepted by MEXT. As you may find in this home page, the contents of this project are far more comprehensive than former two projects. In particular, it attracts attention that a group based on clinical sciences is included as one of the main components. Furthermore, the organizers of this project intended to bring up young researchers for glial cells by offering chances to attend international meetings and symposiums. Some other attractive features of this research group will be found in this home pages.

Besides enough financial support, one of the most important requirements to make the project successful is recruiting the active collaborators. Fortunately, the main project team consists of established scientists, with many active young researchers in their laboratories. Furthermore, a lot of excellent researchers were invited as collaborators. Among them, I found experts for dealing with new techniques required for unveiling the unknown profiles of glial cells.

Now I believe this project will develop successfully owing to excellent members, who all keep tight interaction among them and also their worldwide colleagues. The scientific outcomes from this project will contribute the big development of the glial cell research and thus understanding the new profiles of the brain in the future.

(Published Jun 10, 2015)