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O-GlcNAc Signaling Orchestrates the Regenerative Response to Neuronal Injury in *Caenorhabditis elegans*

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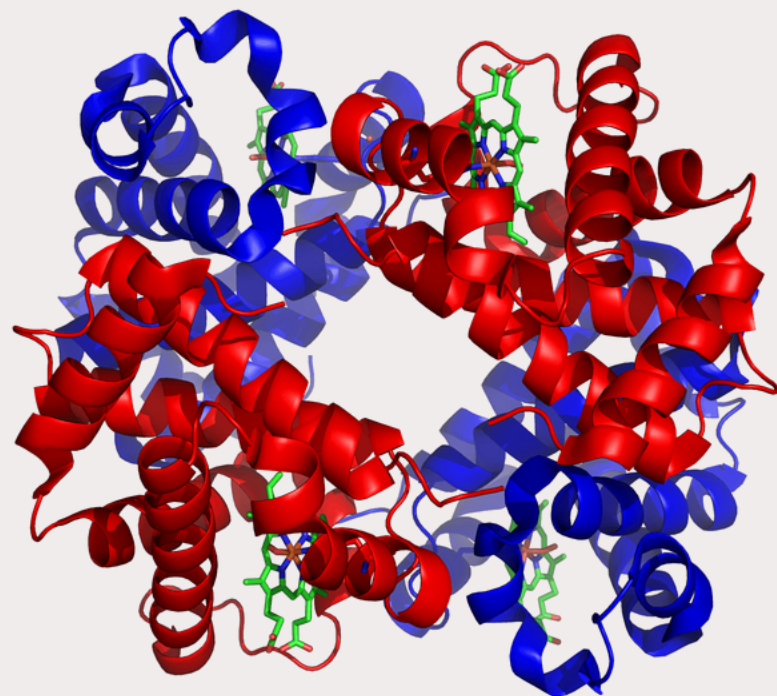
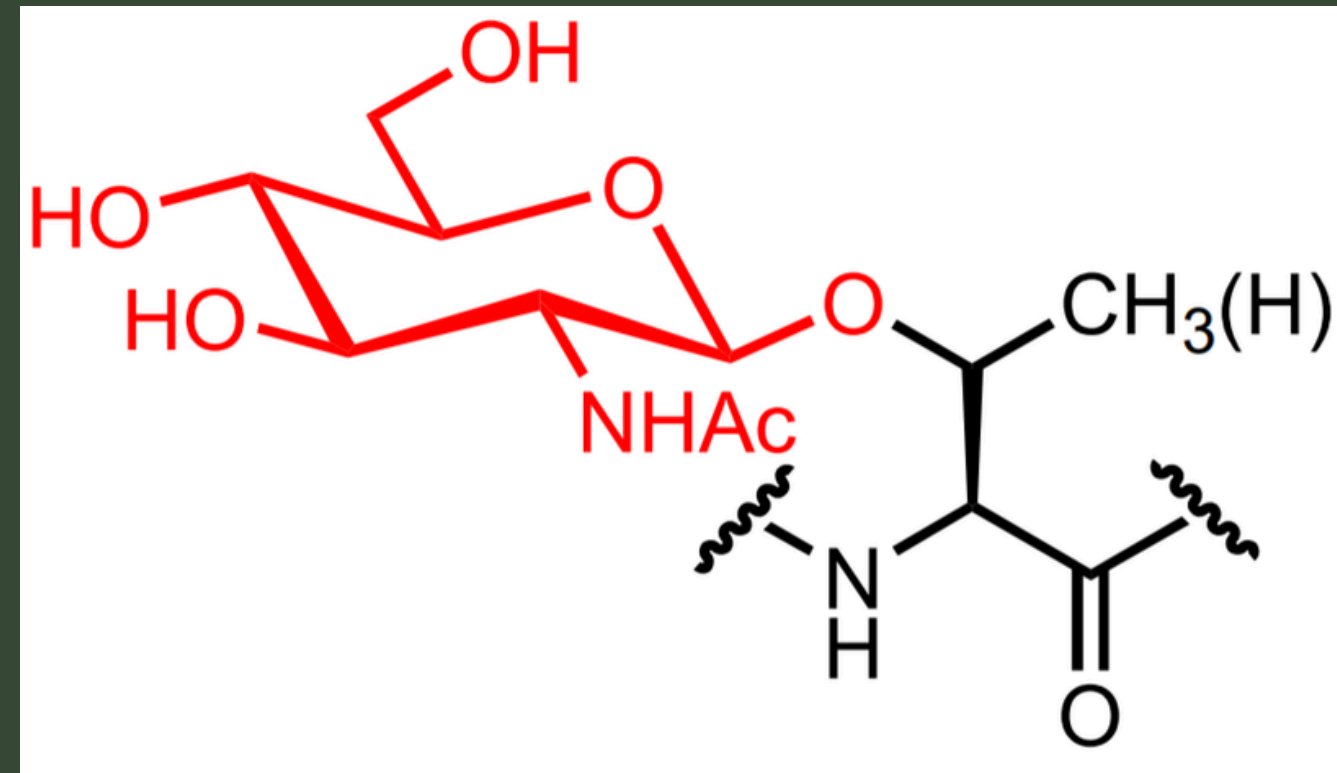
Abstract

