Cellular Chinese whispers: The impact of mistranslation on phenotypic variability and fitness

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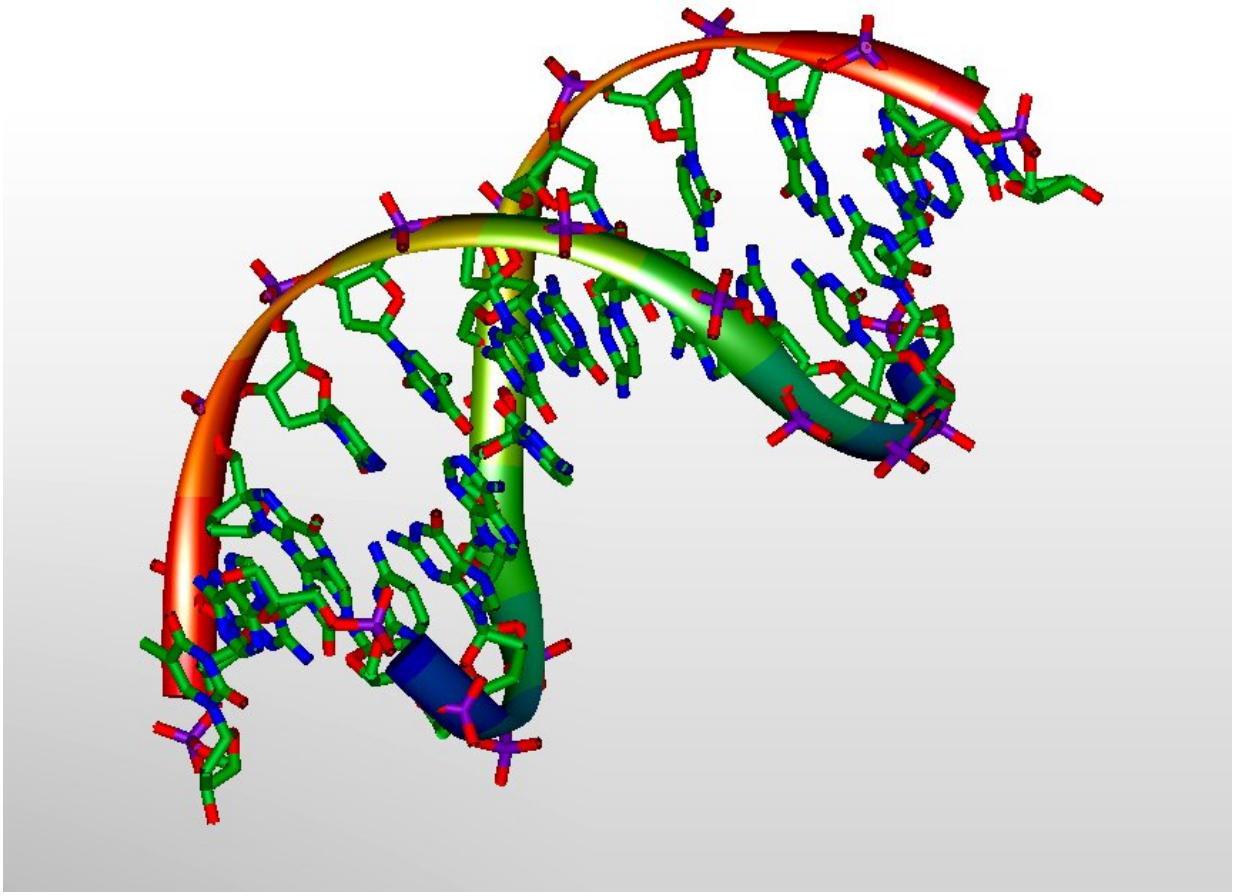

3D-model of DNA. Credit: Michael Ströck/Wikimedia/ GNU Free Documentation License

The immense diversity in the living world and how it came into being has always been a subject of human enquiry. After centuries of playing detective in search of the basis of the parities and disparities that we see among living beings around us, the past century stood witness to some marvelous discoveries in biology and today the Central Dogma of life has been disclosed to us: DNA makes RNA and RNA makes protein (a facile view of a much more complex sequence of events). Together with contributing environmental factors, proteome(s) (total protein content of a cell) collectively influence 'traits' or characteristics of organisms that vary among individuals of a population.

In a population, individuals with traits better suited to their environment have a higher chance at survival and reproduction than their competitors and hence percolate through the sieve of natural selection and end up transmitting these 'adaptive' traits to the next generation. Changes in the number of individuals carrying each trait, be it due to natural selection or simple chance (genetic drift), add up over generations, and this is how populations evolve over time. We might like to think that this simplistic view of variability and evolution is the whole story, but the roads linking genotype to phenotype and hence to evolution are hardly this straightforward. By the logic of the Central Dogma, individuals with identical genotype residing in the identical environment should have the identical phenotype. But is that always the case? Think about twins for example. Identical twins are born from splitting apart of an embryo inside the womb. This means that all cells in both of their bodies originate from a single zygote (fertilized egg cell) and hence have the same genetic repertoire. If you look close enough, however, you can find subtle differences in appearance by which you can tell apart identical twins reared even in the same environment. Whatever is the source of these differences, it's definitely not in the genes. So, where do such differences come from and do they influence survival and adaptation?

