DYNAMICS OF GENE REGULATION, FROM THE NUCLEUS TO MITOCHONDRIA

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The life cycle of RNAs are varied and diverse. To map the fate of RNA transcripts across the cell, we developed subcellular TimeLapse-seq, a technique that combines metabolic RNA labeling (4sU), subcellular fractionation, and nucleotide conversion chemistry to measure RNA flow rates across different cellular compartments. We measured how nuclear-encoded transcripts move through the cell by quantifying and modeling their half-lives on chromatin, in the nucleus, in the cytoplasm, and on polysomes. This revealed remarkable variations in RNA flow rates between genes and compartments. We identified genes that undergo substantial nuclear degradation by the exosome, and discovered associations between RNA-binding proteins and nuclear export rates. We also applied this approach to study mitochondrial gene expression, revealing striking differences between nuclear and mitochondrial transcripts. Mitochondrial mRNAs are produced at much higher rates (1,100-fold more), degraded faster (7-fold), and accumulate to higher levels (160-fold) than their nuclear-encoded counterparts. We found that mitochondrial RNA turnover is regulated by LRPPRC and that slow mitochondrial translation is required to balance production of OXPHOS subunits encoded in both genomes. These studies provide comprehensive characterization of RNA life cycles throughout the cell and reveal previously unknown regulation mechanisms in both nuclear and mitochondrial gene expression.