Distinctive tRNA Repertoires in Proliferating versus Differentiating Cells

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http://dx.doi.org/10.1016/j.cell.2014.08.031

Transfer RNAs (tRNAs) deliver amino acids to the ribosome during mRNA translation. Gingold et al. now provide evidence that alterations in the cellular tRNA repertoire are tightly coordinated with changes in mRNA expression. These changes in the tRNA repertoire dictate translational programs that distinguish differentiating from proliferating cells.

Information encrypted in the messenger RNA (mRNA) codons is deciphered by the anticodons present in transfer RNAs (tRNAs). Individual tRNA levels and kinetics of anticodon-codon pairing determine translation rates of synonymous codons (that is, codons encoding the same amino acid) (Novoa and Ribas de Pouplana, 2012). In this issue of *Cell*, Gingold et al. (2014) now provide evidence that the changes in tRNA composition are a part of a deeper program of translational regulation. They show that tRNA expression profiles vary depending on the differentiation or proliferation status of the cells and are coordinated with the changes in mRNAs expression (Figure 1).

Gene expression changes underpin pivotal physiological processes such as proliferation, differentiation, and apoptosis, whereas aberrant regulation of gene expression engenders diseases, including cancer. mRNA translation plays a major role in the regulation of gene expression, being positively correlated with proliferation and dysregulated in cancer (Silvera et al., 2010). Although translational efficacy is determined in part by the tRNA repertoire, little is known of how changes in tRNA levels affect cellular functions. Comparisons of tRNA composition in breast cancer versus nontransformed tissue have revealed that cancer cells not only overexpress tRNAs but also perturb expression of isoacceptor tRNAs (tRNAs with different anticodons that carry the same amino acid) to optimize codon usage of tumor-promoting, but not lineage-specific or house-keeping genes (Pavon-Eternod et al., 2009). These findings suggest that cancers adjust their tRNA pools to selectively bolster translation of mRNAs that are required for tumor progression.

Gingold et al. (2014) catalog the tRNA composition and determine transcriptional activity of corresponding tRNA genes in normal and cancer specimens. They discover that the composition of tRNA pools in proliferating cells is diametrically opposite to those of differentiated and arrested cells. tRNAs that are upregulated in differentiated/arrested cells are repressed in proliferating cells. Conversely, tRNAs whose levels are high in proliferating cells are low in differentiated/arrested cells. Changes in the transcription of tRNA genes parallel the behavior of tRNA pools, inasmuch as the composition of promoter elements of tRNA genes expressed highly in differentiated versus cancer cells and histone modifications in their vicinity are dramatically different. It is possible that these epigenetic modifications and differences in promoter elements are responsible for the selective recruitment of RNA polymerase III to the tRNA genes in differentiating versus proliferating cells.

tRNA pools are highly concordant within the same cancer type, whereas similarities in tRNA repertoires to a lesser degree are also observed across different malignancies. Matching alterations in tRNA pools of proliferating cells are observed irrespective of whether samples are obtained from cancers or normal tissues. Initiator methionine tRNA is overexpressed in proliferating cells but repressed in arrested/differentiated cells. In turn, selenocysteine tRNA is downregulated in proliferating and cancer cells. This is consistent with previous observations that forced expression of initiator methionine tRNA promotes proliferation and growth (Pavon-Eternod et al., 2013), whereas selenocysteine-containing proteins exhibit antineoplastic activity (Hatfield et al., 2014). Although future studies are required to establish whether changes in tRNA levels are the cause or a consequence of cell fate decisions, yeast adapts to deletion of individual tRNA genes via mutations in the anticodons of remaining tRNA genes to meet translational demands (Yona et al., 2013). This suggests that variations in tRNA pools act as a driving force in inducing alterations in the proteome required for proliferation and differentiation.