Phenotypic variability in populations with identical genetic makeup can

be attributed to non-genetic sources which include both cell-extrinsic (environmental) and intrinsic mechanisms. One such cell-intrinsic non-genetic source involves stochastic errors in gene expression. Much like a game of Chinese whispers, the cell makes errors when copying information from DNA to RNA and from RNA to protein, such that the final protein sequence does not always exactly represent the original gene sequence it has been derived from. A large chunk of the error in the cellular game of Chinese whispers comes from the last step in the gene expression cascade, which is the process of translating RNA into a protein, owing to its exceptionally high error rates (~1 in 10^4). Theoretically, it seems obvious to assume that translation errors will result in proteome heterogeneity, generating a wide range of phenotypic variability in the population that will allow individuals to respond differently to identical environmental requirements and hence help the population better adapt to it. But there are a number of catches in this assumption! Firstly, the cell has many strategies to safeguard itself against protein mistranslation and thus errors in translation might not always lead to phenotypic variability. Secondly, protein production errors being random and unpredictable, the resulting variability is most likely to have maladaptive consequences for a population already optimized to a certain environment. Thirdly, proteome level variability is not heritable and hence might not even persist over generations to have implications on an evolutionary timescale. So, is our obvious assumption actually incorrect?

To give some empirical ground to these conjectures, researchers Laasya Samhita and Parth Raval from Dr. Deepa Agashe's lab at NCBS turned to our good ol' friend, the gut bacterium E. coli! They altered global mistranslation rates (protein translation error rates) in the bacteria through genetic and environmental manipulations and assessed how it impacts population-level parameters like growth rate, lag time and growth yield. To measure phenotypic variability at the single-cell level, they teamed up with researcher Godwin Stephenson from Dr. Shashi

Thutupalli's lab at NCBS. Godwin pored over individual E. coli cells trapped inside channels of a microfluidic device to investigate how the manipulation of mistranslation rates affects single-cell parameters like cell length (indicative of the physiological state of the cell) and division time (indicative of the reproductive rate of the bacterium). The results were interesting! E. coli modified to have higher mistranslation rates showed higher variability in cell length and division time, while the reverse was observed when mistranslation rates were reduced. Mysteriously, however, similar correlations between mistranslation levels and variability were not consistently found for population-level growth parameters. These results validate the prediction that higher mistranslation can result in higher phenotypic variability, addressing the first catch in our assumption. However, the results open up another question: why does the correlation between mistranslation and variability seen for single cells not hold at the level of the population? Maybe variability at the single-cell level is predictable and uniform across populations such that it evens out and does not show up as variation between populations. Or perhaps increased cell-to-cell variability leads to the generation of more cells with sub-optimal phenotypes which end up getting eliminated from the population due to selection, and hence cannot contribute to parameters like population growth rate. There can be different possibilities, but we can't say yet which one is correct.

Now that we have some idea about how mistranslation affects variability, lets head on to the second catch of our assumption and see if mistranslation-induced variability is adaptive or maladaptive for the population. Laasya and Parth found that both increase and decrease in mistranslation-induced variability turns out to be disadvantageous for the bacteria under optimal environmental conditions. To puzzle out what this observation implies, imagine cells as walking a tightrope when trying to balance between accuracy and speed of protein translation. Just like too much mistranslation is likely to lead to gravely malformed proteins that fail to do their job, being super accurate entails very slow and calibrated

steps in protein production that may lengthen cell division time and hence slow down population growth. So, a tilt in either direction can make the cell fall off the rope.

Surprisingly, however, mistranslating cells were often found to survive better when faced with stressful situations such as high temperature or starvation. This does make sense because the higher the mistranslation, the higher the variability and the higher the chance of some individuals of the population being better suited for stressful environmental conditions. To be noted, this is just a hypothesis. Thus, though higher variability is seen to be linked with higher survival under stress, it is not known if the relation between the two is that of direct cause and effect as seems intuitive, or if indirect pathways linking them are at play. What's more, just a brief initial pulse of altered mistranslation rates was sufficient to elicit better stress survival across generations; and there goes the third catch of our assumption which questioned if the effects of mistranslation can be carried forward through generations! This last observation is strange, as variability arising due to alterations solely in the proteome is not supposed to be heritable. The reasons behind this observation can be manifold but coming to any definite conclusion will require further experiments. So, as of now, this question is wide open for investigation.

The study under focus is one of the few attempts made to connect errors in cellular processes with variability and evolution. "The discovery that translation errors can increase phenotypic variability in fitness linked traits is exciting and of potential relevance for evolution. Future work should tell us more about the significance of this observation for natural bacterial populations", says Laasya Samhita, lead author of the paper that resulted from this study. Thus, while the study addresses some key questions in evolutionary biology, it also ends up uncovering some new ones. Why does mistranslation induced cell-to-cell variability not show up at the population-to-population level? How do cells with higher

mistranslation rates survive better under stressful conditions? How does proteome heterogeneity persist over generations of cell division? There's a treasure chest of answers, and perhaps even more questions, waiting to be unearthed. We are bound to stumble upon many such questions and 'obvious' assumptions as we keep playing detectives in the quest to decode nature. But the important thing to remember while we do that is a maxim by none other than our favorite consulting detective, Sherlock Holmes: "There is nothing more deceptive than an obvious fact."

More information: Laasya Samhita et al, The impact of mistranslation on phenotypic variability and fitness, *Evolution* (2021). DOI: 10.1111/evo.14179

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