News Release

Title

The mechanisms of axonal regeneration inhibition has been disclosed

Key Points

- **Axonal regeneration after injury is highly restricted.**
- **Its mechanisms had been unclear.**
- **The team revealed action mechanisms of two glycans that regulate axonal elongation**
- **The team demonstrated that disruption of autophagy flux is one of the causes of axonal regeneration inhibition.**
- **A new molecular target to treat traumatic neural injury was identified.**

Summary

The research team led by Prof. Kenji Kadomatsu, Dr. Kazuma Sakamoto and Dr. Tomoya Ozaki (Department of Biochemistry) of Graduate School of Medicine, Nagoya University (Dean: Prof. Kenji Kadomatsu, M.D., Ph.D.), collaborating with Prof. Shang-Cheng Hung (Academia Sinica, Taiwan) and Prof. Jun-ichi Tamura (Tottori University), revealed that two different glycans regulated axonal growth in our central nervous system (CNS). In particular, the team identified molecular and cellular mechanisms in which chondroitin sulfate (CS) transformed a healthy growth cone into a so-called dystrophic endball and inhibits its regeneration after CNS injury.

Axons of neuronal cells play roles of transmission wires in our body. They transduce several information as electronic signals. As wires are easily cut by an accident, our axons are also vulnerable. The wires can be fixed, while axons can not. This is mainly because CS transforms axonal tips into dystrophic endballs through its receptor PTPRσ and inhibits axonal growth. In this study, the team reveled that PTPRσ dephosphorylates cortactin and disrupt autophagy flux at axonal tips, leading to axonal regeneration inhibition. The findings can be developed to understand and treat traumatic nervous injury and neurodegenerative disease. These achievements were published online in Nature Chemical Biology on May 6, 2019 (4 p.m. UK time).

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Research Background

The human neural circuit is about 50 thousand kilometers in length which is connected by axons. During development of the neuronal network, neurons connect with one another by extending their axons. The longest axon in human can stretch up to approximately 1 meter.

