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A New Start for Protein Synthesis

Thomas E. Dever

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Similar trajectories for the development of grinding technologies are known from the Levant as well. Thus, technological change should not be conceived of as the consequence of one-off innovations, but rather as a long-term process that involves not only technological improvements but also the adaptation and change of economic habits and negotiations over cultural norms.

It is possible that pottery and other early technologies were invented independently in different places. However, the fact that early pottery is widely distributed in East Asia among different societies in many different environments, but not found among preagricultural societies elsewhere, suggests that it spread in East Asia through intersocietal interactions, perhaps along with other ideas and technologies.

Research endeavors such as those led by Wu *et al*. are fundamental for a better understanding of socioeconomic change during the LGM and the developments that led to the emergence of sedentary agricultural societies. However, anthropological perspectives on the context of pottery invention should help to broaden scientific attention from discovery and dating to the functions of early pottery and its social context. Research of this kind could elucidate the development of human societies in East Asia, as well as opening up new perspectives on the evolution of human societies and the origins of social complexity in general. More general issues awaiting serious consideration include, for example, whether the fact that in East Asia pottery predates agriculture by some 10 millennia, whereas in the Levant it postdates the transition to agriculture, signifies a fundamental difference in the socioeconomic development of the two regions.

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MOLECULAR BIOLOGY

A New Start for Protein Synthesis

Protein synthesis that does not initiate with methionine is used by the mammalian immune system to process antigen.

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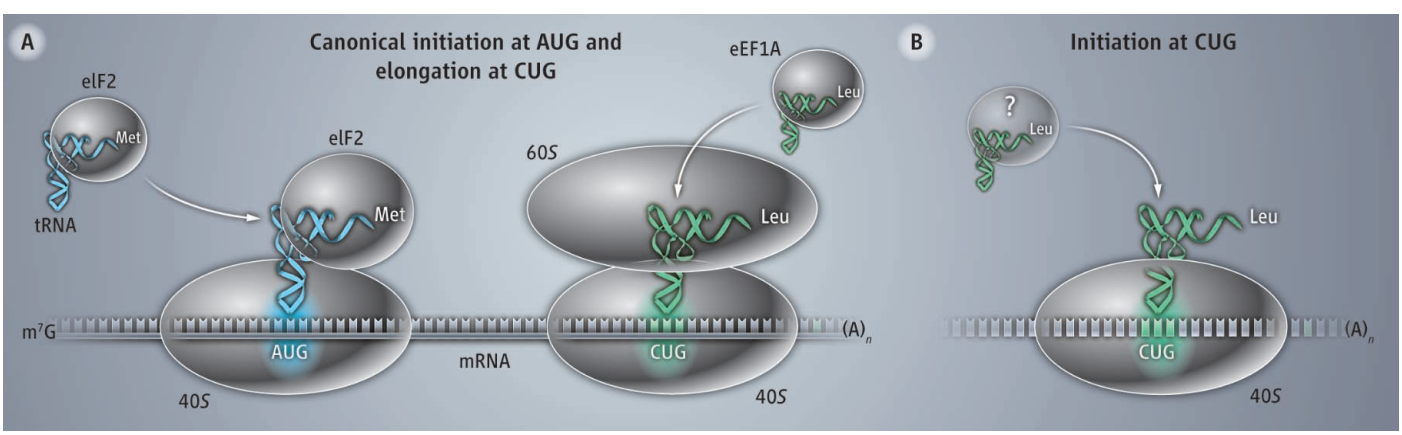
Recent technical advances have led to the accumulation of vast amounts of DNA sequences, highlighting the importance of understanding how the information in DNA is translated into amino acids and proteins. To decipher this information, the cell first transcribes a "coding" segment of DNA into messenger RNA (mRNA). Next, the ribosome decodes the mRNA in blocks of three consecutive nucleotides, or codons, that each specify an amino acid. But, how does the ribosome know where to start reading on the mRNA? To ensure faithful translation, and thereby yield a functional protein, cells restrict translation initiation to AUG codons that specify the amino acid methionine (Met). In mammals and other eukaryotic cells, translation typically initiates at the AUG codon closest to the beginning of the mRNA. But on page 1719 of this issue, Starck *et al*. (*1*) show that in addition to the canonical AUG-methionine initiation pathway, CUG-leucine can also be used to initiate protein synthesis.

When decoding an mRNA, ribosomes rely on transfer RNA (tRNA) molecules, each of which is covalently attached to a specific amino acid at one end, while three nucleotides in the so-called anticodon loop at the other end pairs with a codon on the mRNA. Cells express two types of methionyl-tRNA: elongator $tRNA_e^{Met}$ decodes AUG codons within reading frames, whereas initiator $tRNA_i^{Met}$ is used exclusively to initiate translation. The eukaryotic translation ini-



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How to begin? In the canonical initiation pathway (**A**), eIF2 delivers Met-$tRNA_i^{Met}$ to the ribosome. Base-pairing between $tRNA_i^{Met}$ and the mRNA directs protein synthesis to start at an AUG codon. During translation elongation, the translation elongation factor eEF1A delivers Leu-$tRNA^{Leu}$-CAG to decode CUG codons. Starck *et al*. show (**B**) that Leu-$tRNA^{Leu}$-CAG can also direct protein synthesis to start at a CUG codon.

