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MODEL OF PRENUCLEIC REPLICATION CYCLICALLY COUPLING ENCODING TO DECODING OF PEPTIDE TEMPLATES

BY

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ABSTRACT

Model of prenucleic replication cyclically coupling encoding to decoding of peptide templates. - Proposal is made that the informational tape heat produced as a sequence of anticodon doublets of nucleobases phosphoramidate bonded as dibasetetraphosphates is 1) primarily encoded by stereospecific recognition of the amino acids of randomly produced peptides and 2) further decoded by acylation-amination into new template peptides bonded at the expense of the transitorily broken phosphoramidate (P-N) linkages, in coupled self-reinforcing cycles.

Key-words: Encoding; Prenucleic; Decoding; Peptide template; Coupling cycle

PROLOGUE

In all "modern" cells, RNA messenger molecules serve as intermediates in the transfer of genetic information between DNA and ribosomes made of RNA and particular protein molecules. These microstructures perform their vital functional sequences with the concurrence of transfer or t-RNAs which scavenge the cytoplasm for the amino acids. Before such DNA-based life, living things might have been sustained only by RNA-based material in a so-called "RNA world" based on particular RNA molecules or ribozymes also functioning as catalytic enzymes (see GESTELAND *et al.*, 1999). However, although there are many who believe it to be the likely outcome, for others, it did not require that RNA molecules were the first prebiotic replicators (MADDOX, 1998; JOYCE & ORGEL, 1999), their main handicap being in the difficult prebiotic synthesis of ribose (SHAPIRO, 1988; COHEN, 1996; DE DUVE, 1998; SCHWARTZ, 1998).

A first clue in the effort to circumvent RNA synthesis might be provided by "reinventing" simple self-replicating systems in the laboratory. Such processes of molecular self-replication have recently been conceptualized in a three-step minimal model by BURMEISTER (1998) who used it for the development of non-enzymatic self-replicating systems based not only on nucleotidic but also nonnucleotidic precursors as initiated by

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REBEK's team (1994). These were based on the minimal system proposed by TERFORT & VON KIEDROWSKI (1992) who used the condensation of 3-aminobenzenidine and (2-formylphenoxy)-acetic acid.

Many other systems of interacting molecules can be envisaged which could have yielded prebiotic replicators capable of further evolution by mutation - selection. Among those there are our riboseless prenucleic infopolymers directly, i.e. phosphoramidically, condensing on polyphosphate nucleobase doublets having specifically encoded the amino acid sequence of a primitive, spontaneously formed peptide (TURIAN, 1996-1998). From what is known of the catalyzed synthesis of peptides on polyphosphates (SCHRAMM & WISSMANN, 1958; RABINOWITZ *et al.*, 1969; YAMANAKA *et al.*, 1988), it could then be visualized that the prenucleic sequence can be further decoded into peptides similar to the original ones, produced by sequential amino acid bondings, themselves catalyzed by the phosphoramide (P-N) bonds of the nucleobases. The thereby translated peptides could then have functioned as templates for further affinity encoding by additionally produced polynucleobasephosphates (PBP) functioning as primary replicators by positive feedback in coupled self-reinforcing cycles.

CYCLING ROUNDS

1. *Primal encoding of informational PBP*

The primary coding event concerned some spontaneously self-assembled, primitive peptide endowed with the quality of a selective advantage of structural conformation possibly liable to some degree of primitive precoding self-replication (CALVIN, 1969; TURIAN, 1996a; LEE *et al.*, 1996). The peptide encoding would imply the selective, stereospecific recognition of its amino acids by "archedoublets" of nucleobases hooked by phosphoramidic bondings on triphosphates (TURIAN, 1996b, 1998), most plausibly the cyclic trimetaphosphates freeing bonding energy by their nucleophilic opening to linear triphosphates (TURIAN *et al.*, 1999) and secondarily thermopolymerized to polybase-diphosphates (Fig. 1) by splicing 1 P_i per triphosphate (unpublished ³¹P NMR results).

