Does transcription-replication interaction impact cellular metabolism?

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Abstract

Bacterial chromosome replication is one of the main drivers of gene expression throughout the cell cycle. In species like *Escherichia coli*, high growth rates induce a switch to mero-oligoploidy, where multiple active replication forks create a gene dosage gradient along the chromosome (multiplicity), from origin to terminus. Origin-proximal genes are present in higher copy numbers and may show increased expression, whereas terminus-proximal genes may be comparatively underrepresented. While the impact of DNA replication on gene expression is well-established, it remains unclear whether this effect also extends to other cellular processes, particularly cellular metabolism. Here, we integrate genomic position, multiplicity, and expression data into the *E. coli* genome-scale metabolic model to explore the role of the multiplicity-driven unbalanced expression of *ori*- vs. *ter*-proximal genes on the metabolic phenotype of the cell. We further formalize the theoretical concept that gene expression results from both regulatory control and gene copy number, and thereby try to quantify the relative contribution of multiplicity to overall expression and its metabolic impact. To experimentally support these predictions, we are currently implementing an integrated ^{13}C-based fluxomics/RNA-seq framework in *E. coli* grown under controlled glucose-limited conditions to induce distinct growth rates and, consequently, multiplicity profiles for a direct comparison/tuning of model predictions. Our work will reveal whether the effect of transcription-replication interactions, besides impacting gene expression, also propagate to the metabolic level or, rather, cells have evolved any mechanism to buffer it.