Seeking to avoid 'full lockdown,' cells monitor ribosome collisions

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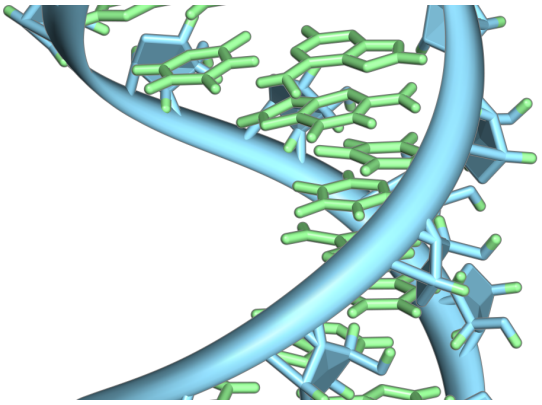

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

Ribosomes are the machines in the cell that use instructions from mRNA to synthesize functional proteins. There are hundreds of thousands of ribosomes in each cell, and they mostly process their instructions faithfully. But sometimes ribosomes get stuck or stall on roadblocks along defective mRNA molecules.

New research from Washington University in St. Louis shows that cells monitor for ribosome collisions to determine the severity of the problem and how best to respond when things start to go awry.

The research from the laboratory of Hani Zaher, associate professor of biology in Arts & Sciences, is published online Dec. 17 in the journal *Molecular Cell*.

"The cell has two methods of stress response that are triggered by this very same signal of ribosomes running into each other," Zaher said. "However, the quality control mechanism of ribosome rescue and mRNA degradation responds more swiftly—to resolve the problems and to prevent premature activation of the integrated stress response.

"Only after cells have exhausted the capacity of the quality control system do they move to shut down the entire translation system by activating the stress response," Zaher said.

Leo Yan, a graduate student in biology and the first author of the study, used an analogy relevant to human experience during the COVID-19 pandemic.

"Integrated stress response is like a city going through full lockdown," Yan said. "If you only have 10 cases, you don't want to come out and tell the city, 'Let's just hunker down and not do anything,' or shut down all the productivity. You want the city to have a system to evaluate the severity of the stress—and to deal with it according to its severity.

"The value of our paper is in describing the dynamic within the system that the cell can use to evaluate the level of stress—from local, individual events, to events that require shutdown of the entire translation machinery," he said.

Yan and Zaher discovered that cells are using ribosomes like sensors to alert them about changes in their environment.

The scientists used drugs and genetic manipulations to alter ribosome speed and density, providing compelling evidence that both major kinds of stress response are activated in response to ribosome collisions.

When ribosomes are evenly distributed, rarely running into each other, cells know that conditions are good. When some ribosomes run into each other, cells recognize that there are problems—and call on quality control factors to resolve the collisions. When many ribosomes are colliding with each other, cells go on high alert and shut things

down.

"There's a communication between these two pathways," Zaher said. "And the reason for that is that, even though the integrated stress response is a pro-survival pathway, it comes at a cost of shutting the cell down. You don't want to activate it prematurely, unless you're certain that there is a problem."

The researchers made their observations using a yeast model system, but the findings are applicable to mammal cells, too, they said. In humans, dysregulation of integrated stress response signaling has been linked to diseases including diabetes, cancer and neurodegenerative disorders such as Alzheimer's and Parkinson's disease.

More information: Zaher, Hani S. et al.: "Ribosome-quality control antagonizes the activation of the integrated-stress response on colliding ribosomes" *Molecular Cell* (2020). DOI: 10.1016/j.molcel.2020.11.033 , www.cell.com/molecular-cell/fu … 1097-2765(20)30833-9

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