Morphological changes of large layer V pyramidal neurons in cortical motor-related areas after spinal cord injury in macaque monkeys
サル脊髄損傷後の運動関連領野における 5 層巨大錐体細胞の形態学的変化

Kyoto University Graduate School of Science
Yu Takata

Chapter 1: General introduction

The motor-related areas of the frontal lobe give rise to the corticospinal tract (CST) for conveying motor commands to the spinal cord contralaterally. These long-descending CST fibers connect to spinal interneurons and/or motoneurons for achieving motor behavior volitionally. The CST fibers, especially in phylogenetically higher primates with dexterous movements, travel through the lateral funiculus, and a large part of them terminate directly on motoneurons. It is generally considered that such direct corticomotoneuronal pathways are associated closely with the development of skilled motor behavior, i.e., manual dexterity. A previous study in macaque monkeys have shown that manual dexterity becomes severely impaired after spinal cord injury (SCI) involving the cervical enlargement, and that sprouting/regenerating CST fibers dynamically re-innervate spinal motoneurons to recover motor functions from SCI. While the reorganization of the CST at the spinal terminal level is now well understood, little is known about how the CST is reorganized at the cortical neuron level along with the motor recovery. It is therefore important to examine, by using a similar monkey model, the correlation between the impaired and restored manual dexterity and the plastic changes of CST neurons for understanding the mechanisms underlying functional recovery from SCI. The CST originates from large pyramidal neurons in layer V of the frontal motor-related areas, including the primary motor cortex (M1), the supplementary motor area (SMA), and the dorsal and ventral divisions of the premotor cortex (PMd, PMv). The large layer V pyramidal neurons generally possess apical and basal dendrites with enriched dendritic spines. It has been demonstrated that both dendrites and dendritic spines receive excitatory inputs from other cortical neurons and are reorganized in response to central nervous system disorders and during motor learning. In the present study, we therefore focused on the morphological changes in dendrites and dendritic spines of large layer V pyramidal neurons in the motor-related areas after SCI.

Chapter 2: Morphological features of large layer V pyramidal neurons in cortical motor-related areas of macaque monkeys: analysis of basal dendrites

In Chapter 2, we first compared the morphological features of large layer V pyramidal neurons (i.e., putative CST neurons) among the motor-related areas in macaque monkeys by analyzing the complexity of dendrites and the density of dendritic spines, with special reference to basal dendrites. Briefly, we have found that the structure of basal dendrites of the large layer V pyramidal neurons in the PMd is different from those in the other motor-related areas. In the PMd, not only the complexity of basal dendrites (i.e., total dendritic length and branching number) was poorly developed, but also the density of dendritic spines was so low, as compared to the other areas. Moreover, we have shown that thin-type (more immature) spines are prominent in the PMd in comparison with stubby- and mushroom-type (more mature) spines, while both thin- and stubby-type spines are marked in the other areas. It has been considered that the basal dendrites of large layer V pyramidal neurons in the motor cortex receive excitatory input via recurrent axon collaterals derived from neighboring pyramidal neurons. Thus, the dendritic complexity and perhaps also the spine density of large layer V pyramidal neurons might reflect input-dependent motor activity in each of the motor-related areas.

Chapter 3: Morphological changes of layer V pyramidal neurons in the motor-related areas in primate models of spinal cord injury

In Chapter 3, we examined the plastic changes of basal dendrites and their spines for individual motor-related areas after SCI by using a monkey model to understand the correlation between the reorganization of large layer V pyramidal neurons and the motor recovery from SCI. The patterns of morphological alterations in acute and early recovery models of SCI were compared with those in the normal control to explore the correlation between the reorganization of large layer V pyramidal neurons in the motor-related areas and the motor recovery from SCI. We have demonstrated that both the complexity and the spine density of basal dendrites of large layer V pyramidal neurons in the acute SCI model are highly reduced throughout the motor-related areas, as compared to the normal control. Likewise, our dendritic spine analysis has confirmed that the densities of thin-, stubby-, and mushroom-type spines are decreased in all motor-related areas, whereas the density of filopodia-type spines is increased in the M1, SMA, and PMd. When the morphology of basal dendrites in the early recovery model was compared with those in the acute SCI model and the normal control, two intriguing results were obtained: (1) The

plastic changes of dendritic spines precede those of basal dendrites *per se* to promote the reorganization of large layer V pyramidal neurons; and (2) The morphological recovery of basal dendrites from SCI is delayed in the PMv, as compared to the other motor-related areas. The latter could be accounted for by the functional specialty of the PMv that has been implicated in dexterous motor behavior, including the formation of precision grip and was, in fact, impaired in the present experimental paradigm. Thus, such distinct plastic changes in individual motor-related areas might provide an effective rehabilitation strategy toward the functional restoration from SCI.

Chapter 4: General discussion

Previous studies have shown that administration of a neutralizing antibody against repulsive guidance molecule-a (RGMa) exerts a therapeutic effect in a monkey SCI model. As the next step, we would like to propose a research project for revealing the plastic changes in the morphology of CST neurons in the motor-related areas of the monkey SCI model with anti-RGMa antibody treatment. Moreover, the diversity of plastic changes of CST neuron morphology in the motor-related areas after SCI might be ascribed to gene expression within individual neurons. However, the possible differential patterns of gene expression specific to individual motor-related areas remain to be investigated. To address this issue, detection of single cell RNA-sequences is needed to identify the existence of distinct genetic types of CST neurons to induce varying plastic changes.