DRT3 system: An extraordinary evolutionary innovation or a challenge to the central dogma?

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The recent discovery of the Defense-associated Reverse Transcriptase 3 (DRT3) bacterial anti-phage defense system, as reported by Deng et al. (2026),[1] has been hailed as a paradigm-shifting revelation that "challenges the Central Dogma" of molecular biology. The system's Drt3b subunit synthesizes long, sequence-specific poly(AC) DNA strands using its own amino acid residues as a template, a feat of "protein-templated" synthesis unprecedented in scale and specificity. While the mechanistic findings are undeniably brilliant and novel, a more measured evaluation is warranted. Is this truly a fundamental challenge to the principles governing all life, or is it a remarkable but highly specialized adaptation in the arms race between bacteria and phages? This commentary argues for the latter perspective, contending that the DRT3 system, for all its ingenuity, remains a fascinating exception rather than a rule-breaker, and its biological context limits its broader implications for the Central Dogma (Figure 1).

THE CENTRAL DOGMA: CORE VS. EXCEPTION

The Central Dogma, in its modern understanding, describes the general, directional flow of genetic information in cells: from DNA to RNA to protein. Its core components: DNA-dependent DNA polymerases for replication, DNA-dependent RNA polymerases for transcription, and the ribosome (an RNA-

