us of the dynamics of the expanding photosphere. And the temperature of the surface at the time of the explosion constrains the mass of the white dwarf.

The lesson from this observation is that a brief, unexpected detection can allow an astute team to figure out that a rare event has occurred and capitalize on it. Lest it sound too easy, the X-ray source was actually too bright for the detector, which was severely affected by 'pile-up' – photons arrived faster than the detector could count them. This severely complicated the data analysis. But by overcoming the problem, König and colleagues have filled a gap in our understanding of how classical novae occur. And all this from 35.8 seconds in the cross hairs.

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Origins of life

A possible path towards encoded protein synthesis

Claudia Bonfio

How did the biological machinery for protein synthesis evolve from simple chemicals on ancient Earth? Experiments suggest an intriguing role for modified RNA nucleotides in directing stepwise peptide synthesis. **See p.279**

DNA and RNA serve as the primary information carriers that make up the genetic material of living cells – which puts nucleic acids such as these at the heart of most theories of the origins of life. In particular, the 'RNA world' hypothesis posits that self-replicating RNA molecules acted both as information carriers and as catalysts for biochemical processes before DNA and proteins evolved. However, this hypothesis does not explain why, how and when proteins replaced RNA to become the largest and most diverse class of catalyst in modern cells. On page 279, Müller *et al.*[1] report findings that suggest how RNA could have directed the emergence of proteins on early Earth.

The interplay between RNA and proteins remains central to arguably the most fundamental cellular process: translation. This involves biomolecular machines called ribosomes – themselves composed of RNA and protein components – that use sequences encoded by messenger RNAs as templates for protein synthesis (Fig. 1a). Ribosomes recognize codons (triplets of nucleotides) in mRNA sequences, and induce them to bind to complementary sequences in transfer-RNA molecules. The bound tRNA carries the amino acid specifically encoded by the codon. This amino acid is attached to the nascent protein chain by the ribosome, and the translation cycle begins again as the ribosome moves on to decode the next codon in the mRNA.

How could translation have emerged on prebiotic Earth? Chemical processes have been discovered that can drive the non-encoded stepwise elongation of peptides (short chains of amino acids)[2]. Moreover, peptide-bond formation directed by an RNA template in the absence of a ribosome has been reported[3], involving single nucleotides loaded with amino acids. But processes that enable encoded protein synthesis without ribosomes have remained elusive.

DNA and RNA mainly consist of just four 'canonical' nucleotides, each of which contains a specific base: adenine, guanine, cytosine and either thymine (in the case of DNA) or uracil (RNA). However, DNA and RNA also commonly include non-canonical nucleotides, which are modified versions of the canonical ones. Among their key cellular roles, these modified nucleotides participate in translation by stabilizing and diversifying the tertiary (3D) structures of tRNAs, and by coordinating base pairing of tRNAs with mRNA[4]. For example, the non-canonical nucleotide N^6-threonylcarbamoyladenosine (t^6A) is an essential and universally evolutionarily conserved nucleotide responsible for decoding codons whose first nucleotide contains adenine.

The ubiquity of non-canonical nucleotides suggests that they were present early on during the emergence and evolution of life. Previously published work[5] from the same research group as that of Müller *et al.* showed that modified nucleosides (non-canonical nucleotides that lack a phosphate group), including those in which the bases have amino acids attached, could have been synthesized alongside canonical ones, starting from simple molecules thought to have been readily available on early Earth. However, if modified and unmodified nucleosides were indeed mixed together before the advent of life, how could RNA sequences predominantly consisting of

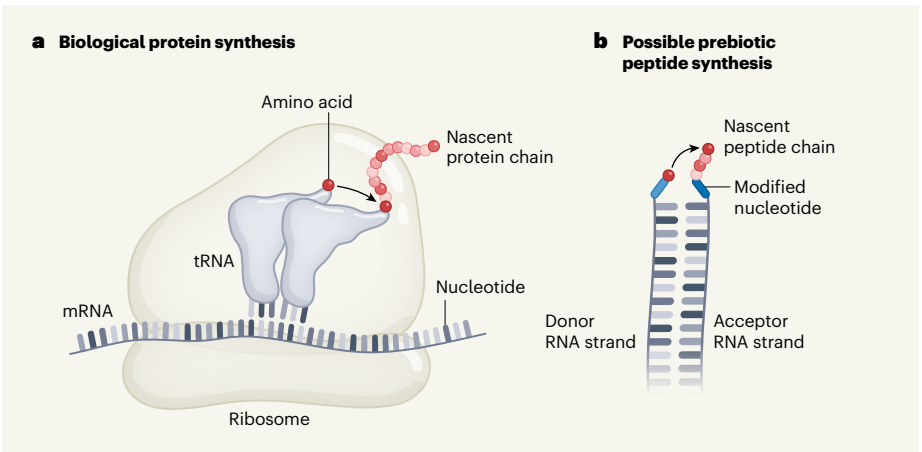

Figure 1 | A plausible evolutionary precursor to biological peptide-synthesis machinery. a, In the biological process of translation, a protein–RNA complex called the ribosome uses messenger RNAs as templates for protein synthesis. Ribosomes recognize codons (triplets of nucleotides) in mRNA sequences and induce them to bind to complementary sequences in transfer-RNA molecules. The bound tRNA carries the amino acid specifically encoded by the codon. This amino acid is transferred by the ribosome to elongate the nascent protein chain, which is attached to a second tRNA bound to the mRNA. **b**, Müller *et al.*[1] report a chemical system in which an RNA duplex promotes peptide synthesis. A modified nucleotide on the 'donor' strand can be loaded with an amino acid, which is then transferred to extend a nascent peptide on a modified nucleotide on the 'acceptor' strand of the duplex. This system could have formed on prebiotic Earth to act as a starting point for the evolution of ribosomal peptide synthesis.

the four canonical nucleotides have emerged to perform the replicating and catalytic processes that RNA carries out in modern biology?