Regrowth of an axon after injury is an inherently metabolic undertaking. Yet the mechanisms of metabolic regulation that influence repair following injury are not well understood. O-linked β -N-acetylglucosamine (O-GlcNAc) is a post-translational modification of serines and threonines that functions as a sensor of cellular nutrients. Performing in vivo laser axotomies in *Caenorhabditis elegans*, we find that neuronal regeneration is substantially increased by disruptions of either the O-GlcNAc transferase or the O-GlcNAcase that decrease and increase O-GlcNAc levels, respectively. A lack of O-GlcNAc induces the AKT-1 branch in the insulin-signaling pathway to use glycolysis. In contrast, increased O-GlcNAc levels activate an opposing branch of the insulin-signaling pathway whereby SGK-1 modulates the FOXO transcription factor DAF-16 to influence mitochondrial function. The existence of this toggle-like mechanism between metabolic pathways suggests that O-GlcNAc signaling conveys cellular nutrient status to orchestrate metabolism in a damaged neuron and maximize the regenerative response.

Key Definitions

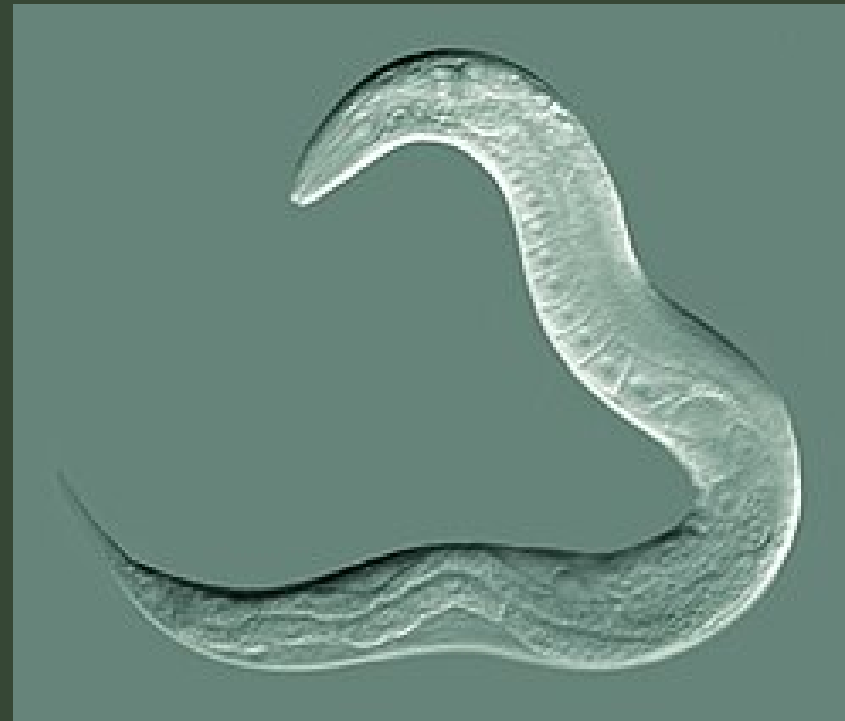
Key Definitions

O-GlcNAc



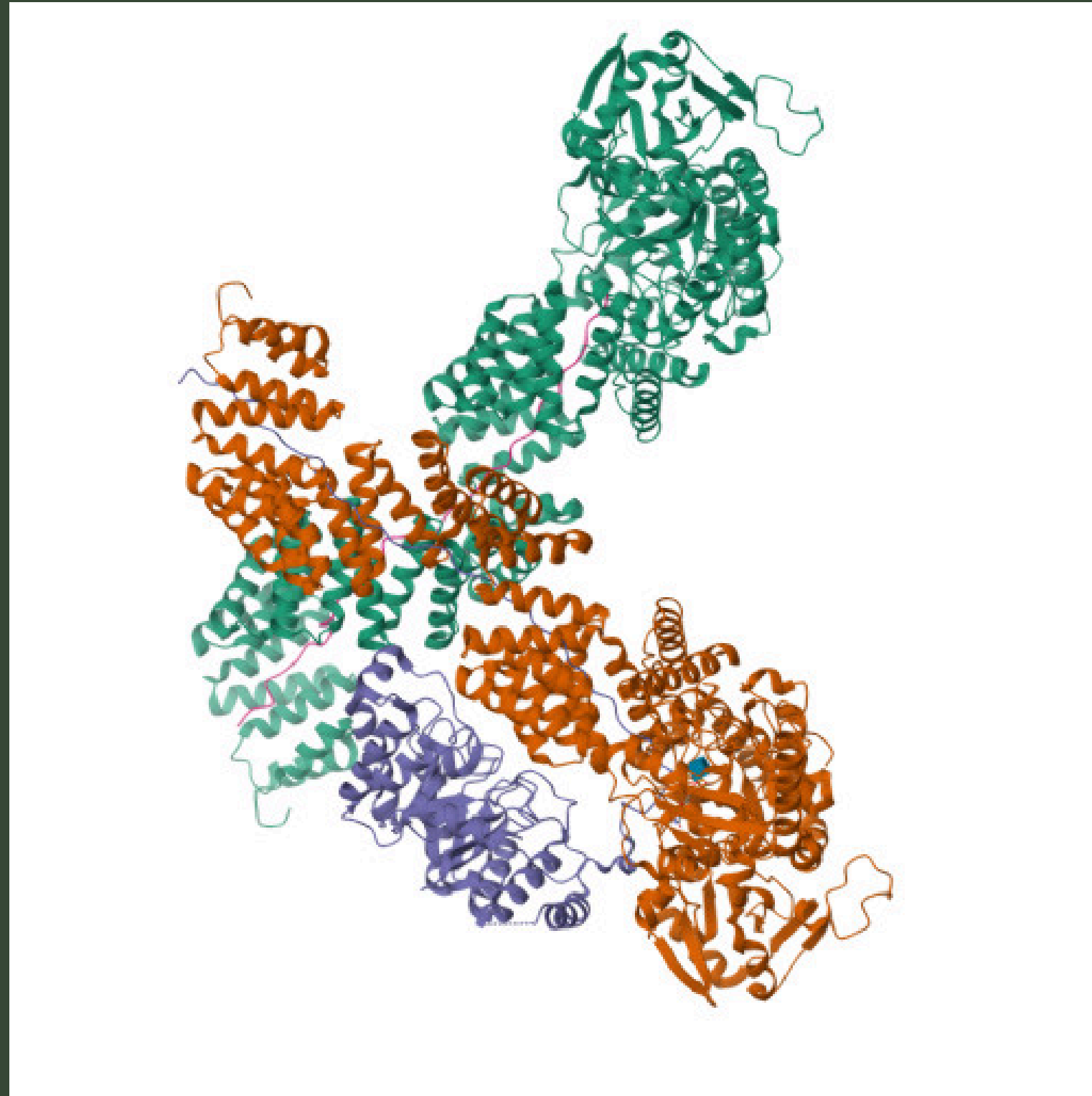
Key Definitions

Caenorhabditis
elegans



Key Definitions

OGA/OGT



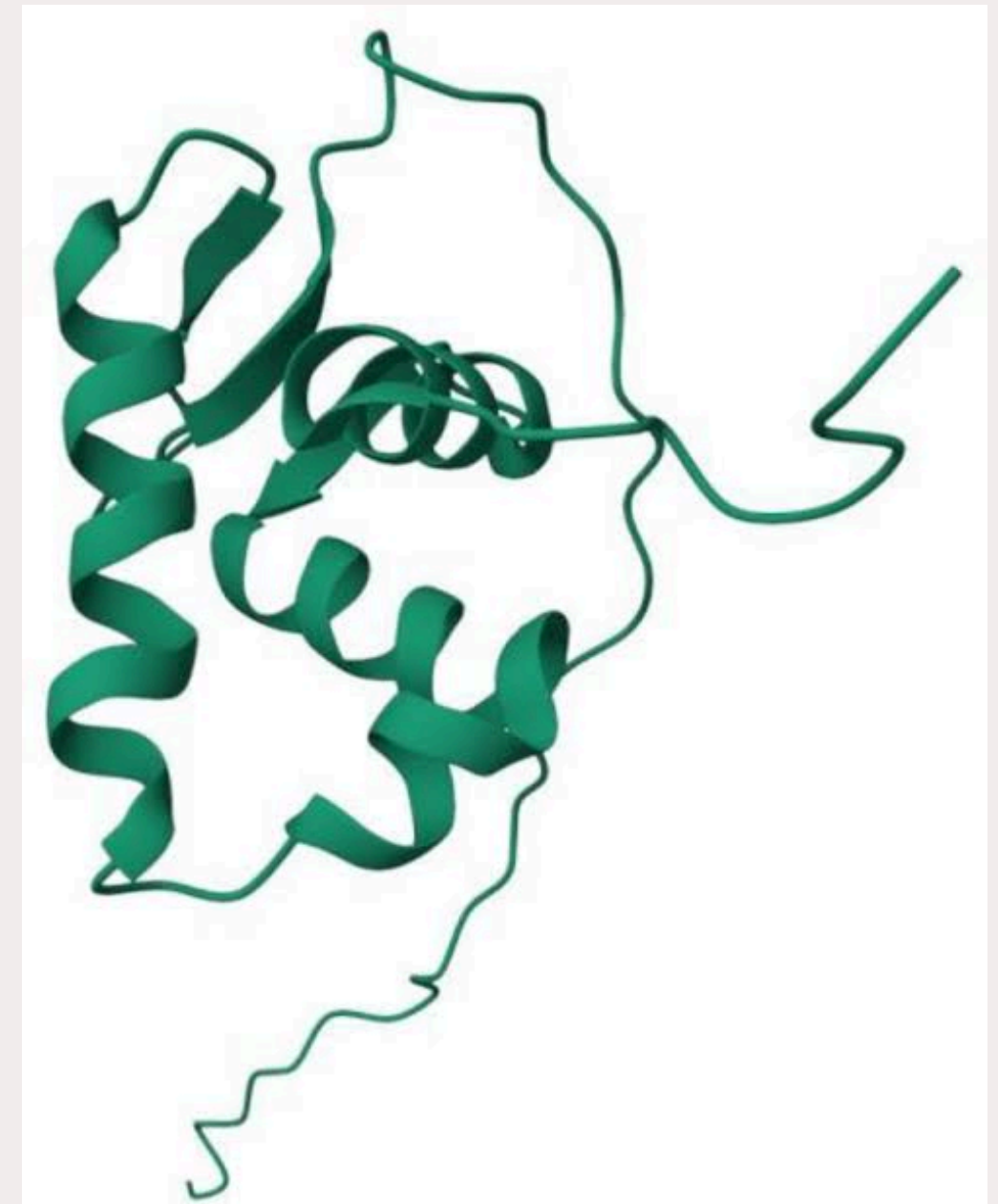
The Study

Why?

We don't yet understand what exactly happens when a neuron is damaged and tries to repair itself. We know O-GlcNAc is a nutrient sensor, but we don't know how it impacts healing.