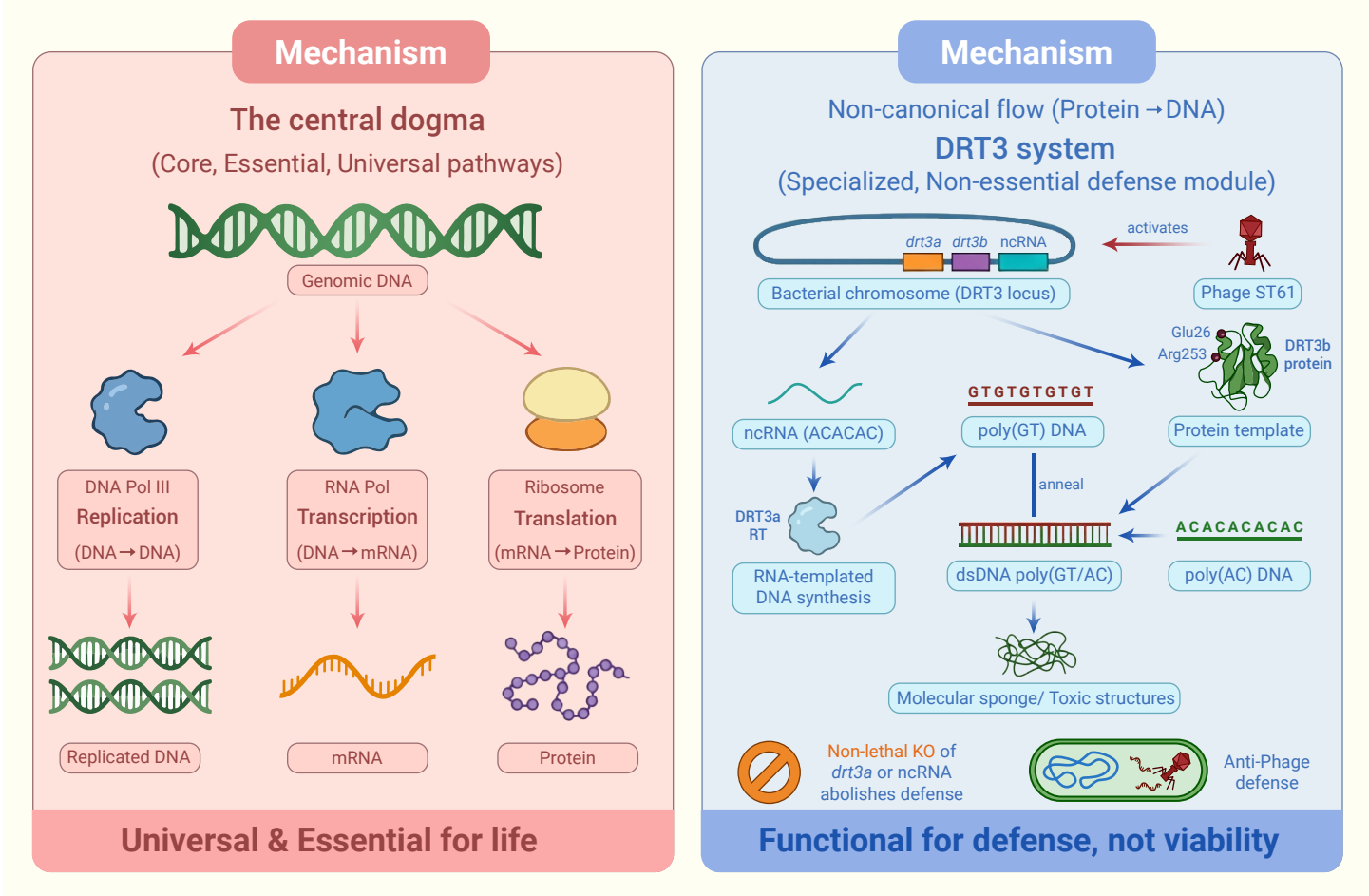

Figure 1. Protein-templated DNA synthesis in bacterial DRT3 system: A novel non-canonical genetic information flow for phage defense This schematic compares the canonical Central Dogma of molecular biology with the recently discovered DRT3 bacterial defense system, highlighting a novel non-canonical genetic information flow from protein to DNA. Left Panel: The Central Dogma, The canonical pathway of genetic information transfer is illustrated, including DNA replication (DNA Polymerase III-mediated DNA synthesis), transcription (RNA Polymerase-mediated RNA synthesis from DNA template), and translation (ribosome-mediated protein synthesis from mRNA). These processes are universal and essential for cellular viability, as knockout (KO) of core components like DNA Polymerase III or RNA Polymerase is lethal. Right Panel: DRT3 System, the DRT3 system represents a specialized, non-essential defense module against bacteriophages. It comprises two reverse transcriptases (DRT3a and DRT3b) and a non-coding RNA. DRT3a follows the canonical RNA-templated DNA synthesis, producing poly(GT) DNA from the conserved "ACACAC" sequence of the non-coding RNA. In contrast, DRT3b utilizes its own protein structure as a template, with specific amino acid residues (e.g., Glu26 and Arg253) guiding the synthesis of poly(AC) DNA without any nucleic acid template. The two complementary strands anneal to form double-stranded poly(GT/AC) DNA, which acts as a "molecular sponge" to sequester phage nucleic acids or form toxic structures that inhibit phage replication. This system is activated by the phage-encoded protein ST61, and knockout of DRT3a abolishes phage defense but is non-lethal, underscoring its role as a defense-specific, non-essential pathway.

protein machine) for translation are, all of which are **universally essential**.[2] Knockout of genes encoding this core machinery is almost invariably lethal across all domains of life. This universality and essentiality are what make them "central".

The DRT3 system operates outside this canonical flow. Drt3b uses a protein to template DNA synthesis, representing a form of information flow from protein to DNA. This is indeed a conceptual expansion of possible biochemical mechanisms. However, to claim it "challenges" the Central Dogma overstates the case. The Central Dogma was never an absolute law forbidding other flows; it is a framework describing the primary, essential pathways. Exceptions and additions, like reverse transcription (RNA→DNA) or prions (protein→protein conformation), have been incorporated without overturning the framework.[3] DRT3 adds another, highly specialized exception.

GENE ESSENTIALITY: A LITMUS TEST FOR CENTRALITY

A critical question, as rightly pointed out, is: **Are DRT3 genes essential?**The available evidence strongly suggests they are not. The study shows that catalytic mutations in Drt3a or Drt3b, or deletion of the ncRNA, abolish antiphage defense activity. This proves the system is functional for defense but says nothing about its necessity for bacterial viability. In the absence of phage pressure, bacteria lacking the entire DRT3 locus are almost certainly viable and capable of normal growth and division. This is in stark contrast to genes for DNA polymerase III or RNA polymerase core subunits, whose loss is catastrophic.

The DRT3 system is a **specialized defense module**, likely acquired through horizontal gene transfer and maintained because it provides a fitness advantage in phage-rich environments.[4] Its phylogenetic distribution, while spanning at least 20 bacterial phyla, is described as "widespread but scattered", indicative of a mobile genetic element rather than a core, vertically inherited component of bacterial biology. Its function is analogous to an immune system component in humans: crucial for survival in a hostile world, but not required for the basic cellular processes of life. You can live without a specific antibody, but not without a ribosome.

