When ribosomes collide: How bacteria clean up after molecular crashes

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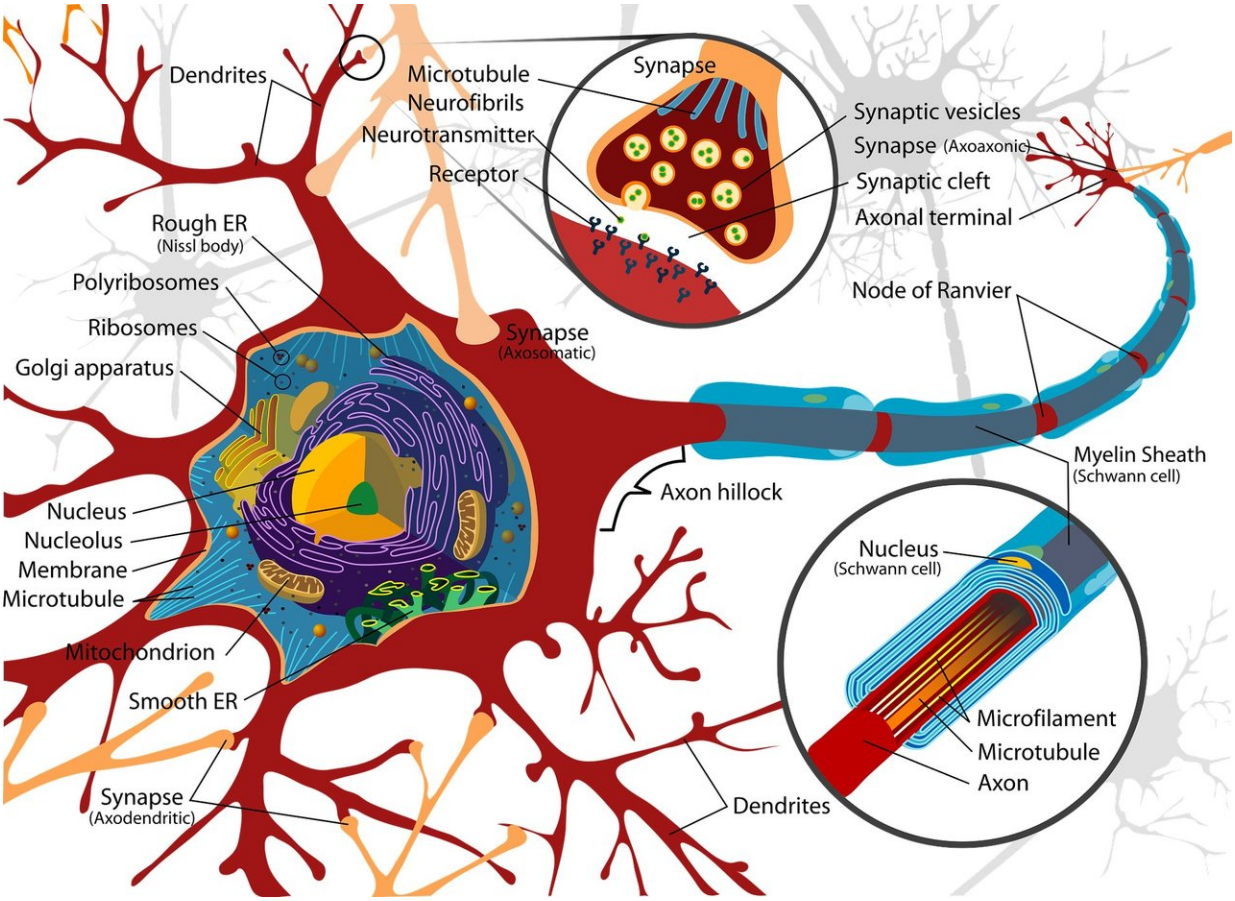

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The knobby, 3D structure on the screen in front of Rachel Green showed an intracellular car wreck never before seen by scientists. It also

confirmed a hypothesis a team in her lab had been working on for months.