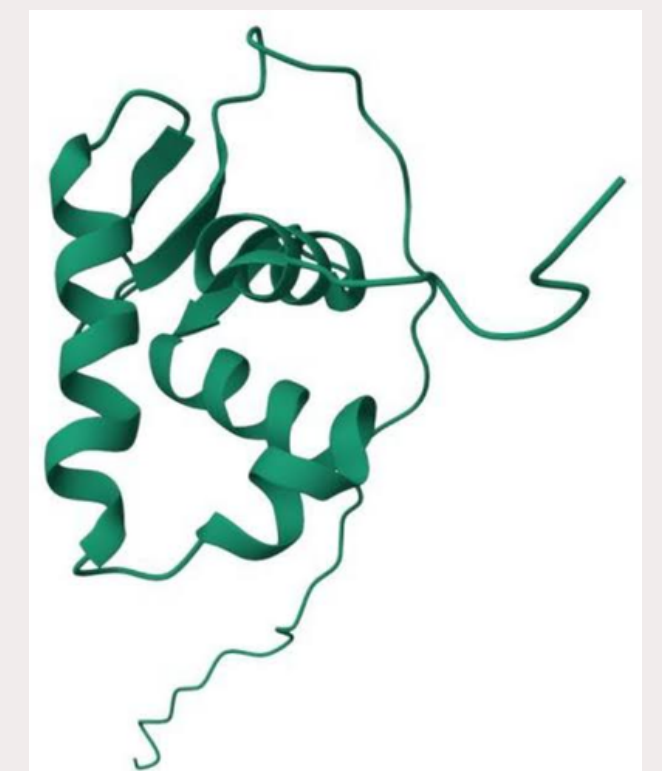
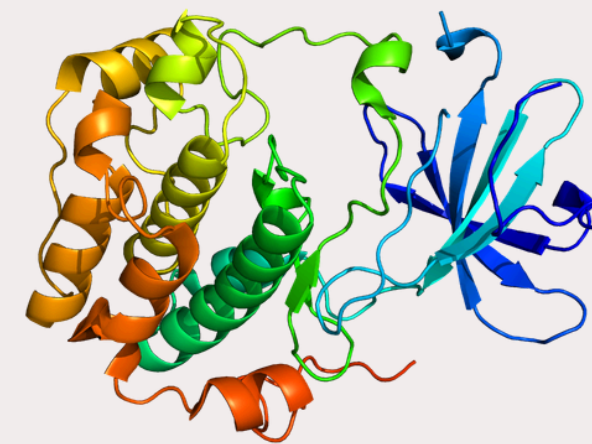
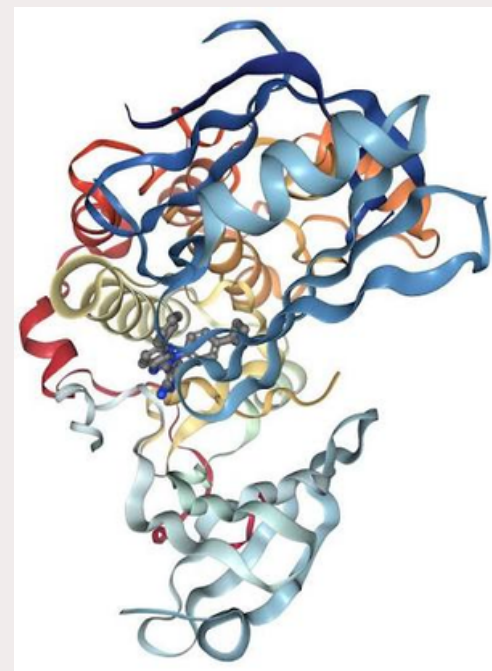
