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Quality over quantity: optimizing co-translational protein folding with non-‘optimal’ synonymous codons

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Protein folding occurs on a time scale similar to peptide bond formation by the ribosome, which has long sparked speculation that altering translation rate could alter the folding mechanism or even the final folded structure of a protein *in vivo*. Recent results have provided strong support for this model: synonymous substitutions to codons with different usage frequency, which are often translated at different rates, have been shown to significantly alter the co-translational folding mechanism of some proteins, leading to altered cell function. Here we review recent progress towards understanding the connections between synonymous codon usage, translation rate and co-translational protein folding mechanisms.

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Introduction

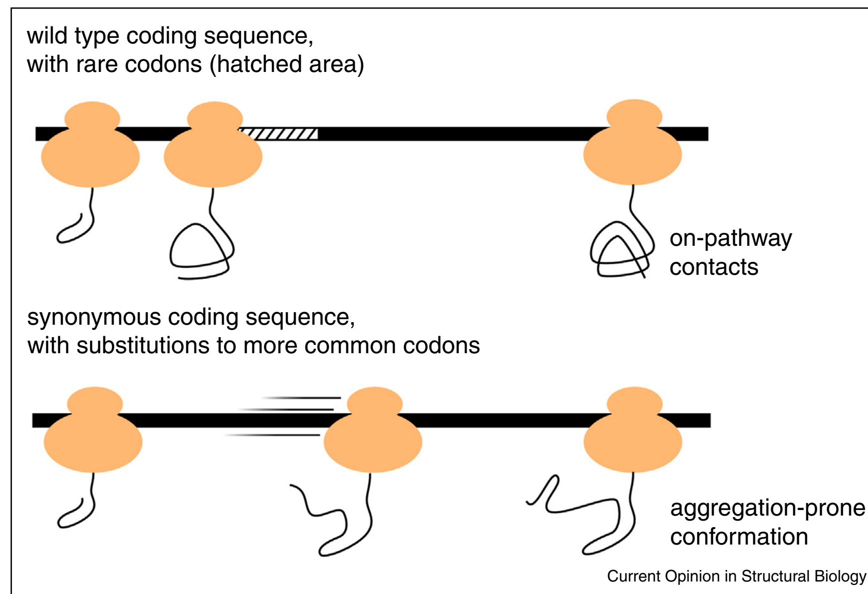
Most amino acids are encoded by more than one codon. However, these synonymous codons are not used with equal frequency. In general, common codons are translated by the ribosome more quickly than their synonymous rare counterparts. For this reason, synonymous common codons were historically considered ‘optimal’ for gene expression, as faster translation will facilitate rapid accumulation of a protein in the cell. Consistent with this hypothesis, many highly expressed genes are enriched in common codons [1]. For genes encoding less abundant proteins, synonymous codon usage was presumed to be essentially ‘silent’, representing an evolutionarily neutral mutation of one synonymous codon for another. Indeed, the presumption that synonymous mutations represent merely genomic ‘background noise’ is the basis of the widely used dN/dS calculation (the ratio of non-synonymous vs synonymous substitutions in a coding sequence; also referred to as Ka/Ks) for functional selection [2].

However, the longstanding focus of the effects of synonymous codon usage on protein *level* disregards another effect, on protein *folding*. Recent results have now provided irrefutable evidence that synonymous codon usage is non-random, and that synonymous substitutions can significantly perturb the folding efficiency of the encoded protein, in some cases leading to adverse effects on cell function (Figure 1). Clearly, for codons in these coding sequences, ‘common’ and ‘optimal’ cannot be used interchangeably [3]. These results are shifting attention to the specific effects on co-translational protein folding that can be achieved by modulating local translation rate. Questions include: What codon usage is ‘optimal’ for each gene? Can codon usage affect the folding mechanism and/or native topology of the encoded protein? If so, how? More broadly, of the enormous numbers of rare codons found in naturally occurring coding sequences, which ones are most likely to impact co-translational folding or another aspect of protein production, *versus* have no effect (be truly ‘silent’)? Below we discuss the effects of synonymous codon substitutions on translation rate, several recent exciting studies reporting the effects of synonymous codon substitutions on the co-translational folding of specific proteins, and highlight other mechanisms available to modulate the local rate of protein synthesis *in vivo*.

