

Plant enzymes build RNA from scratch

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Canonical RNA synthesis strictly requires a pre-existing nucleic-acid template or primer. In a recent study published in *Vita*, Li and colleagues identify a conserved family of plant nucleotidyltransferases that assemble canonical 3'-5'-linked RNA polymers directly from free NTPs, expanding the known biochemical landscape of RNA generation¹.

Every known cellular pathway for making RNA begins with something already there — a DNA template to copy, an RNA primer to extend, or an NDP substrate to reverse-phosphorylate. DNA-dependent RNA polymerases transcribe from templates; terminal nucleotidyltransferases extend pre-existing RNA 3' ends; polynucleotide phosphorylase builds chains from NDPs. Whether a protein alone could stitch free NTPs into long, canonical RNA polymers — with 3'-5' linkages and no nucleic-acid cofactor — has remained unknown. Li *et al.* now answer this question, revealing that *de novo* RNA synthesis may be hiding in plain sight within a familiar enzyme family¹ (Fig. 1).

The authors found their candidates by structural shape rather than sequence. Using human cGAS — whose nucleotidyltransferase core defines a conserved architecture for nucleotide binding and phosphodiester-bond formation² — as a DALI query, they searched AlphaFold-predicted plant proteomes for proteins sharing that catalytic fold. Filtering 266 initial hits for a conserved acidic catalytic triad yielded nineteen candidates, among which rice OsNTP4 emerged as the lead. Purified OsNTP4, incubated with NTPs alone, generated RNase-sensitive polymers. Two relatives — rice OsNTP10 and Arabidopsis AtURT1 — shared the activity, defining a conserved family of template- and primer-independent RNA polymerases¹.

The claim of *de novo* synthesis demands rigorous exclusion of contaminants, and the authors delivered¹. Mass spectrometry revealed no covalently bound nucleotide cofactor; nucleic-acid extraction from proteinase-K-digested samples detected no free nucleotides. Most decisively, extensively washed OsNTP4 crystals retained full RNA-synthesis activity after dissolution, while matched noncrystalline material did not — proving polymerization is intrinsic to the protein. NMR confirmed that products carry authentic 3'-5' phosphodiester linkages, distinct from the 2'-5' linkages of immune sensors such as oligoadenylate synthetase². The reaction requires divalent metal ions and shows ribose specificity; under identical conditions these enzymes cannot generate DNA from dNTPs¹.

These enzymes are not newcomers to nucleotidyltransferase biology. AtURT1 was previously characterized as an RNA 3'-end uridylyl transferase in microRNA turnover³, and OsNTP4 likewise retains RNA-tailing activity. *De novo* synthesis and RNA tailing thus represent alternative catalytic outputs of the same scaffold¹. *In vitro* sequencing revealed heterogeneous product lengths, a pronounced uridine bias (~56% of bases), and recurrent motifs such as GGGGUU and UCCUCU. The authors caution that library-preparation biases and G-quadruplex secondary structures complicate interpretation; these features describe *in vitro* outputs, not programmable sequence-specific synthesis¹.

The central mechanistic puzzle is initiation. How does an enzyme form the first phosphodiester bond without a primer? Does a transient dinucleotide intermediate precede elongation? How is product length controlled, and how does release couple to further synthesis? AlphaFold models of OsNTP4 position the RNA 3'-OH near the UTP α -phosphate, suggesting a geometrically plausible configuration for phosphodiester-bond formation, yet these docking predictions remain to be validated experimentally. The conserved acidic residues Asp100, Asp102, and Asp157 are essential, consistent with a metal-assisted mechanism. High-resolution structures of substrate- or intermediate-bound states will be required to resolve these questions¹.

This discovery joins a growing catalogue of unconventional protein-directed nucleic-acid synthesis but occupies a distinct niche. Mammalian TENT4B was recently reported to mediate primer- and template-independent RNA polymerization, though without NMR confirmation of linkage⁴. DRT-family reverse transcriptases catalyze protein-primed⁵ or protein-templated⁶ DNA synthesis. Against these precedents, plant NTP proteins use NTPs to produce RNA — not DNA — without protein priming or immune-sensing activation¹. The structure-guided search also recovered sixteen additional candidates with conserved catalytic architectures, suggesting *de novo* RNA synthesis may be only the first glimpse of a broader enzymatic landscape¹.

