ESCRT protein Vps4 protects injured axons from degeneration

With the support by the National Natural Science Foundation of China, the National High-tech R&D Program (863 Program), and the Chinese Academy of Sciences, the research team led by Prof. Fang YanShan (方燕姗) at the Interdisciplinary Research Center on Biology and Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, together with the collaborators from the Hong Kong University of Science and Technology and Jinan University, reveal a novel mechanism of regulating axonal degeneration, which was published in *Science Advances* (2019, 5(2): eaav4971).

Axonal degeneration is a prominent feature of acute neural injury and chronic neurodegenerative diseases. In particular, the distal segment of injured axons undergoes a progressive self-destruction process, termed Wallerian degeneration. Wallerian degeneration is an active and highly regulated cellular process; however, the underlying mechanism remains poorly understood.

By performing a transgenic RNAi screen in flies, they identify the ESCRT component Vps4 as a novel essential gene for axonal integrity. They find that the upregulation of Vps4 significantly delays the degeneration of injured fly wing axons. They further reveal that Vps4 is required and sufficient to promote autophagic flux in axons and mammalian cells. They show that the basal levels of axonal autophagy are low in general, even in aged flies. However, upon axotomy, there is a rapid and massive autophagy induction in the distal segment of the injured axons. The response can be seen as early as 3 hr after injury and is much earlier than when fly axons start to degenerate (12—24 hr).

Cominbing multiple *in vitro* and *in vivo* models including the *Drosophila* wing nerve, primary DRG neurons and the mouse optic nerve, they demonstrate that the function of Vps4 in maintaining axonal autophagy and suppressing Wallerian degeneration is conserved. Finally, they uncover that the Vps4 protein is rapidly depleted in injured mouse DRG axons as well as the spinal cord of monkeys, which may underlie the injury-induced autophagic impediment and the subsequent axonal degeneration. Together, Vps4 and ESCRT may represent a novel signal transduction mechanism in axonal injury and Wallerian degeneration.

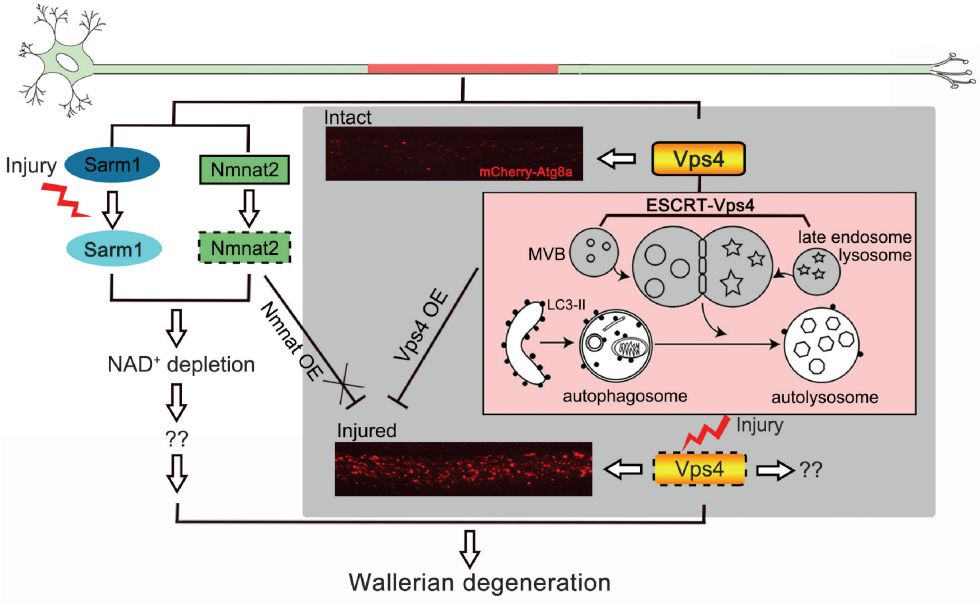

Figure A molecular model of Vps4 in axon injury and Wallerian degeneration.