When cells rush to repair DNA, they also know when to stop

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When ultraviolet light, certain chemical compounds or even normal copying mistakes harm our DNA, cells rush to fix the damage. Doing so means making the right repair proteins – but also not too many.

Using baker's yeast and human skin cells, a new study has shown that cells temporarily slow the step in which protein-building machines read messenger RNA, or mRNA, for specific repair genes. In this process, two guardian proteins act like traffic lights that turn those messages from green to red until the emergency has passed.

The work uncovers a previously hidden layer of the DNA damage response that prevents both under-repair and over-repair. "It is a smart, evolutionarily conserved strategy that helps cells survive," Indian Institute of Science associate professor and study lead investigator Purusharth I. Rajyaguru said. The study, together with researchers at Institut Curie, Paris, was published in *EMBO Reports*.

The researchers attached green fluorescent tags to two proteins, Scd6 (yeast) or LSM14A (humans), and filmed living cells. When the team damaged DNA by treating it with hydroxyurea, the tagged proteins condensed into bright dots called RNA granules. Further analysis revealed that the hydroxyurea made Scd6 clump together while removing the stress dissolved the clumps. This indicated the holding areas were reversible rather than the cell's trash bins.

Inside those granules, the researchers found that Scd6 captured the mRNA for an enzyme called Srs2, which unwinds DNA. This action caused the cells to produce lower quantities of Srs2. The researchers confirmed this by mutating either of Scd6's two RNA-gripping regions and found that it couldn't capture the mRNA to make Srs2. Yeast lacking in the Scd6 protein grew poorly when extra Srs2 was present inside cells when the DNA was treated with hydroxyurea, proving that reducing Srs2 production could actually protect the cell.

The team found a similar process in human cells. The LSM14A protein also formed granules after hydroxyurea treatment. When LSM14A production was knocked down, the cell made more of two enzymes that encouraged the cells to stitch broken DNA ends together in an error-prone way.

"Interfering with RNA granule dynamics might be a way to disrupt stress adaptation in cancer cells, making them more vulnerable to chemotherapy," Dr. Rajyaguru said. "We are also addressing this aspect in the context of neurodegeneration in our laboratory."