Manipulation of a specific neural circuit buried in complicated brain networks in primates

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A collaborative research team led by Professor Tadashi ISA from The National Institute for Physiological Sciences, The National Institutes of Natural Sciences and Fukushima Medical University and Kyoto University, developed a "double viral vector transfection technique" which can deliver genes to a specific neural circuit by combining two new kinds of gene transfer vectors. With this method, they found that "indirect pathways", which were suspected to have been left behind when the direct connection from the brain to motor neurons (which control muscles) was established in the course of evolution, actually plays an important role in the highly developed dexterous hand movements. This study was supported by the Strategic Research Program for Brain Sciences by the MEXT of Japan. This research result will be published in *Nature* (June 17th, advance online publication).

It is said that the higher primates including human beings accomplished explosive evolution by having acquired the ability to move hands skillfully. It has been thought that this ability to move individual fingers is a result of the evolution of the direct connection from the cerebrocortical motor area to motor neurons of the spinal cord which control the muscles. On the other hand, in lower animals with clumsy hands, such as cats or rats, the cortical motor area is connected to the motor neurons, only through interneurons of the spinal cord. Such "indirect pathway"remains in us, primates, without us fully understanding its functions. Is this "phylogenetically old circuit" still in

operation? Or maybe suppressed since it is obstructive? The conclusion was not attached to this argument.

The collaborative research team led by Professor Tadashi ISA, Project Assistant Professor Masaharu KINOSHITA from The National Institute for Physiological Sciences, The National Institutes of Natural Sciences and Fukushima Medical University and Kyoto University developed "the double viral vector transfection technique"which can deliver genes to a specific neural circuit by combining two new kinds of gene transfer vectors.

With this method, they succeeded in the selective and reversible suppression of the propriospinal neurons (spinal interneurons mediating the indirect connection from cortical motor area to spinal motor neurons)

The results revealed that "indirect pathways" play an important role in dexterous hand movements and finally a longtime debate has come to a close.

The key component of this discovery was"the double viral vector transfection technique"in which one vector is retrogradely transported from the terminal zone back to the neuronal cell bodies and the other is transfected at the location of their cell bodies. The expression of the target gene is regulated only in the cells with double transfection by the two vectors. Using this technique, they succeeded in the suppression of the propriospinal neuron selectively and reversibly.

Such an operation was possible in mice in which the inheritable genetic manipulation of germline cells were possible, but impossible in primates until now.

Using this method, further development of gene therapy targeted to a

specific neural circuit can be expected.

Professor Tadashi ISA says "this newly developed double viral vector transfection technique can be applied to the gene therapy of the human central nervous system, as we are the same higher primates.

And this is the discovery which reverses the general idea that the spinal cord is only a reflex pathway, but also plays a pivotal role in integrating the complex neural signals which enable dexterous movements."

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