But at first, Green wasn't so impressed. "That's it?" she remembers thinking wryly.

It was early 2021, and she was on sabbatical, working at Ludwig Maximilian University of Munich with her friend and collaborator, Roland Beckmann. Green, a Howard Hughes Medical Institute Investigator at Johns Hopkins University, had told him about a project in her lab exploring a long-standing biological mystery. They were trying to fill in a key gap in scientists' knowledge about how bacterial cells respond to protein synthesis problems. Because cells need proteins for nearly everything they do, this response is critical for normal function.

Green's team had a good idea of what was going on, but they didn't have the snapshots to prove it. Beckmann, a structural biologist, was intrigued. Using a technique called cryo-electron microscopy, his team revealed what happens at the scene—that is, if you knew what to look for.

"When they first show you a structure, you can't really tell what anything is because everything's gray," Green says. "Roland pointed to some little blob, and said, 'Look, there it is!'"

Her team suspected that the "little blob" acted as a molecular first responder that shows up at the accident. Beckmann's images confirmed the molecule's identity and presented new intel about how this rescue operation, a method of quality control for bacteria, works. Beckmann, Green, and a group of scientists in her lab led by Allen Buskirk first described the research in a preprint on bioRxiv.org and later in the journal *Nature* on March 9, 2022. The work could offer clues about how other, more complex organisms—perhaps even humans—keep protein production on track.

Molecular machines known as ribosomes quite literally follow instructions encoded in a linear strand of genetic material. As they travel along the strand, they build a protein. Sometimes, though, this machinery malfunctions.

Earlier research in yeast, whose cells resemble those of animals, had shown that ribosomes stall when they get into trouble. Like a car that stops too suddenly, a stalled ribosome can be rear-ended by the one behind it. Green's lab had previously identified a yeast molecule that responds to these collisions. Like a tiny Jaws of Life, the molecule cuts the stalled ribosome free. It's the first step in a rescue effort that ultimately lets the cell salvage and reuse these valuable, protein-making machines.

Bacterial cells' ribosomes can get jammed up too, but scientists doubted that bacteria respond to collisions the same way yeast do. That's because researchers already knew that bacteria have their own distinct method for rescuing wrecked ribosomes, says Jamie Cate, a biochemist and structural biologist at the University of California, Berkeley, who was not involved in the project.

No one knew exactly what kicked off the bacterial rescue effort, but they expected that it would be something entirely different from yeast, Cate says. Instead, the new research suggests that both bacteria and yeast initiate this process the same way—by summoning blade-like first responders.

"The cool thing is that both molecules recognize ribosomes that have collided into each other," Cate says.

In Green's lab in Baltimore, Buskirk and first author Kazuki Saito identified the first responder in bacteria as a molecule called SmrB and explored how it carried out its job. Beckmann's structure "was the final

piece of the puzzle," Buskirk says.

Beckmann's group captured the first-ever images of a collision between two bacterial ribosomes, then color-coded them so their components weren't lost in a sea of gray. After adding SmrB to the sample containing the ribosomes, the team saw the molecule appear at the center of the crash.

Biochemical experiments revealed that SmrB, like its yeast counterpart, cuts the wrecked ribosomes apart. And not only do the two molecules share a job description, bacterial SmrB and its yeast counterpart are also close relatives, the team found. Researchers haven't yet been able to visualize how the yeast version interacts with ribosomes during a collision. So, the similar but simpler SmrB may give scientists a foothold for understanding how the process works in other organisms.

"Everything else about these rescue pathways is very different," Green says. "We didn't anticipate we would find an aspect that appears to be universal."

More information: Allen Buskirk, Ribosome collisions induce mRNA cleavage and ribosome rescue in bacteria, *Nature* (2022). DOI: 10.1038/s41586-022-04416-7.
www.nature.com/articles/s41586-022-04416-7

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