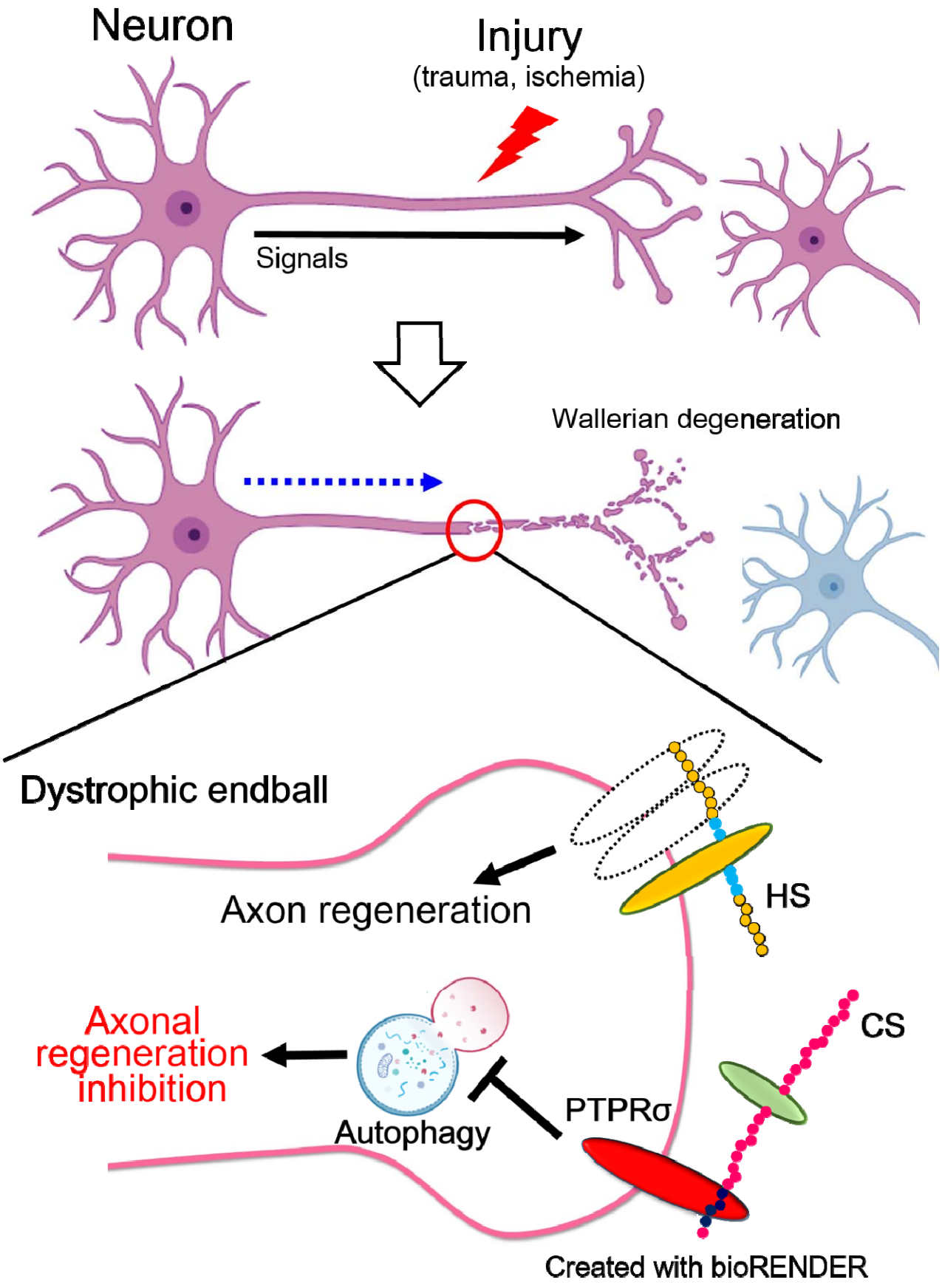
The delicate neural circuit can be easily disrupted by physical forces. For example, spinal cord injury can cause a series of damage to the neuronal axons. Distal part of neurons undergo Wallerian degeneration and removed from tissue, while proximal part of neurons are still alive and try to extend their axons again to reconnect neural circuits. However, their efforts end up in vein. As a result, neural network permanently remains disconnected and patients suffer from paralysis for life. One of the reasons is the accumulation of chondroitin sulfate (CS) at the injury site. In contrast, heparan sulfate (HS) promotes axon growth. Interestingly, HS and CS are similar in molecular structure and bind to the same receptor, PTPRσ (a receptor type tyrosine protein phosphatase). However, it has been elusive why or how these similar glycans cause opposite effects on the axon regeneration through the same receptor.

Research Results

The research team chemically synthesized a series of HS and CS, which are different both in length and sulfation patterns. The team found that HS could polymerize PTPRσ and promote axonal extension, while CS monomerized it and disrupted the extension. Upon binding to PTPRσ, CS activated this receptor's enzymatic activity, and consequently dephosphorylated cortactin. As cortactin is critical for autophagy, CS-induced cortactin de-phosphorylation stopped autophagy and transformed axon tips to ball-like structures, so-called dystrophic endballs, the hallmark of injured axon. Indeed, an artificial disruption of autophagy induced dystrophic endballs (see Figure).

Research Summary and Future Perspective

Importance of the current findings is that the research team have verified the mechanism of the inhibition of axon regeneration, namely the axis of CS-PTPRσ-cortactin-autophagy. The findings have provided important molecular targets to cure neuronal injuries. For example, HS oligosaccharides or PTPRσ inhibitors could be candidate therapeutics. In addition, since autophagy disruption is often observed in neurodegenerative diseases such as Parkinson's disease and Alzheimer disease, our findings have provided insight into the mechanism of these diseases.


Neuron
Injury
(trauma, ischemia)
Signals
Wallerian degeneration
Dystrophic endball
Axon regeneration
HS
Axonal
regeneration
inhibition
Autophagy
PTPRσ
CS
Created with bioRENDER

Publication

“Glycan sulfation patterns define autophagy flux at axon tip via PTPRσ-cortactin axis.”

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