2. *Translational PBP decoding to templating peptide*

Decoding of the information contained in PBPs would mediate the translation into peptides as suggested by FOX & HARADA who, in 1960, thermally polycondensed free amino acids with polyphosphoric acids and further proposed (HARADA & FOX, 1965) a route to polypeptide synthesis via mixed carboxylic-phosphate anhydrides starting with amino acids and polyphosphates. In 1958, SCHRAMM & WISSMANN. envisioned the origin of self-reproducing systems by synthesizing polypeptides with the help of ethylpolyphosphate in which the amino group of one component was made reactive by forming a phosphoramide ester reacting subsequently with the carboxyl group of the 2nd component. Peptide bond formation into di-triglycine was further obtained by RABINOWITZ (1970) in aqueous solutions of either linear or cyclic triphosphates. It could result either of intermediary formation of a cyclical acylphosphate (CHUNG *et al.*, 1971; YAMANAKA *et al.*,

1988) or of an acylphosphate of amino acid secondarily reacting with the amino group of another amino acid molecule (RABINOWITZ & HAMPAL, 1978).

Interestingly, the process of acylation-amination leading to the peptide bond formation can be catalytically activated by imidazole presumably phosphoramidically bonded on the triphosphate (RABINOWITZ & HAMPAL, 1978, 1980), an effect which is imitated by other azoles such as the 4 nucleobases as recently evidenced by ^{31}P -NMR (TURIAN *et al.*, 1999). Consequently, we have thought that the process of P-N phosphoramidate locking of nucleobases and its possible opening for peptide bond formation should be highly relevant for the decoding of the PBP sequences (Figs 1+2). However, to be fully effective and repetitive, such phosphorylamide acylation on the N-H groups of bases should be followed by their P-N rebonding to restore the continuity of the decoding chain as tentatively presented in Fig. 3. During its bonding process, the assembled peptide