Coordinated expression of functionally related genes is achieved via orchestration of various steps of the gene expression pathway. Using gene ontology analysis that groups functionally related genes, Gingold et al. (2014) show that alterations in the tRNA repertoire of proliferating and differentiated cells correspond to codon usage predilections of proliferation- and differentiation-regulating genes. Thus, the alterations in tRNA levels are coordinated with the changes in the transcriptome to

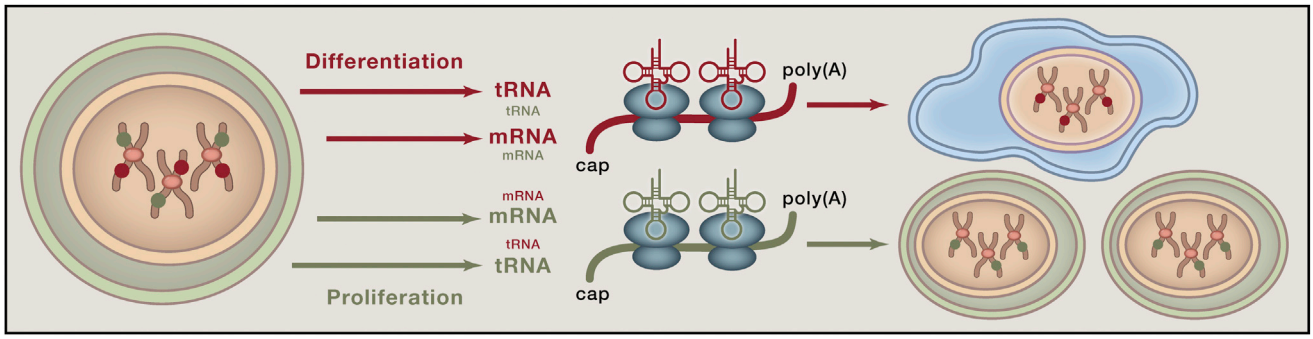

Figure 1. Transfer RNA Pools Are Coordinated with the Alterations in the Transcriptome

Optimal differentiation (red) and proliferation (green) require distinct changes in the transcriptome. The repertoire of tRNAs in differentiating cells (red) is opposite to that observed in proliferating cells (green). This appears to be a consequence of changes in transcription of tRNA genes caused by specific epigenetic modifications (red and green circles). During differentiation, tRNAs that increase in the abundance (red) harbor anticodons that are optimal for translation of codons found in differentiation-promoting mRNAs (red), whereas tRNAs that are elevated during proliferation (green) are tuned for the optimal codon usage of proliferation-promoting mRNAs (green).

optimize codon usage of genes that are being expressed. In addition to humans, discrepancy of codon usage of "proliferation" versus "differentiation" genes is observed in other vertebrates (e.g., mice and chicken) and flies. In stark contrast, in *C. elegans* codon usage correlates with translation efficacy of the mRNAs irrespective of the function of their encoded proteins. Thus, it appears that gene function is a major factor that underlies translational selection in vertebrates and insects, but not worms, which is likely a consequence of distinct mechanisms that underlie cell fate acquisition in different species. Although the effects of fluctuations in tRNA pools on translation of individual mRNAs will require biochemical characterization, these results suggest a model whereby the changes in tRNA repertoire are orchestrated with transcriptional programs to enable timely expression of functionally related genes. Moreover, these findings suggest that changes in tRNA pools decrease translation efficacy of genes whose untimely expression would be deleterious, therefore constituting a hitherto unappreciated quality control mechanism of gene expression.

Factors that coordinate the alterations in tRNA and mRNA repertoire remain to be identified. Significant differences in histone modifications in the vicinity of tRNA genes, between proliferating versus differentiated cells, raise the intriguing possibility that the same epigenetic regulators that are responsible for changes in tRNA pools may dictate transcription of proliferation- and differentiation-promoting genes. The transcription factor Myc may play such a role as it modulates tRNAs levels and expression of proliferation- and differentiation-regulating genes (Silvera et al., 2010). It is also not clear how the changes in mRNA and tRNA levels are coordinated with the rate-limiting translation initiation step (Sonenberg and Hinnebusch, 2009). The target of rapamycin (TOR) is an evolutionarily conserved kinase that preferentially bolsters translation of mRNAs encoding proliferation-promoting proteins in response to various stimuli, including nutrients, mitogens and growth factors, chiefly by increasing their translation initiation rates (Roux and Topisirovic, 2012). TOR controls tRNA and ribosome biogenesis, in addition to proliferation and differentiation, and is dysregulated in cancer (Roux and Topisirovic, 2012). Therefore, TOR is likely to play a critical role in the coordination of the levels of tRNA pools, mRNAs, and translational activity. Indeed, TOR stimulates tissue and organismal growth by increasing transcription of tRNA genes in flies (Marshall et al., 2012). In conclusion, by unraveling a tRNA-centered mechanism for achieving optimal expression of functionally related genes, Gingold et al. (2014) provide a starting point for deciphering cellular networks that govern this process.

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