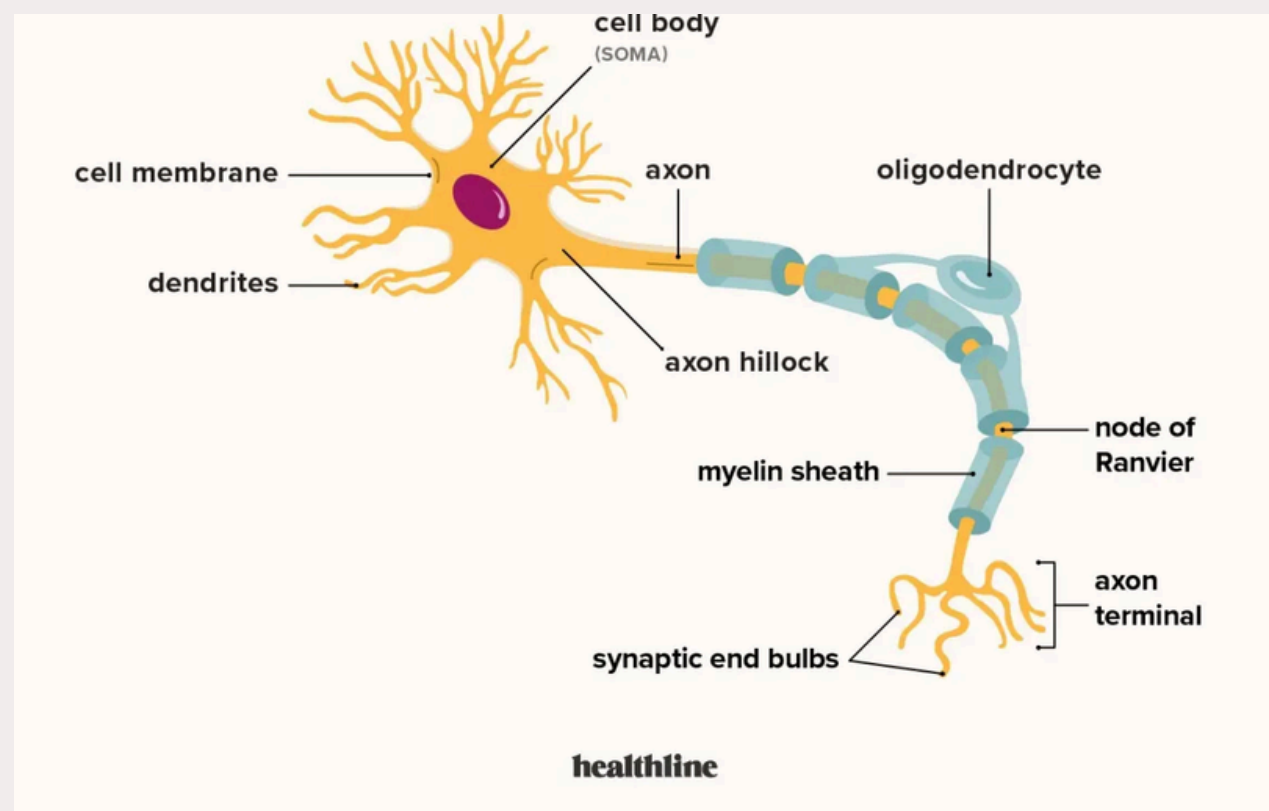
They asked what role O-GlcNAc might play in conveying nutrient status within a damaged and regenerating neuron

