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BALANCED PRODUCTION OF RIBOSOMAL PROTEINS

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Abstract

Eukaryotic ribosomes contain one molecule each of 79 different proteins. The genes encoding these proteins are usually at widely scattered loci and have distinctive promoters with certain common features. This minireview discusses the means by which cells manage to balance the production of ribosomal proteins so as to end up with equimolar quantities in the ribosome. Regulation at all levels of gene expression, from transcription to protein turnover, is considered.

Keywords

ribosomal proteins; eukaryotic ribosomes; equimolarity; Haploinsufficiencies

Ribosomes are vital organelles that catalyze protein synthesis in all living organisms. In eukaryotes, the ribosomes are composed of four RNA molecules and one molecule each of 79 different proteins. In vertebrates, the genes encoding the ribosomal proteins (RP genes) are at widely scattered loci and have distinctive promoters with certain common features (Perry, 2005). A similar situation occurs in yeast (Zhao et al., 2006).

An important issue, which has yet to be fully resolved, concerns the means by which cells manage to balance RP production so as to end up with equimolar quantities in the ribosome. Since a large proportion of a cell's energy is expended in ribosome production (Warner, 1999), one might expect RP synthesis to be tightly regulated at various levels of gene expression.

Transcription of the RP genes, processing of the transcripts, and mRNA turnover usually result in similar, but not identical, amounts of the different RP-mRNAs. In the yeast *Sacchromyces cerevisiae*, where there are one or two copies of each RP gene, a difference in RP-mRNA abundance of up to five-fold in exponentially growing cultures has been reported, although most RP-mRNAs are within a two-fold range (Holstege et al., 1998). In these cells, transcription of the RP genes is continually required owing to the relatively short half-life of the RP-mRNAs (Warner, 1999). In mammalian cells, where there is a single expressed copy of each RP gene, the RP-mRNA abundance values are also narrowly distributed with some notable exceptions that are apparently cell-type specific (Bortoluzzi et al., 2001; Angelastro et al., 2002; Ishii, 2006). Although there is some uncertainty about the accuracy of

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abundance measurements when comparing one mRNA species to another (Quackenbush, 2006), it seems reasonable to conclude that the structure of various RP genes has evolved so as to keep variations in mRNA abundance within a fairly narrow range.

In *Drosophila* and mammals, there is evidence that for some RPs, a decrease in mRNA abundance by a factor of two, as occurs in either naturally occurring or experimentally produced haploinsufficiencies, leads to a ribosome deficit with a consequential decrease in the capacity for protein synthesis (Saeboe-Larssen et al., 1998; Oliver et al., 2004; Gazda and Sieff, 2006; Panic et al., 2006; Choesmel et al., 2007) and references cited therein}. Such deficits are associated with a growth-restricted phenotype, termed minute in *Drosophila,* and with abnormalities in certain cell lineages in mammals. An analysis of the diverse effects of these haploinsufficiencies has led to the idea that there is a threshold value in mRNA abundance, which varies among the different RPs and in different cell types (Enerly et al., 2003). The variation among different RPs may reflect their relative importance for the maturation and assembly of the ribosome or possible involvements in nonribosomal functions. In Zebrafish, haploinsufficiency of some, but not all, RP genes leads to tumorigenesis by an as yet unknown mechanism (Amsterdam et al., 2004). Haploinsufficiency of RP genes has also been observed in yeast (Deutschbauer et al., 2005). In this study, different sensitivities to the diminution of particular RP-mRNAs were also indicated by variable reductions in growth rate when either one of the duplicated or nonduplicated RP genes was deleted.

Are differences in RP-mRNA abundance compensated for by reciprocal differences in translation efficiency? In vertebrate cells, the RP-mRNAs are relatively stable and the overall regulation of RP synthesis is primarily at the level of translation. The 5′ terminal oligopyrimidine (TOP) sequence, which is a ubiquitous feature of all vertebrate RP-mRNAs, is required for modulating the efficiency of their translation (Meyuhas, 2000). The translation efficiency in vivo of a particular RP-mRNA can be estimated from two parameters: the proportion of the mRNA that is engaged with ribosomes (ribosome occupancy) and the spacing of ribosomes on a translating mRNA (ribosome density). Measurements of these parameters in cultured mammalian cells have been made for six RP-mRNAs (Meyuhas et al., 1987). These measurements revealed an interesting behavior, typified by a bimodal distribution of RP-mRNAs superimposed on polyribosome profiles, with a ribosome occupancy of only 59 to 76% under ideal growth conditions and a near maximum ribosome density of the translated fraction (about 33 codons per ribosome). Similar bimodal distributions of RP-mRNA were also observed in *Xenopus* embryos (Amaldi and Pierandrei-Amaldi, 1990) and growing mouse myoblasts (Agrawal and Bowman, 1987). Although no large difference in translation efficiency was observed in the limited study of six RP-mRNAs, it would be interesting to evaluate these parameters for RP-mRNAs that are believed to differ significantly in abundance.

Experiments with *S. cerevisiae* have attempted to estimate the translation status of various mRNAs in a genome-wide analysis using the two parameters described above (Arava et al., 2003). A comparison of RP-mRNAs previously reported to differ by four- to five-fold in abundance (Holstege et al., 1998) did not appear to have any significant differences in translation rates. Despite a caveat about the uncertain accuracy of these measurements

(Arava et al., 2003), they would tend to argue against compensatory effects at the level of translation.

The use of feedback mechanisms to regulate RP-mRNA translation, which are a mainstay in prokaryotes, are apparently not operative in eukaryotes, although a few feedback mechanisms at the levels of processing and turnover of RP-mRNA have been described in both yeast and vertebrates (Dabeva et al., 1986; Presutti et al., 1995; Tasheva and Roufa, 1995; Fewell and Woolford, 1999; Badis et al., 2004).

The turnover of RPs that are not assembled into ribosomes is the final level at which stoichiometry can be achieved, but, of course, this represents a mechanism of last resort because it is energetically wasteful for the cell. Evidence for efficient degradation of unassembled RPs has been found in both yeast and mammalian cells when excess proteins are produced by amplification of particular RP genes (Agrawal and Bowman, 1987; Maicas et al., 1988) or when ribosomal RNA synthesis is inhibited (Craig and Perry, 1971; Craig, 1971; Warner, 1977).

In summary, ribosome biogenesis is a highly resources-consuming process and therefore requires tight regulation and balanced synthesis of all of its constituents. Despite this demand, some RP mRNAs seem to escape from this tight regulation and accumulate in excess. For those RP-mRNAs whose abundance is above the optimal threshold that satisfies the growth requirements of the cell, there is as yet no compelling evidence for a compensatory diminution in translation efficiency. The excess proteins encoded by these mRNAs may be used for other purposes (Wool, 1996; Schroder and Moore, 2005; Komili and Roth, 2007) or simply turned over by normal degradation mechanisms. There is evidence that certain unassembled RPs can signal cells to enter the apoptosis pathway by directly binding to MDM2 and consequently stabilizing p53 (Rudra and Warner, 2004).

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