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The molecular mechanism of axonal transport of tetanus toxin in vivo and in vitro

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Axonal transport is essential for the maintenance of neuronal function. Motor neurons appear particularly vulnerable to transport defects since mutations in this pathway induce motor neuron death in humans and mice. However, how impairments in this process relate to disease progression remains unclear.

In this study we established an in vivo assay allowing the visualization and quantitative analysis of axonal transport in the sciatic nerve of living mice during disease progression. To fulfill this task, we exploit a fragment of tetanus toxin (HC). HC enters motor neurons at the NMJ and is targeted to the soma located in the spinal cord. HC entry relies on a specialized clathrin-mediated pathway, which requires a specific subset of small GTPases. The transport route of HC is shared with several neurotrophins and their receptors.

After intramuscular injection of fluorescent HC, wild-type and mutant mice were anaesthetized and retrograde transport was visualized by high-resolution multiphoton microscopy. Transport defects were detected before the appearance of other pathological signs, demonstrating that the impairment of axonal transport is causal to motoneuron degeneration and an early disease indicator of this pathology. Moreover, these defects worsened at an early symptomatic stage. This novel assay therefore provides a method to closely examine and potentially dissect out the mechanisms underlying axonal transport defects in mouse models of motor neuron disease.