- The O-GlcNAc sugar tags track cellular nutrition and help direct how a damaged neuron metabolizes energy to fix itself.
- Reducing or mutating the insulin receptor signals the cell to regenerate broken nerve fibers, which requires the FOXO/DAF-16 protein.
- Advanced testing proves that O-GlcNAc sugar tags physically attach themselves directly to the critical control proteins in this pathway (AKT and FOXO/DAF-16), altering how well the nerve can regrow after being damaged

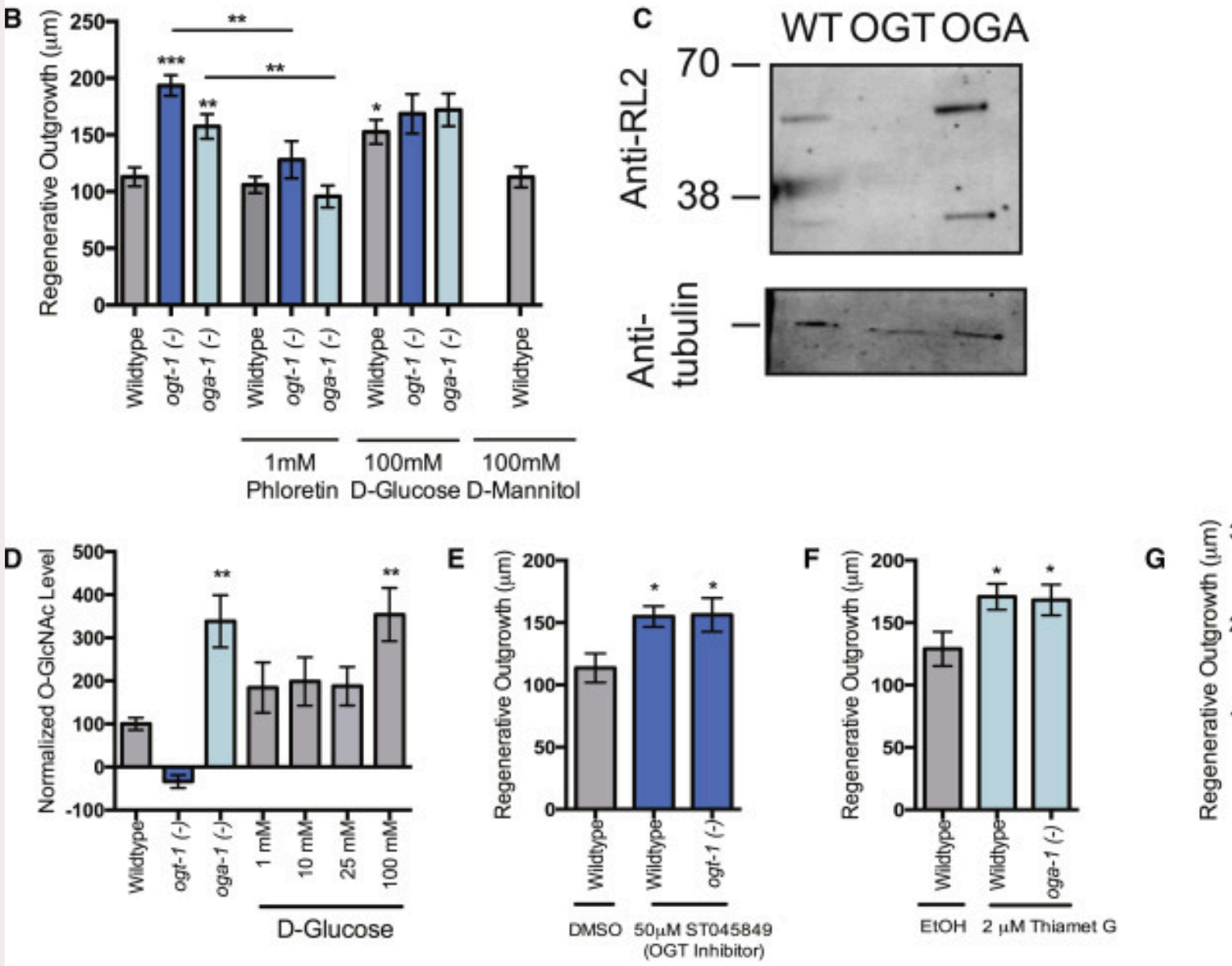
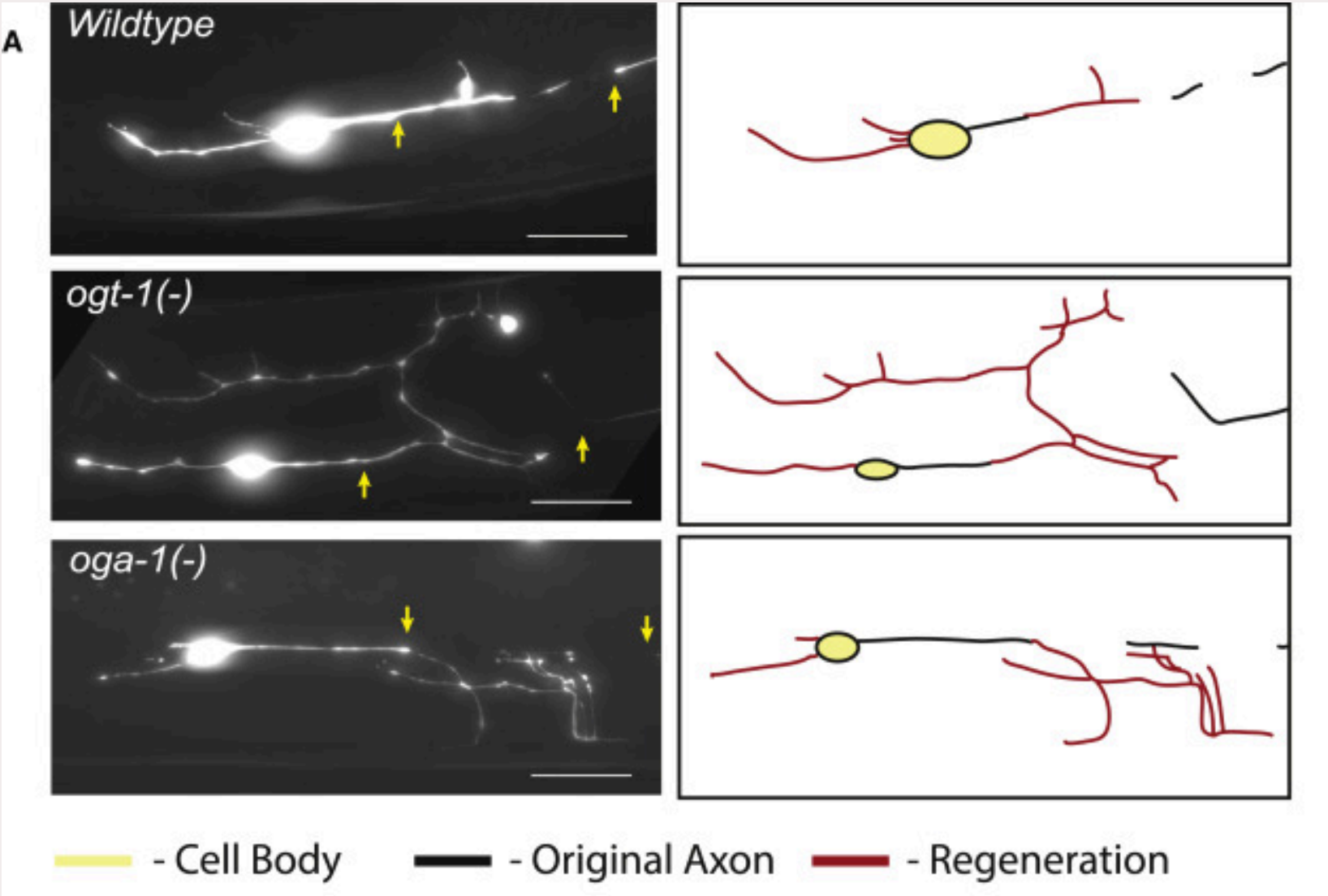