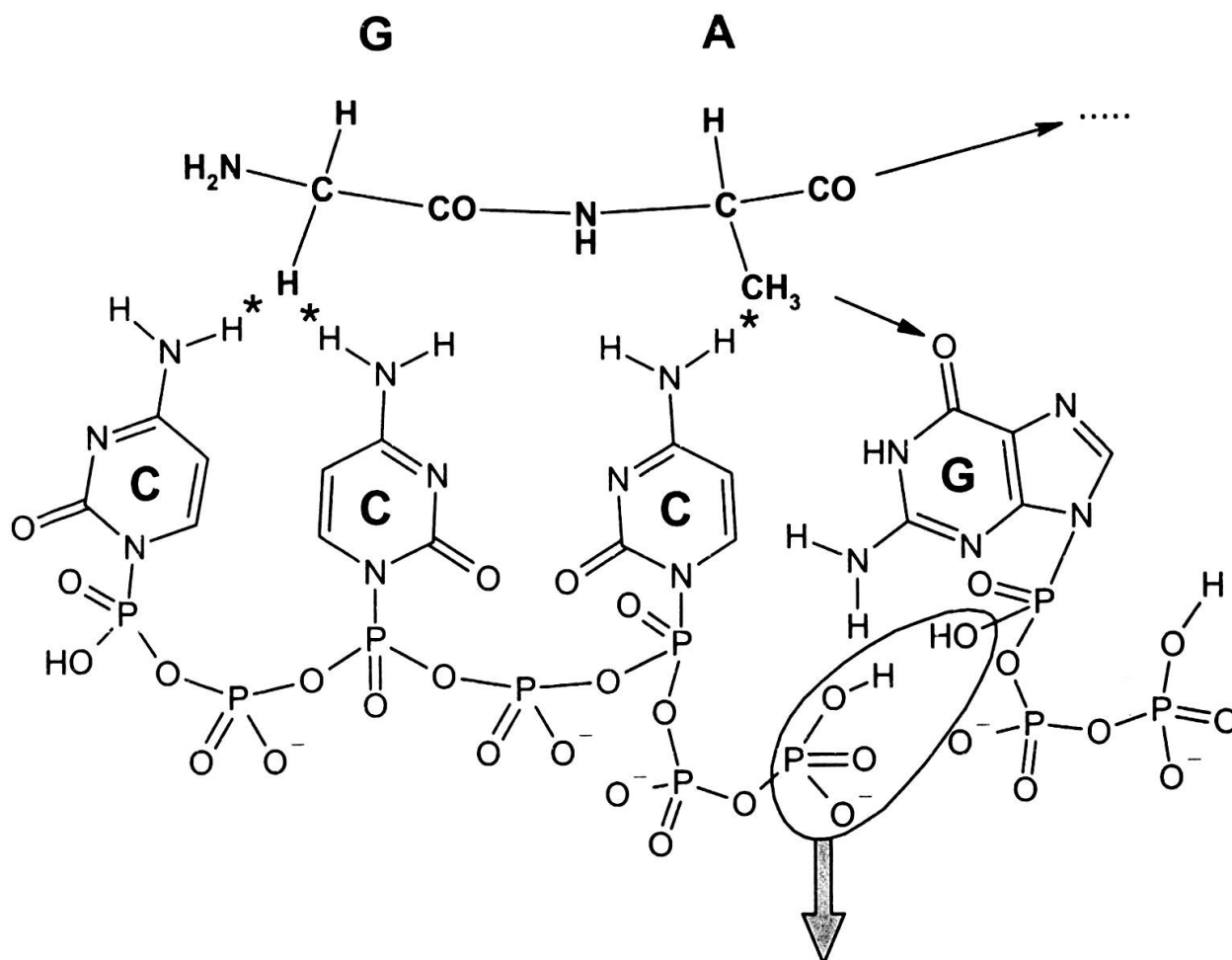


FIG. 1.

Molecular modelling of progressive retrotranslation and thereby primeval coding of two peptidic amino acids (glycine G, alanine A) stereospecifically recognized and weakly bonded (van der Waals *, $\text{H} \rightarrow$) by doublets of anticodonic nucleobases (cytosines CC, cytosine + guanine G), themselves "frozen" by phosphoramidic bondings (P-N) on the opened rings of trimetaphosphates catalytically produced from linear triphosphates. Contrarily to our previous graphics in Fig. 1 (TURIAN, 1998), ligation of one P-N bond to the next is figured here by a di(pyro) chain as recently suggested by the ^{31}P NMR detection of a PO_4 (Pi) peak during heat-induced polyphosphate polymerization (progressing work).

strand would be polarly displaced and freed to become available as additional template for the next PBPs replicative encodings, thereby reinforcing the number of PBP copies available for the following cycles as modelled in Fig. 4.