Taking inspiration from the involvement of non-canonical nucleotides in biological mRNA-encoded protein synthesis, Müller and co-workers now show that RNA molecules containing these nucleotides could have had a role in driving stepwise peptide synthesis on prebiotic Earth (Fig. 1b). The authors report a process in which an amino acid or a peptide is loaded onto the non-canonical base of the terminal nucleotide of an RNA molecule (the donor strand). The formation of a duplex between two such nucleotide-modified RNA molecules enables the amino acid or peptide to be transferred to a non-canonical base — or to a nascent peptide attached to that base — on the other RNA strand in the duplex (the acceptor strand). In other words, this transfer step either initiates peptide synthesis on the acceptor's non-canonical base, or elongates a nascent peptide on that base.

The conditions under which the reported reactions take place could plausibly have occurred on prebiotic Earth. The authors also observe that simultaneous binding of multiple donor RNAs to a single acceptor allows peptide synthesis to occur at multiple RNA positions.

The peptide-synthesis process involves the generation of a chimeric peptide–RNA intermediate molecule in which the newly formed peptide bridges the donor and acceptor RNAs to form a hairpin-like structure, increasing the thermodynamic stability of the RNA duplex. The observation of these and other peptide–RNA chimaeras[6] suggests ways in which duplex formation between short RNA sequences can be achieved — overcoming the problem that unassisted base pairing between short complementary RNA molecules does not provide a sufficiently stable interaction for efficient non-enzymatic RNA elongation. In addition, peptide–RNA chimaeras might have been a platform for the evolution of primitive systems in which peptides drive catalytic processes and RNA directs replication of nucleic acids.

Müller and colleagues demonstrate that their chemistry is robust by showing that it works efficiently (it generates products in relatively high yields), with a range of coupling agents (needed to generate the peptide–RNA intermediate) and with a large library of amino acids. However, stepwise peptide elongation requires the donor RNAs to contain at least three nucleotides — which is an interesting parallel with the codon system used in modern translation. The degree of complementarity between the donor and acceptor RNAs governs how effectively peptide synthesis occurs in the presence of competing RNA molecules: amino acids loaded onto highly complementary RNA sequences are more efficiently transferred than are those on less-complementary competitor sequences, because they form more-stable donor–acceptor duplexes.

The author's system lacks the ability to read genetic information encoded in RNA sequences and to translate them into specific peptides, as happens in modern translation. Nevertheless, it is attractive as a possible prebiotic system for modern peptide synthesis, because it opens the way to molecular recognition being used in subsequently evolved systems to decode sequences in RNA acceptors and to specifically target them to complementary sequences in RNA donors.

Complex chemical mixtures composed of competing reactants would have most probably participated in the first stages of life's emergence on early Earth. In this milieu, modified nucleotides could have reduced the efficiency of key processes carried out by canonical nucleotides, or driven the synthesis of by-products that act as dead ends for those processes. The peptide synthesis proposed by Müller *et al.* offers an alternative function for RNA sequences containing non-canonical nucleotides, and could have promoted the evolutionary selection of canonical RNA sequences for replicating and catalytic functions.

The new findings intriguingly highlight the possible existence of a 'peptide–RNA world' on early Earth: canonical and non-canonical nucleotides might have had orthogonal chemical roles in driving life's emergence, being key to nucleic-acid replication and peptide synthesis, respectively. At a higher level of biochemical complexity, RNA might have acted as templates for peptide synthesis, whereas peptide bridges might have been used to stabilize short RNA duplexes. Whether a chemical ancestor of today's peptide-synthesis machinery involved modified nucleotides or not, the investigation of possible synergies between life's building blocks — the peptides and nucleic acids — will be crucial to advancing our understanding of the trajectory that connected prebiotic chemistry to modern biology.

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Neuroscience

Flipping a switch for movement

Oliver M. Gauld & Chunyu A. Duan

Experiments on the mouse brain reveal that neuronal signals from the midbrain to the cortex act as a switch that transforms the dynamics of cortical neuronal activity and, in turn, initiates movement.

Starting a sprint at the right moment is crucial for winning a 100-metre race. A slow start will cost you valuable time, but a premature movement might disqualify you. How does the brain mediate the rapid and precise transition between planning and movement that is required for this type of goal-directed behaviour? Writing in *Cell*, Inagaki *et al.*[1] reveal a multi-regional neural circuit that triggers a transformation in the neuronal dynamics of the brain's motor cortex, enabling a switch from motor planning to movement.

Neural mechanisms for motor planning and execution are typically studied using the delayed-response task[2,3], in which a future action is planned on the basis of transiently presented sensory information (such as a visual signal on a screen), but can be executed only after an explicit 'go' cue. During the delay between receiving the information and the 'go' cue, the activity of neurons in the motor cortex increases. This activity encodes the upcoming action, and has been interpreted as a neural signature for planning[4]. These preparatory activity patterns are qualitatively similar to the signals that later trigger actions. But this begs the question: how can preparation occur without causing movement?

One theory posits that, even when individual neurons are active during both planning and execution, there could be differences in the pattern of activity at the population level