Lay Abstract

The brain, a network formed by neurons connected with each other, determines and mediates our behavioral responses to environmental stimulation. Our behavioral responses are frequently modified by experience. This behavioral plasticity may arise from the rewiring of neuronal network. Yet it is not clear to what extent the connectivity of individual neurons in adult brains remains stable or changes dynamically. Rewiring has been difficult to examine in the brain due to the lack of techniques to track the connectivity of given neurons over time. This technical hurdle has prevented us from gaining a mechanistic understanding of the basic brain functions such as learning and memory; it has also hindered the design of better therapies for associated diseases. Here we propose to develop a molecular tool to directly compare the connectivity of neurons at two different time points. The key to this technique is to engineer an efficient yet non-toxic trans-neuronal tracer protein. The tracer will be expressed selectively in a group of genetically or anatomically identifiable neurons (starter neurons). It will enable trans-neuronal transport of an inducible DNA recombinase which will permanently label neurons connected to the starter neurons at a time point when the recombinase is activated (time point A), by making a modification on the genome. The tracer protein will also contain an epitope visualizable by direct fluorescent imaging or immunohistochemistry. Due to the fast turnover of the tracer protein itself, the detection of this epitope tag will reveal the connectivity of the starter neurons at the time of brain fixation and observation (time point B). By comparing the connectivity patterns at these two time points, we will be able to visualize how static/dynamic the neuronal connectivity is in the brain and if behavioral plasticity involves alteration in connectivity.