Ribosome structure and the logistics of co-translational protein folding

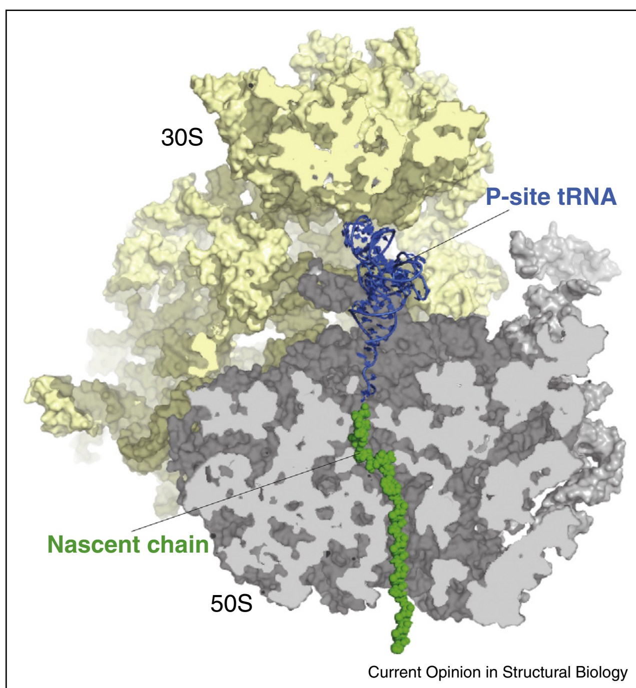
In the cell, every protein is synthesized from N-terminus to C-terminus by a ribosome. Peptide bond formation occurs deep within the ribosome, and the nascent polypeptide chain first passes through the ribosome exit tunnel (Figure 2) [4,5]. The narrowness and length of the exit tunnel ($\sim 20 \times 100$ Å) significantly constrains the most C-terminal residues of the nascent polypeptide chain to a small range of mostly extended or α-helical conformations [6,7]. The formation of bulky tertiary structure does not begin until the nascent chain is long enough to emerge from the exit tunnel (>35 aa), although there is evidence that the broader ‘vestibule’ near the end of the tunnel is wide enough to enable the nascent chain to fold back on itself to make some local tertiary structure contacts [8,9]. Synonymous codon substitutions near the 5′ end of a coding sequence are therefore unlikely to affect co-translational protein folding, as very little of the

Figure 1



Effects of local translation rate on co-translational folding of the nascent chain. When translation is slow due to synonymous rare codons (shown here; hatched area within black mRNA), the partially synthesized nascent chain can achieve an equilibrium or near-equilibrium conformation that may not be kinetically accessible when C-terminal portions of the nascent chain are translated more quickly via synonymous common codons. See Figure 3 for an energy landscape perspective of these processes.

Figure 2



Cross-section view of the *E. coli* ribosome (yellow and grey represent space-filling structures of the 30*S* and 50*S* ribosomal subunits, respectively). Shown are the position of the P-site tRNA (blue) and the path of the bound nascent chain (green, 36 aa polyalanine sequence) modeled through the exit tunnel to the ribosome surface.
Source: Image adapted from [4,5].

nascent chain has been translated and the portion that has been synthesized is constrained within the tunnel. Indeed, 5′ synonymous codon substitutions instead tend to alter protein abundance, due to altered translation initiation efficiency [10,11]. Synonymous substitutions farther within the coding sequence are more likely to affect co-translational folding mechanisms and are the focus of this article.

Synonymous codon calculations and effects on translation rate

The effect of a single synonymous codon substitution on absolute *in vivo* translation rate has proven difficult to measure directly, or predict accurately. In general, there is an inverse correlation between codon rarity and translation rate [12••,13], and codon usage frequencies have proven useful for predicting total translation time over an entire sequence [1]. However, there are clearly additional factors (including nutrient levels and codon context [14–16,17••]) that affect the rate of translation of a single specific codon, although the relative importance and interplay between these factors is still poorly understood. For these reasons, codon usage frequency is less predictive of translation rate for an individual codon or short region than for an entire coding sequence. Nevertheless, the current paucity of absolute translation rate measurements and incomplete understanding of the specific mechanisms that regulate local translation rate has lead to the widespread use of codon usage frequency as a very convenient (albeit limited) proxy for local translation rate.

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