The largest open question is physiological relevance. Endogenous triggers, substrates, and biological roles remain unknown; do these enzymes generate functional non-coding RNAs in plants? Is their activity mobilized during stress or development? Genetic analysis of loss-of-function alleles and *in vivo* RNA identification will be essential. Beyond plants, this activity reopens an evolutionary conversation — if modern proteins can synthesize RNA from free nucleotides, could

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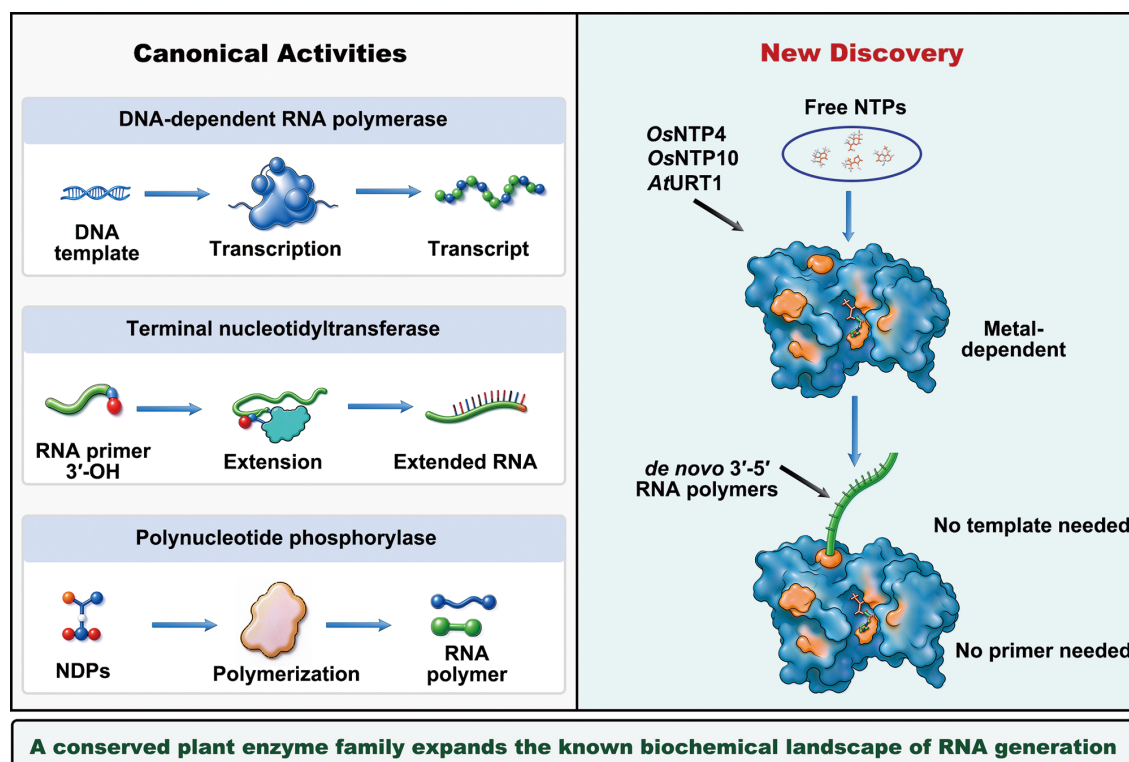


Fig. 1 *De novo* synthesis of RNA polymers by conserved plant nucleotidyltransferases. Canonical RNA biogenesis requires a DNA template, an RNA primer, or an NDP substrate. A conserved family of plant nucleotidyltransferases that assemble 3'-5'-linked RNA polymers directly from free NTPs, defining a previously unrecognized pathway for *de novo* RNA generation. This figure was created with the assistance of generative AI.

analogous enzymes have bridged prebiotic chemistry and the RNA world^{7,8}? By uncovering *de novo* RNA polymerization in conserved plant enzymes, Li *et al.* provide a platform for dissecting mechanism and exploring the evolutionary significance of protein-driven, template-independent RNA production¹.

COMPETING INTERESTS

The authors declare no competing interests.

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ADDITIONAL INFORMATION

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