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Translation Factors Specify Cellular Metabolic State

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In this issue of *Cell Reports*, Shah et al. present evidence that a subcomplex of the eIF3 translation initiation factor regulates translation of mRNAs encoding components of the mitochondrial electron transport chain and glycolytic enzymes, thus linking translational control with energy metabolism.

Translation initiation in eukaryotic cells requires ribosomal subunits and a number of ancillary proteins called eukaryotic initiation factors (eIFs). There are at least nine eIFs that are composed of between 1 and 13 polypeptides (Jackson et al., 2010). Although these elements are involved in the translation of every mRNA, evidence is accumulating that some ribosomal proteins (Xue and Barna, 2012) and eIFs, such as eIF3 (Choudhuri et al., 2013; Lee et al., 2015), regulate the translation of specific mRNA subsets. The gene-specific roles of ribosomal proteins and translation factors are not well understood.

eIF3 functions as a scaffold required for multiple processes of translation initiation. eIF3 individual subunits are over- or under-expressed in many cancers, and these changes in expression may affect tumor progression (Hershey, 2015). Moreover, deletion of certain subunits causes developmental defects in zebra fish (Choudhuri et al., 2010). However, how eIF3 malfunction is linked to oncogenic or developmental phenotypes is not understood. Although only 6 of the 13 eIF3 mammalian subunits are conserved in *Saccharomyces cerevisiae*, the fission yeast *Schizosaccharomyces pombe* contains ten subunits that form two distinct complexes, making *S. pombe* an excellent system for investigating the function of non-core subunits of eIF3.

In this issue of *Cell Reports*, Shah et al. (2016) find that *S. pombe* cells lacking the non-essential *eif3e* gene (or its partner, *eif3d*) have general defects in translation initiation. To identify mRNAs whose translation is affected in the mutants, the authors performed mass spectrometry analyses of the 80S ribosome-associated proteome, assuming it would be enriched in newly synthesized proteins. This analysis revealed decreased abundance of mitochondrial respiration complex subunits as well as increases in the levels of proteins involved in glycolysis, alcohol fermentation, and the tricarboxylic acid cycle. Transcriptomic experiments confirmed that changes in protein expression between wild-type and mutant cells were not correlated with altered mRNA levels. Finally, these results were confirmed by pulse-SILAC and direct measurement of synthesis rates of a subset of 80S-associated proteins.

The proteomic analysis pointed to a role of eIF3e in the regulation of metabolism. Indeed, a comprehensive metabolomic approach revealed that *eif3e*-deleted cells have reduced rates of mitochondrial oxygen consumption and show enhanced glucose uptake, suggesting a switch from respiration to glycolysis. These effects were physiologically relevant, given that *eif3e*-deleted cells were unable to grow at low glucose concentrations or use a non-fermentable carbon source. These cells also showed endogenous oxidative stress and premature aging. The authors also found that eIF3e protein levels were elevated under conditions that induce respiration. Thus, eIF3e appears to be essential for regulating the balance between respiration and glycolysis.

Is this regulatory function conserved in higher eukaryotes? eIF3e is present in humans and *S. pombe* (although it is absent in *S. cerevisiae*). Shah et al. (2016) found that eIF3e knockdown on two human cell lines caused a reduction in the protein levels (but not mRNA) of two components of the mitochondrial respiratory chain. A reporter system containing the 5′ UTR of these genes showed a similar behavior, strongly suggesting that eIF3e regulates the expression of these genes by modulating their translational efficiency. Consistently, eIF3e coimmunoprecipitated with mRNAs encoding components of the mitochondrial respiratory chain.

The observation that initiation factors regulate the translation of particular mRNA sets poses a number of mechanistic and physiological questions:

First, which are the mRNAs regulated by eIF3, and how are they recognized? Zhou et al. (2005) pioneered the identification of mRNA subsets associated with eIF3 subunits by performing ribonucleoprotein immunoprecipitation analyzed with DNA chip (RIP-chip) experiments with eIF3e and eiF3m, believed to form part of two separate eIF3 complexes. mRNAs associated with eIF3e overlap with those translationally regulated by the complex, suggesting that the regulation is direct. More recently, two studies used photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) to systematically identify mRNAs directly associated with eIF3 (Lee et al., 2015; Meyer et al., 2015). The majority of eIF3 binding sites were located in 5′ UTRs, including some on mRNAs encoding key regulators of cell proliferation. Interestingly, Meyer et al. (2015) found that eIF3 can be recruited to m6-A-modified mRNA, although how the specificity of the binding is achieved is unclear. Approaches such

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as RIP sequencing and CLIP will allow the identification of the targets of different eIF3 subcomplexes—physiological or abnormal—and shed light on how eIF3 misregulation contributes to cancer.

Second, how do eIFs affect the translation of discrete mRNA sets? Inactivation of *eif3ha* in zebrafish caused decreased translation of ~300 mRNAs (as measured by polysome profiling) (Choudhuri et al., 2013). A key observation of the proteome-wide study of Shah et al. (2016) is that eIF3e can both upregulate and downregulate translation. A similar result has been reported in animal cells (Lee et al., 2015), although it was limited to two transcripts. Future systematic studies employing the kind of proteomic approaches used by Shah et al. (2016) or those measuring translation with ribosome profiling will be required to determine the involvement of eIF3 subunits in mRNA-specific regulation.

How does eIF3 malfunction relate to cancer? The data from Shah et al. (2016) suggest that this connection may arise through global control of energy metabolism via eIF3e. Given that *eif3e* is downregulated in some cancers (Hershey, 2015), these cells may shift to a metabolic state that promotes proliferation. Meyer et al. (2015) identified *c-JUN* as a target of eIF3-mediated translational regulation, suggesting that direct control of cell proliferation may also underlie eIF3 role in cancer. In this respect, a fundamental question is whether there are multiple eIF3 subcomplexes in animals, as is the case in *S. pombe*, and whether these subcomplexes bind to and regulate different mRNA sets. Detailed analysis of eIF3 complex formation indicates that differences in subunit expression levels can lead to the formation of stable complexes of abnormal composition (Smith et al., 2016). If different complexes bind to different mRNA targets (and selectively activate or repress them), then eIF3 heterogeneity would explain the specific phenotypes associated with over- and under-expression of its subunits.

This integrative study by Shah et al. (2016) makes an important contribution to understanding how "core" components of the translational machinery perform gene-specific regulatory functions and how this regulation is coupled to cellular phenotypes.

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