THE SPECIFICITY AND LIMITATION OF THE "PROTEIN TEMPLATE"

The mechanism of Drt3b is a masterpiece of molecular evolution, but its very specificity argues against broad generality. The "protein template" is exquisitely tuned to produce one sequence: an alternating poly(AC) strand. This is achieved through a precise, rigid network of amino acid side chains (Glu26, Arg253) that sterically and chemically enforce dA and dC incorporation in strict alternation. This is not a general-purpose, programmable template capable of arbitrary sequence information transfer. It is a single-purpose molecular machine built to produce a single, repetitive product.

This contrasts sharply with the core machinery of the Central Dogma. DNA and RNA polymerases use universal nucleic acid templates where the sequence information is variable and inherited. The ribosome reads a universal genetic code. The DRT3 system, in contrast, hardcodes its "information" (the alternating sequence) into the very three-dimensional structure of the Drt3b protein. It is a closed loop: the protein's structure dictates a DNA sequence that, as far as we know, does not encode the protein itself. It does not create a heritable, variable information stream. It is a consumable effector molecule, a weapon, not a replicative system.

BIOLOGICAL CONTEXT AND EVOLUTIONARY NOVELTY

The brilliance of DRT3 lies in its evolutionary context. It represents a stunning solution to a specific problem: rapidly generating a large, structured nucleic acid polymer as a defensive weapon. The coordinated action of Drt3a (making poly(GT) from an RNA template) and Drt3b (making the complementary poly(AC) *de novo*) allows for the swift production of long dsDNA repeats. The proposed function of this DNA as a "molecular sponge" or an inducer of toxic non-B DNA structures to halt phage replication is plausible and elegant.

This system showcases the incredible versatility of the reverse transcriptase fold, particularly the "Unknown Group" (UG) RTs, which have been co-opted for various non-canonical synthesis roles in bacterial defense. DRT3 is arguably the most sophisticated example yet. However, viewing it as a challenge to the Central Dogma is like viewing the evolution of a venomous snake's fangs and toxin-production glands as a challenge to the fundamental principles of vertebrate anatomy. It is a spectacular and lethal adaptation, but it does not redefine how bones, muscles, or nerves work in the vast majority of animals.

CONCLUSION: A MARVELOUS EXCEPTION, NOT A NEW RULE

The DRT3 system is a landmark discovery in molecular microbiology and evolutionary biochemistry. It reveals a previously unimaginable mechanism for nucleic acid synthesis and deepens our understanding of the phage-bacteria arms race. It expands the catalog of known biological functions and demonstrates that protein structures can, in highly constrained ways, dictate nucleic acid sequence. Therefore, DRT3 functions as a horizontally transferable accessory module, providing a specialized defensive layer without being integrated into the essential, core processes of bacterial genome replication and maintenance. This further solidifies its status as a peripheral adaptation rather than a central, universal component of the genetic information flow.

However, proclaiming it a challenge to the Central Dogma is an overstatement that risks obscuring its true significance. The Central Dogma describes the essential, universal, and heritable flow of genetic information that underpins all cellular life.[5] The DRT3 system is a **non-essential, specialized, and non-heritable** (in terms of its product encoding its own template) defense apparatus. Its genes are not core; its mechanism is not general; its product is not a replicative genome. Looking forward, the mechanism of protein-templated DNA synthesis opens intriguing avenues for synthetic biology. It suggests the possibility of engineering **directed DNA writing** systems based on specific protein structures or states, creating novel biosensors that convert environmental signals into storable DNA 'memories,' and exploring information transfer pathways that operate beyond traditional nucleic acid templates.

A more fitting description is that DRT3 is a **profound exception that proves the rule**. It operates in the vast, creative space outside the central, essential pathways. It shows that evolution can jury-rig incredible solutions using existing molecular parts (RT domains) for specific niches, without altering the fundamental rules of the cellular economy. The real challenge for future research is not to use DRT3 to dismantle the Central Dogma, but to explore how this exquisite mechanism evolved, how widespread such protein-templated systems might be, and whether we can harness its principles for biotechnology, perhaps to engineer novel polymerases that write custom, protein-defined sequences. The DRT3 story is one of evolutionary ingenuity and mechanistic surprise, a testament to life's complexity, but not a revision of its most central tenets.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.