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Perspective

Cellular mRNA Transcript Regulations in Homeostasis

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DESCRIPTION

mRNA abundance is coordinated with cell size to achieve homeostasis of mRNA concentration. Absolute transcript production rates increase with cell size. RNA polymerase activity and abundance are key checkpoints underlying transcript homeostasis. Feedback mechanisms result in a quantitative interdependence of mRNA production, nuclear export and degradation rates making mRNA concentration homeostasis remarkably robust to perturbations. RNA metabolism, cell size and cell cycle are closely related; therefore the interpretation result of perturbations must take into account changes in cell size and cell cycle distribution and carefully distinguish the concentration and frequency. For most genes, the amount of mRNA transcripts scales with cell size to ensure constant levels. The scaling of mRNA synthesis rates with cell size plays an important role, with the regulation of RNA polymerase II (Pol II) activity and abundance now emerging as a key point of reference.

However, there is also significant evidence for feedback mechanisms that kinetically couple the rates of mRNA synthesis, nuclear export and degradation to allow cells to compensate for changes in one by adjusting the others. Researchers are beginning to integrate findings these different fields to unravel the mechanisms underlying transcript homeostasis. Despite the noisy nature of gene expression, various aspects of single-cell dynamics, such as volume growth are effectively deterministic. Recent measurements of single cells show that cell volume growth is often exponential. These include bacteria, archaea, budding yeasts and mammalian cells. In addition, mRNA and protein numbers are often proportional to cell volume throughout the cell cycle: Homeostasis of mRNA concentration and protein concentration is maintained in an exponentially increasing cell volume with a variable number of copies of the genome.

The exponential growth of mRNA and protein numbers are indicate dynamic transcription and translation rates that are proportional to cell volume rather than genome copy number. However, current gene expression models often assume a constant transcription rate per gene and a constant translation rate per mRNA pattern at a constant rate. Assuming a finite degradation rate of mRNAs and non-degradable proteins, these patterns lead to a constant mRNA number proportional to the number of copies of the gene and a linear growth in the number of proteins incompatible with the proportionality of the mRNA and the number of proteins relative to the exponentially growing cell volume. Cell survival requires controlling the concentration of the biomolecule, the biomolecules must approach homeostasis. With macromolecules carrying information, specific concentration changes depend on each type: DNA is not buffered, but mRNA and protein concentrations are homeostatically controlled, leading to the concepts of ribostasis and proteostasis.

In recent years we have studied the specificities of mRNA ribostasis and proteostasis in the model organism. Here we extend this study by comparing published data from three other model organisms and cultured human cells. We describe how mRNA ribostasis is less stringent than proteostasis. A constant ratio appears between mean decay and dilution rates during cell growth for mRNA, but not for proteins. We postulate that this is due to a trade-off between the cost of the synthesis and the responsiveness. This compromise occurs at the transcriptional level, but it is not possible at the translational level because the high stability of proteins compared to that of mRNAs. We hypothesize that mRNA's central role in the central dogma of molecular biology and its chemical instability make it more suitable than proteins for the rapid changes required for gene regulation.

mRNAs and proteins also have very different stability in all living cells. The half-life of mRNA depends on the Generation Time (GT) between different cells and also between the GTs of a single species. The median half-life of mRNA is usually about 15%-20% of the cell's GT. We have previously proposed that the approximately constant half-life/GT ratio of mRNA may be due to the need for an optimal balance between synthesis costs and responsiveness. Here we propose that this could be a general rule for all cells growing at their highest growth rate.

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