In cellular biology, mistakes can be good

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The easily angered sage Durvasa from Indianmythology is adapted here to representmistranslating cells. The quiet sages on the left depict normal wild type cells, while the angry ones on the right are the short-fused 'Durvasas'. Like their namesake who is rather indiscriminate in his cursing and can, therefore, get into trouble, mistranslating cells incur a cost and are under-represented in the population. However, like Durvasa, they are well prepared to fend off attacksby prior accumulation of Lon protease (shown as yellow fireballs in the chest). In contrast, the quiet sages are not prepared (less Lon) and are likelier to be killed. The demon represents DNA damage, and leads to rapid SOS response activation from the mistranslating cells (thunderbolt thrown by the Durvasas) whereas the unprepared and quiet sages are slow to respond. The aftermath shows that

mistranslating cells show higher survival than their wild type counterparts. Credit: Pranjal Gupta

Mistakes are rarely rewarded. Intuitively, one would imagine that a shoddy typist at an office who keeps generating typos would either quickly lose their job, or at least be overlooked for promotion. The idea that this person could, in fact, benefit from being shoddy and rise above others professionally is counterintuitive, and yet we see this in cells.

Like humans, cells constantly make mistakes. Most of the work within cells is carried out by biomolecules called proteins; without these, cells would not exist. Oddly, protein production has the highest known error rate of any cellular process. Why do cells tolerate this equivalent of the shoddy typist? Is there a secret benefit to being clumsy? These questions have been of interest for quite a while.

After several years of work from groups around the world, we now know that errors made during protein synthesis (mis-translation) can have both positive and negative consequences for the cell. The negative consequences are easy to understand: Proteins that carry incorrect amino acid sequences (differing from what is specified by the DNA) are most often misshapen and no longer suited to do their regular jobs. As a result, they hold back key enzymatic reactions in the cell, and slow it down.

All living cells, including bacteria such as E. coli, have several 'proofreading' mechanisms that usually prevent such errors from happening, or at least keep them at a low level. In reality, such high rates of mistranslation are common—as much as 10% of the total protein content in E. coli is estimated to be mistranslated at any given time, in spite of these error-correction mechanisms.

This has led to the speculation that these mistakes might just be useful for something. The positive effects of mistranslation are broadly observed from two kinds of phenomena. First, when a single protein has a key alteration in its amino acid sequence: Say amino acid X changed to Y, which now makes it more effective than the original protein against a new threat (e.g., a viral attack, or an antibiotic). Second, when a general increase in the level of mistakes throws up a whole bunch of novel protein sequences, of which some are useful in a specific condition. The kind of mistranslation observed in cells is like the second phenomenon. Because these mistakes are largely unpredictable and not targeted toward a specific subset of proteins, it is difficult to see how they can produce a consistent benefit, particularly one large enough for cells to maintain the error rate at a high level.

In a new study, scientists from Deepa Agashe's group at NCBS report that irrespective of which proteins are impacted, there is a benefit to non-specific and generalized mistranslation. Postdoctoral fellow Laasya Samhita and project assistant Parth Raval induced different kinds of mistranslation in E. coli, manipulating both the genetic makeup of the cells and the environment in which they lived. No matter how cells mistranslated, it led to the accumulation of a special protein quality guard molecule, whose usual job is to straighten any messed-up proteins. This molecule, called Lon, also targets some proteins that are involved in a key bacterial DNA damage response, aptly named "SOS."

It turns out that increasing Lon tips the balance toward activating this response, but doesn't actually activate it until there is DNA damage. Like all stress responses, the SOS response can only be sustained for a brief period before it starts getting too expensive for the cell and causes self-damage. Therefore, under normal circumstances, mistranslating cells grow more slowly than regular cells. But under stress, Laasya and Parth found that normal cells were hit so badly that the error-prone cells now survived better in comparison. As an analogy, think of Durvasa, the short-

tempered sage from Indian mythology. In a group of peaceful sages, he represents mistranslating cells: always worked up and on the verge of losing his cool. This constant temper is unhealthy, and like mistranslating cells, there are very few Durvasas around. However, because he is on 'high alert' (high Lon in cells), when a real threat like a demon appears, Durvasa quickly throws a thunderbolt, killing the demon (SOS response in cells quickly repairs DNA damage). Meanwhile, the demon manages to kill most of the unprepared, peaceful sages.

In their study, Laasya and Parth induced DNA damage primarily through the antibiotic ciprofloxacin. Ciprofloxacin is commonly used to treat bacterial infections, and acts by chopping up DNA into fragments, killing the cell. Usually, to survive in ciprofloxacin over long periods of time, cells require genetic mutations that help them resist the antibiotic. But the team found that immediately after exposure to Cip, there are no mutations in any of the cells, and survival relies on a robust SOS response. This is where the mistranslating cells had an edge: They were already armed and quickly repaired the damaged DNA, whereas most of the normal cells died on encountering the antibiotic. The mistranslating ones therefore became greater in number. Both kinds of cells eventually sampled the same set of mutations that provide resistance to ciprofloxacin, but simply because there were more mistranslating ones that survived the initial antibiotic stress, there were many more resistant cells in the mistranslating group. Thus, mistranslation led to an early, non-mutational change (SOS activation), which in turn provided a larger population of cells in which resistance mutations could occur.

These new results throw up several exciting implications and possibilities for further exploration. We already know of some non-genetic mechanisms that help bacteria to survive antibiotic stress, such as making spores and forming biofilms. Could mistranslation be another way for bacteria to escape stresses in nature? In a given population, do all cells mistranslate to the same degree, and how is this regulated? Are

DNA damage and protein synthesis linked because the same stresses damage both DNA and proteins, or are there other unknown layers? The study also emphasizes the role of non-genetic responses in survival and unravels a hidden link in the fascinating labyrinth of cellular pathways.

More information: Laasya Samhita et al, Global mistranslation increases cell survival under stress in Escherichia coli, *PLOS Genetics* (2020). DOI: 10.1371/journal.pgen.1008654

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