Non-optimal Microbial Response to Antibiotics Underlies Drug Interactions

Bacterial cells respond to antibiotic stress by regulating gene expression. Of particular importance for survival and growth is the expression level of ribosomal genes, which control the overall cellular translation rate. While ribosome synthesis is known to be optimally tuned in different nutrient conditions to maximize growth, much less is known about the optimality of regulation of ribosomal production under environmental stresses such as antibiotics. Recent observations have shown that inhibition of translation by small molecule drugs can relieve the inhibitory effect of antibiotics that target DNA synthesis, suggesting a higher than optimal expression of ribosomal genes under DNA stress. Here we test this hypothesis by measuring and manipulating gene expression under various antibiotic stresses. Using automated high time-resolution measurements of GFP transcription reporters to about 200 genes in Escherichia coli, we find that cells non-specifically down-regulate ribosomal gene expression with decreasing growth rate in response to antibiotics inhibiting DNA replication and up-regulate it in response to translation inhibitors. While down-regulated, protein synthesis under DNA stress is still high leading to large cells with increased protein content. The hallmark of non-optimality is the possibility for improvement; indeed, using strains in which ribosomal gene expression has been genetically manipulated, we show that decreased ribosomal expression actually increases survival and growth under DNA stress. Further, we find that genetically optimizing ribosomal expression completely removes the suppressive drug interaction between DNA and protein synthesis inhibitors, showing that these drug interactions result from non-optimal gene regulation. To rationalize these observations, we present a mathematical model of bacterial growth which shows how optimal growth rate-dependent regulation of ribosome synthesis can lead to (a) non-optimal regulation in the presence of antibiotics and (b) suppressive drug interactions. Our results highlight the importance of addressing the optimality of microbial stress responses for the design of drug combinations.