Methods:

- Modified OGT/OGA levels to increase or decrease O-GlcNAc (KO/TMG, OSMI-1)
- They cut neuronal axons with a laser to damage them.
- They tracked and measured how well the damaged axons grew back after the laser cut
- They analyzed how these changes switched on different branches of the insulin-signaling pathway to control how damaged cells use energy:
 - Lowering O-GlcNAc activated the AKT-1 branch, which boosted glycolysis to help the neuron regenerate.
 - Raising O-GlcNAc activated an opposing branch (SGK-1 and DAF-16), which altered mitochondrial function



Results:



Discussion/Conclusion

- **Disrupting either OGT or OGA substantially increases neuronal regeneration after injury.**
- **Two Opposing Branches of the Insulin-Signaling Pathway Control This Response:**
 - **Lack of O-GlcNAc → AKT-1 branch → glycolysis**
 - **Excess O-GlcNAc → SGK-1 kinase → modulates the FOXO transcription factor DAF-16 → drive mitochondrial function for cellular repair**
- **Axon regeneration is inherently bound to a cell's nutrient and energy status; bypassing or altering O-GlcNAc levels forces the cell to reorganize its core metabolic pathways to optimize healing.**

Questions

[https://www.cell.com/cell-reports/fulltext/S2211-1247\(18\)31196-3?
returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%
2Fpii%2FS221124718311963%3Fshowall%3Dtrue](https://www.cell.com/cell-reports/fulltext/S2211-1247(18)31196-3?returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS221124718311963%3Fshowall%3Dtrue)