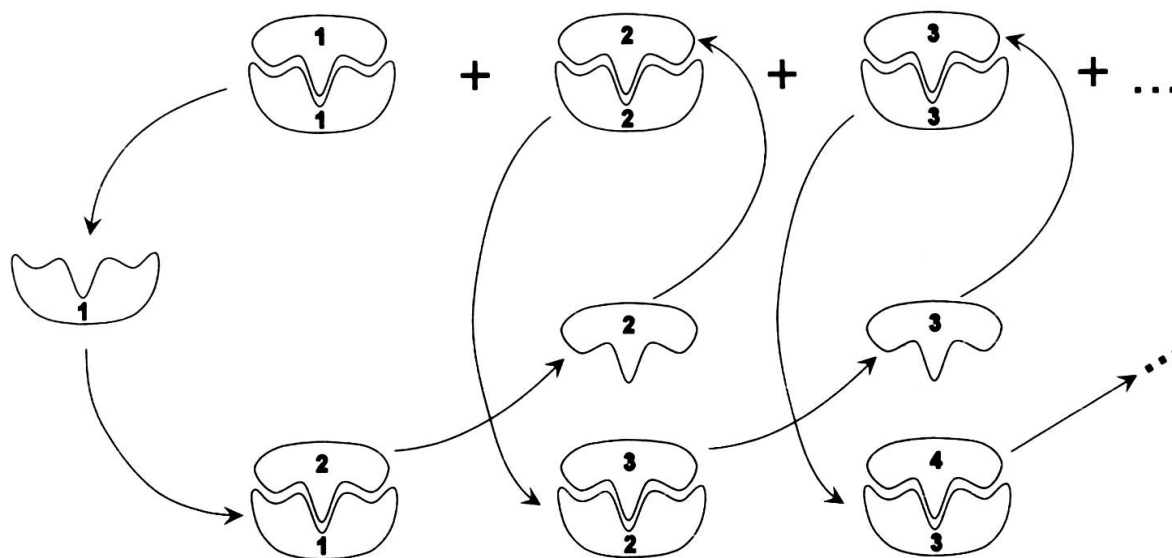


FIG. 4.

Cyclic coupling of primitive template replicators schematized by two complementary symbols: 1-peak (grey) with the peck corresponding to the 3 amino acid (G-G-A) residues of our modelized oligopeptide template (Fig. 2); 2-peaks (white) with bumps corresponding to the specific nucleobase doublets P-N bonded as prenucleic hexabasedodecaphosphates. The self-reinforced mechanism of replication is represented by circling arrows toward increasing intrasymbol numbers (1-4-...).

EPILOGUE

Our modelled replicative scenario finds its originality in the linking of the process of peptide bonding with the ordered sequences of nucleobases on a polyphosphate chain, thereby conferring it pregenetic, evolutionary significance. Such ordering of amino acids on macromolecular templates is therefore of prime concern to provide the necessary surfaces to specifically attract them and thereby line them up in the correct sequence. From this point of view, our prenucleic polybasephosphate system would provide specific lining up of amino acids and thereby a primitive type of peptide synthesis as a coding sequence, satisfying the criteria of specificity and, even though still approximately, ordering on templates. Evidently, our system is at a lower evolutionary level than that presented by YARUS' team (1998; see also JAMES & ELLINGTON, 1998) who has actively pursued the implications of a direct RNA-template theory for the origin of coded peptides synthesis.

By a positive feedback cyclic process, the PBP primal template could secondarily, non enzymatically replicate on the decoded peptide now serving as template in a self-reinforced, *living-like* type of renewal, cyclic mechanism. Our primitive pre-RNA model would thus combine - in cyclically coupling them - the replication ability of prenucleic infopolymers with their direct translation into peptides insuring further self-reinforced

complementary template replication of the prenucleic polymers thus completing a self-promoting molecular information loop as defined by LOEWENSTEIN (1999). It admittedly awaits more compelling experimental evidence while being satisfactorily in phase with MAYNARD SMITH & SZATHMARY'S (1999) comments that "our best hope seems to lie in seeking a polymer with a chemically simpler backbone than RNA, thus reducing the number of ways in which the monomers can be linked".

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RÉSUMÉ

MODÈLE DE RÉPLICATION PRÉNUCLÉIQUE COUPLANT CYCLIQUEMENT L'ENCODAGE AU DÉCODAGE DE SÉQUENCES PEPTIDIQUES

Le ruban informationnel thermogénéré en séquence de doublets anticodoniques de nucléobases phosphoramido-liées comme dibasetétraphosphates est 1) primairement encodé par reconnaissance stéréospécifique des amino acides de peptides aléatoirement produits et 2) décodé ensuite par acylation-amination aux dépens des liaisons phosphoramidiques (P-N), transitoirement ouvertes, en peptides additionnels servant à leur tour de modèles de réplication répétitive couplée en cycles auto-renforcés.

Mots-clés: Encodage; Prénucléique; Décodage; Modèle peptidique; Couplage cyclique.

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