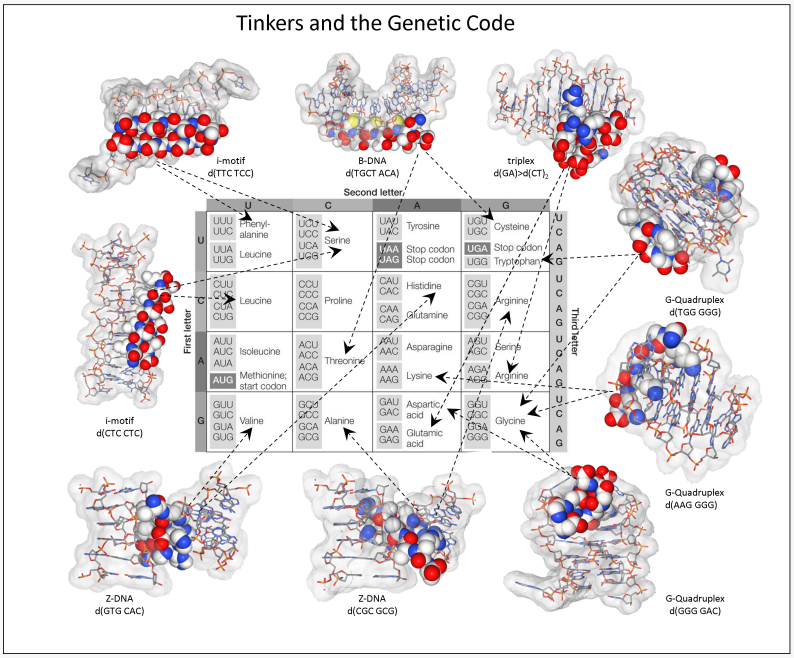
New insights in the origins of the genetic code

Where did the modern genetic code come from? The paper provides a surprising answer whereby unusual DNA structures called flipons map codons to amino acids.



Tinkers are complexes of amino acid polymers (colored spheres) and DNA flipons (wireframes). Tinkers self-amplify with DNA and peptide strands promoting the synthesis of each other. Early on, tinkers quite naturally evolved a non-overlapping, triplet genetic code.

CHARLESTOWN, MA, UNITED STATES, January 22, 2025 /EINPresswire.com/ -- One of the last remaining biological mysteries is how the genetic code arose. This code maps DNA codons to protein sequence and was elucidated over 50 years ago following Watson and Crick's description of the right-handed B-DNA double helix. Since then, many proposals have been advanced for the origin of the genetic code, with some even wondering whether the source was extraterrestrial. Dr. Herbert from InsideOutBio has described another possibility in today's release of the journal Royal Society Biology Letters. The new work shows how a triplet, non-overlapping genetic code could arise through self-replicating entities called "tinkers", a reference to the Nobelist Francois Jacob's famous description of Nature as a tinkerer.

> Evolution is a tinkerer, not an engineer"
>
> *François Jacob*

The work draws on recent advances in our understanding of alternative DNA structures. These nucleic acids fold into conformations that differ from the canonical right-handed B-DNA helix made famous by Watson and Crick. The alternative structures include left-handed Z-DNA, three stranded triplets and four stranded G-quadruplexes and i-motifs (as shown in the Figure). They form under many different conditions and were until recently considered by many as oddities that could not possibly exist inside cells. However, there is now overwhelming experimental evidence that these non-canonical conformations enable

cells to respond in novel ways to infections and environmental changes. Sequences able to switch conformation under physiological conditions within cells are called flipons. The particular alternative DNA structure formed depends on a characteristic nucleotide repeat pattern that defines each flipon type.

The work in the current paper was set in motion by results obtained with the latest version of the prize-winning DeepMind Alphafold3 program. With this approach, an amazing result emerged: the best forming Z-DNA nucleotide sequence bound specifically to the amino acids that the modern-day genetic code specifies. There is no a priori reason why there should be a match between a DNA consisting of alternating cytosine and guanine bases and the arginine and alanine amino acids. Previous studies had reported the interactions between Z-DNA and the dipeptide were of high affinity, so the Alphafold3 result was not an error.

Dr. Herbert wondered whether similar interactions between other types of flipons and the amino acids they encoded might explain the origins of the genetic code. He used the Alphafold3 program to test this possibility. The results provided further support for the existence of many stereospecific interactions between flipon sequences and the peptides encoded by the modern-day genetic code. These findings are described in the Royal Society Biology Letters paper.

The formation of the stereospecific complexes raised the possibility that these entities can promote their own synthesis, with the DNA templating the addition of amino acids to the peptide polymer, and the peptide polymer promoting the elongation of the DNA helix. Interestingly, the binding of metals by the peptide polymers provides a catalytic mechanism to promote both reactions. Indeed, metals bound by cysteine and histidine clusters are at the core of many modern-day enzymes involved in cellular metabolism, while repeat aspartate and glycine motifs are present in many DNA polymerases. These modern-day enzymes may therefore echo the flipon/peptide complexes formed according to the model and amplified early on by Darwin's primordial soup.

The flipon/peptide complexes capable of self-replication are called tinkers by Dr. Herbert. Tinkers are agents that work with metals. Their subsequent elaborations enabled Nature to explore and select novel outcomes. The genetic code arose quite naturally from the way tinkers operate. The code could not by an even numbered count of nucleotides as this will only specify a single amino acid. It therefore must be based on an odd number of bases if a sequence is to specify a mix of different amino acids. Also, due to the stereospecific nature of the interaction between the DNA flipons and amino acids, the coding must be non-overlapping with each DNA codon binding only a single amino acid. Through such interactions, the 3-dimensional tinkers settled on the mapping of codons to amino acids that we know today. Tinkers quite naturally gave rise to a triplet, non-overlapping genetic code.

The question of whether the peptide or RNA world arose first in the evolution of living things is often debated. Tinkers provide a different answer to that particular question. They explain the origin of the genetic code without requiring a particular chemistry or set of reactions. Of note,

Gobind Khorana, who helped decipher the genetic code, observed that DNA can be translated into protein by the ribosome under certain conditions. The result raises the possibility that RNA took over after tinkers created a primordial genetic code that initially was based on the translation of DNA. Subsequently, RNA became the protein template and a more efficient catalyst for peptide bond synthesis. At this stage, the RNAs were protected from the metals that otherwise caused their degradation by the proteins elaborated earlier by tinkers. Prior to that, the harsh conditions of Darwin's prebiotic soup were exactly those that favor the adoption of non-B-DNA conformations by flipons and the use of metals by tinkers to catalyze their own replication.

Tinkers provide a solution to the origin of the genetic code question. Later, the genomes made by further elaborating tinkers likely used flipons to encode information. By changing conformation, flipons acted as switches to turn on or off different reactions. Tinkers also likely participated in the evolution of new chemistries, with their peptide components adopting different folds, while nucleating condensates to facilitate particular reactions. The self-replicating nature of tinkers and the ability to incorporate different building blocks may continue to be of use in the current day. Potential applications include the directed evolution of new chemistries by selection and the construction of self-repairing materials.

About InsideOutBio: InsideOutBio is a start-up focused on developing a novel class of proprietary therapeutics to 'light' up tumors for the immune system to kill. Dr. Herbert leads discovery at InsideOutBio. His work on Z-DNA was foundational to the discovery of flipons. These statements about InsideOutBio comply with Safe-Harbor laws. They are forward-looking. They are not guarantees of future performance.

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