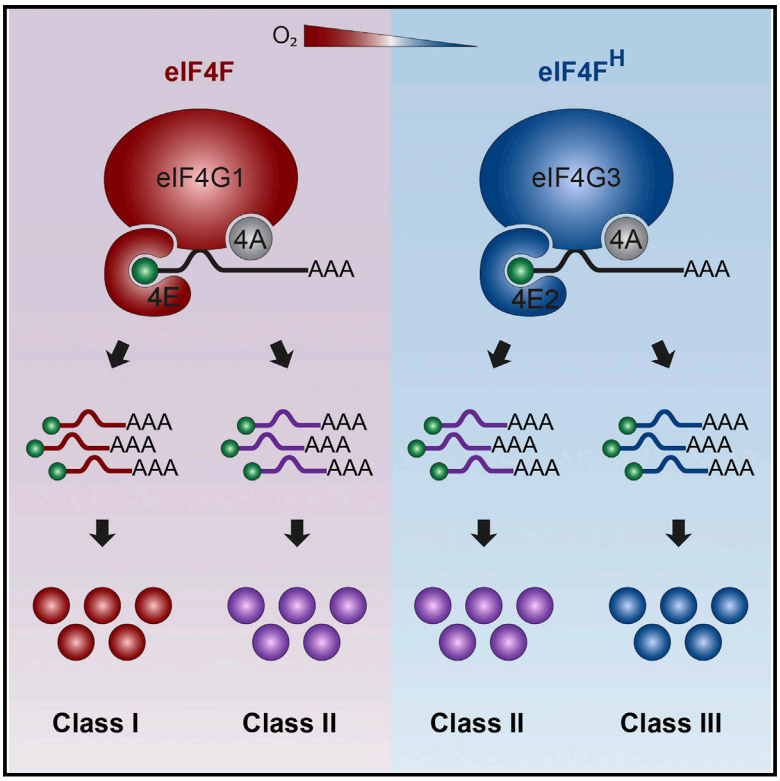
Report

Cell Reports

Systemic Reprogramming of Translation Efficiencies on Oxygen Stimulus

Graphical Abstract



Highlights

- O_2 stimulus reprograms protein output by altering mRNA translation efficiency
- eIF4F^H mediates hypoxic cap-dependent protein synthesis
- eIF4F and eIF4F^H triage mRNAs to generate O_2-responsive translatomes
- Hypoxia-inducible proteins are controlled by translation efficiency, not mRNA levels

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In Brief

Ho et al. show that cells rely on a switch in mRNA translation efficiency, and not mRNA levels, to alter protein output on O_2 stimulus. Two distinct cap-dependent protein synthesis machineries mediate this process: the normoxic eIF4F and the hypoxic eIF4F^H. The O_2-regulated eIF4F and eIF4F^H generate complex and adaptive translatomes.

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Systemic Reprogramming of Translation Efficiencies on Oxygen Stimulus

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SUMMARY

Protein concentrations evolve under greater evolutionary constraint than mRNA levels. Translation efficiency of mRNA represents the chief determinant of basal protein concentrations. This raises a fundamental question of how mRNA and protein levels are coordinated in dynamic systems responding to physiological stimuli. This report examines the contributions of mRNA abundance and translation efficiency to protein output in cells responding to oxygen stimulus. We show that changes in translation efficiencies, and not mRNA levels, represent the major mechanism governing cellular responses to [O_2] perturbations. Two distinct cap-dependent protein synthesis machineries select mRNAs for translation: the normoxic eIF4F and the hypoxic eIF4F^H. O_2-dependent remodeling of translation efficiencies enables cells to produce adaptive translatomes from preexisting mRNA pools. Differences in mRNA expression observed under different [O_2] are likely neutral, given that they occur during evolution. We propose that mRNAs contain translation efficiency determinants for their triage by the translation apparatus on [O_2] stimulus.

INTRODUCTION

It is assumed that steady-state mRNA levels represent an accurate proxy for protein expression. In most studies, the protein synthesis machinery is perceived as a passive participant in the regulation of gene expression that reflexively translates mRNA abundance into protein output. Recent studies have challenged this assumption by demonstrating a lack of correlation between protein and mRNA levels (Schwanhäusser et al., 2011; Tian et al., 2004; Vogel et al., 2010; Wang et al., 2013). These studies provide strong evidence that translation efficiency (T_e) is a superior predictor of steady-state protein levels compared to mRNA levels, mRNA stability, and protein stability (Schwanhäusser et al., 2011). Interestingly, a comparison of primates established that protein expression evolved under stronger constraints than mRNA levels, the latter being effectively neutral (Khan et al., 2013). These findings point to the evolution of complex regulatory processes of the translation apparatus to titrate protein output from highly divergent levels of cellular mRNAs. A biological role for alternative T_e was recently reported for the transcriptionally silent system of *Drosophila* oocyte-to-embryo transition (Kronja et al., 2014) and in stem cell differentiation (Lu et al., 2009). How mRNA and protein abundance are coordinated in dynamic systems responding to a stimulus remains a fundamental question (Vogel, 2013).

Perturbations in environmental [O_2] are observed in a wide array of physiological and pathological conditions including development, cardiovascular disease and cancer (Ratcliffe, 2013; Semenza, 2014). Cells exposed to hypoxia (i.e., low [O_2]) activate a robust transcription program by the hypoxia-inducible factor (HIF) (Wang et al., 1995). HIF promotes the synthesis of key mRNAs that encode proteins involved in cellular O_2 homeostasis. Hypoxia also elicits a fundamental reorganization of the cellular translation apparatus. In normoxia, the eIF4F complex typically initiates protein synthesis (Sonenberg and Hinnebusch, 2009). The cap-binding eIF4E, the RNA helicase eIF4A, and the scaffold eIF4G constitute the three major components of eIF4F