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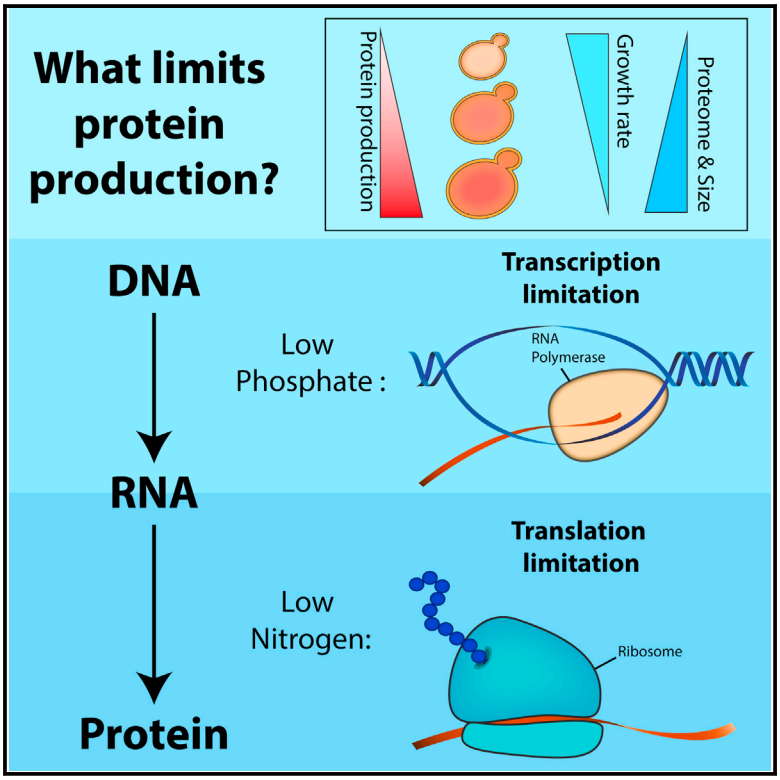
Cell Reports

The Cost of Protein Production

Graphical Abstract



Highlights

- Libraries expressing increasingly high protein amounts are extensively studied
- Processes that limit protein production vary, depending on growth conditions
- Ribosomes are not universally limiting in rapidly growing cells
- Cells adapt by increasing their size and the abundance of endogenous proteins

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In Brief

Kafri et al. investigate the processes that limit protein production. They find that enforcing either gene transcription or protein translation reduces growth rate, depending on growth conditions. Cells adapt by increasing their size and endogenous proteome content, suggesting that rapidly growing cells are not resource limited.

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The Cost of Protein Production

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SUMMARY

The economy of protein production is central to cell physiology, being intimately linked with cell division rate and cell size. Attempts to model cellular physiology are limited by the scarcity of experimental data defining the molecular processes limiting protein expression. Here, we distinguish the relative contribution of gene transcription and protein translation to the slower proliferation of budding yeast producing excess levels of unneeded proteins. In contrast to widely held assumptions, rapidly growing cells are not universally limited by ribosome content. Rather, transcription dominates cost under some conditions (e.g., low phosphate), translation in others (e.g., low nitrogen), and both in other conditions (e.g., rich media). Furthermore, cells adapted to enforced protein production by becoming larger and increasing their endogenous protein levels, suggesting limited competition for common resources. We propose that rapidly growing cells do not exhaust their resources to maximize growth but maintain sufficient reserves to accommodate changing requirements.

INTRODUCTION

Protein production in living cells is tightly coordinated with external conditions and intracellular demands. This regulation ensures that needed proteins are produced, while those whose function is not compatible with current needs are not. It may also serve to minimize the cost of protein production; indeed, making proteins consumes cellular resources by using energy and nutrients as building blocks and also by occupying common cellular machineries such as ribosomes, polymerases, or chaperones, whose abundance may be limiting. Defining the cost of protein production, and the molecular processes limiting this production, is a central challenge in cellular physiology, which is relevant in particular for understanding the interplays among cell growth, cell division, and cell size.

The cost of protein production is commonly attributed to protein translation (Andrews and Hegeman, 1976; Emilsson and Kurland, 1990; Kurland, 1992; Marr, 1991; Molin et al., 1974; Scott and Hwa, 2011; Scott et al., 2010; Vind et al., 1993). A major fraction of the cellular GTP pool is used for amino acid polymerization, while significantly lower quantities are invested in other processes including gene transcription and protein folding (Russell and Cook, 1995; Schimmel, 1993). Ribosomes were implicated as the major factor limiting growth of rapidly growing cells (Dennis et al., 2004; Emilsson and Kurland, 1990; Klumpp et al., 2013; Maaløe and Kjeldgaard, 1966; Marr, 1991; Russell and Cook, 1995; Scott et al., 2010, 2014; Vind et al., 1993), following the discovery that most of the cellular biosynthetic activity is devoted to making ribosomes (Bremer and Dennis, 1996) and the observation that ribosome content is tightly coordinated with cell growth rate (Bremer and Dennis, 1996; Schaechter et al., 1958; Warner, 1999). However, there is still a need for experimental data that directly map the molecular mechanisms limiting protein expression.

The cost of protein production was extensively studied in *E. coli*. Forced overexpression of the Lac operon in medium lacking lactose leads to reduced cell growth and arrested the cell cycle when reaching ~30% of total proteome (Dong et al., 1995; Horiuchi et al., 1962; Nguyen et al., 1989; Novick and Weiner, 1957; Scott et al., 2010). This reduced growth was broadly interpreted as the cost of protein production (Dong et al., 1995; Klumpp et al., 2013; Scott et al., 2010; Stoebel et al., 2008; Zamenhof and Eichhorn, 1967), although a recent study provided an alternative interpretation (Eames and Kortemme, 2012). Only limited data are available describing protein burden in eukaryotic cells (Hauf et al., 2000; Lang et al., 2009; MacLean, 2007), and it is not clear whether results inferred from one cell type, or from specific conditions, can be generalized to other organisms and environments.

In this paper, we examined the relative contributions of gene transcription and protein translation to the cost of protein production in budding yeast, *S. cerevisiae*, and mapped the limitation to the initiation versus elongation steps of each process. We found that transcription and translation can both be limiting, depending on the growth conditions. In particular, our data challenge the hypothesis that ribosome content is a universal limiting factor defining growth rate of rapidly growing cells, as only slow-growing cells appeared to be limited in ribosome content. Notably, endogenous protein expression was increased, rather than decreased, upon forced production of inert proteins, suggesting that the protein production capacity can readily adapt to increasing demands. We discuss the implications of our data for describing the interplay between protein production and cell growth.