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tiation factor 2 (eIF2) binds Met-tRNA$_i^{Met}$ to the small (40*S*) ribosome in the first step of translation initiation (*2*) (see the figure). This complex then binds near the 5′ end of an mRNA and scans the mRNA sequence to identify a start site. Base-pairing interactions between the anticodon loop of the Met-tRNA$_i^{Met}$ bound to the ribosome and an AUG codon in the mRNA cause the ribosome to stop scanning and set the reading frame for protein synthesis (*3*). Typically the ribosome initiates protein synthesis at the AUG codon closest to the 5′ end of the mRNA, though context nucleotides flanking the start codon can influence the efficiency of translation initiation (*4*).

Exceptions to the rules limiting translation initiation to an AUG codon and to methionine have been reported. Naturally occurring non-AUG start codons have been reported for some cellular mRNAs (*5*); and seven out of the nine possible single-nucleotide substitutions at the AUG start codon of dihydrofolate reductase were functional as translation start sites in mammalian cells (*6*). In all of the cases in which it was examined, the amino-terminal residue of these proteins was methionine (*6*), suggesting that translation initiation relied on mis-pairing between the anticodon of Met-tRNA$_i^{Met}$ and the non-AUG start codon in the mRNA. In an alternate approach, proteins beginning with valine or glutamine were synthesized by expressing anticodon mutants of initiator tRNA$_i^{Met}$ that were mis-acylated in vivo (*7*). Notably, in both of these studies, translation initiation depended on tRNA$_i^{Met}$. Starck *et al*. reveal that in addition to the canonical Met-tRNA$_i^{Met}$ and AUG codon pathway, mammalian cells can initiate translation with leucine using a specific leucyl-tRNA that decodes the codon CUG.

Immune surveillance in vertebrates depends on the presentation of endogenously synthesized peptides on the cell surface by the major histocompatibility complex (MHC) (*8*). These peptides are encoded in conventional open reading frames, but also in alternate reading frames, in mRNA sequences 5′ or 3′ to the main protein coding reading frame, and in reading frames lacking an AUG start codon (*9*). CUG codons initiating these cryptic open reading frames can be decoded as leucine (*10*), and other Leu codons (CUC, CUA, UUG) cannot substitute (*11*). Moreover, the synthesis of these leucine-initiated peptides is enhanced under conditions that cause phosphorylation and inactivation of eIF2. These results indicate a mechanism of translation initiation for these cryptic antigenic peptides that relies neither on eIF2 nor on tRNA$_i^{Met}$. Starck *et al*. demonstrate that tRNA^{Leu} with the anticodon CAG (Leu-tRNA^{Leu}-CAG) participates in translation initiation at CUG start codons (tRNA base pairs with mRNA in antiparallel format with the C of the tRNA anticodon pairing with the G of the codon). The authors found that ribosomal initiation complexes assembled in vitro on mRNAs with an AUG start codon primarily contain tRNA$_i^{Met}$, whereas initiation complexes assembled on mRNAs with a CUG start codon contained both tRNA$_i^{Met}$ and tRNA^{Leu}-CAG. Further, mutating the anticodon of tRNA^{Leu}-CAG to CUA enabled translation of antigenic peptides in antigen-presenting cells to initiate in vivo at a UAG codon that normally functions as a termination codon.

The findings of Starck *et al*. raise interesting questions. How is Leu-tRNA^{Leu}-CAG delivered to the initiating ribosome? Does initiation at a CUG codon rely on any of the initiation factors that function in the AUG initiation pathway? Although the authors found that inhibiting expression of the factor eIF2A impaired initiation by Leu-tRNA^{Leu}-CAG, the involvement of other initiation factors in this pathway is not known. Perhaps there is something special about tRNA^{Leu}-CAG that enables it to initiate translation, or maybe other tRNAs also function in noncanonical initiation pathways. Does the Leu-tRNA^{Leu}-CAG initiation pathway contribute to the synthesis of cellular proteins other than antigenic peptides? Ribosomal profiling studies of mammalian cells have identified widespread use of CUG and other non-AUG initiation sites (*12*). Starck *et al*. demonstrated association of Leu-tRNA^{Leu}-CAG with initiation complexes assembled at the CUG start codon of the *Myc* oncogene, and a CUG start codon of human trypsinogen 4 is decoded as leucine (*13*). These results suggest that the Leu-tRNA^{Leu}-CAG initiation pathway may play an important role in cellular protein synthesis, and it will be interesting to learn how cells maintain the fidelity of protein synthesis in the face of this alternate initiation pathway.

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PALEONTOLOGY

Old and Groovy

Mary L. Droser[1] and James G. Gehling[2]

The discovery of furrowed and backfilled trace fossils, claimed to be at least 585 million years old, raises questions about their origins.

Since Darwin's time, paleontologists and biologists have searched for evidence for the first bilaterian animals, which have a front and a back end as well as an upper and a lower side. Bilateral symmetry alone does not define this group, and confident interpretation of fossil embryos has proven difficult. On the other hand, evidence of sediment furrowing over extended distances has been widely accepted as evidence of bilaterian life: Flatworms may glide along a surface (*1*) and deep-sea protists can produce short furrowed surface traces (*2*), but making a long furrowed trace fossil with evidence of backfill requires a bilaterian body plan. On page 1693 of this issue, Pecoits *et al*. (*3*) describe furrowed, backfilled trace fossils dated to over 585 million years, which they interpret as the oldest bilaterian trace fossils and thus the oldest evidence of bilaterians.

Before this report, the oldest widely accepted evidence of bilaterians comes from simple furrow trace fossils of millimeter-scale width dated to 558 million years ago (*4*); similar trace fossils are known from several locations worldwide dated to ~560 to 542 million years ago, at the end of the Ediacaran period. They occur in rock units that preserve elements of the macroscopic soft-bodied animal fossil assemblages called the Ediacaran biota; however, trace fossils are found at far

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