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How Were Porphyrins and Lipids Synthesized in the RNA World?

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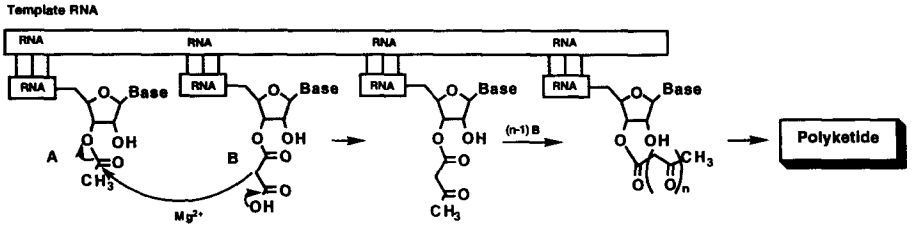
Abstract: It has been suggested that the most primitive organisms use RNA's as catalysts for their metabolic pathways. Molecular mechanisms are proposed for carbon-carbon bond forming processes in the RNA world leading to the lipids necessary for the membranes and to the production of porphyrinoids in these organisms. © 1997 Elsevier Science Ltd.

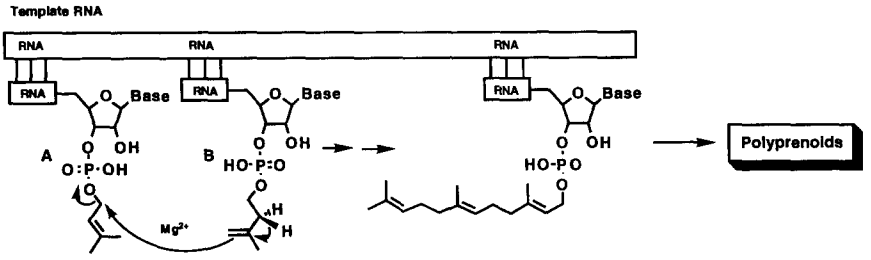
Based on sequence data and phylogenetic arguments, it has been suggested[1] that, in addition to the contemporary role of catalytic RNA's which participate in transesterification and hydrolysis of phosphodiester and aminoacyl linkages,[2] a "breakthrough" organism existed *ca.* 2.5 billion years ago whose metabolism was mediated by ribozymes rather than the proteinaceous enzymes which appeared later in the "protogenome," the most recent common ancestor of the archea, eubacteria, and eukaryotes.

In surveying the chemistry required for a catalytic RNA capable of synthesizing the membrane lipids of the first primitive organisms, it is clear that a mechanism (so far undetected among contemporary RNA catalysts) must have been in place for formation of carbon-carbon bonds as a requirement for the oligomerization process leading to both polyketide (fatty acid) and polyprenoid (terpenoid/cholesterol) structures which form an integral part of the lipid bilayer of the cell membrane. In addition to these key reactions, it has also been suggested[1] that the last ribo-organism could perform aldol, Claisen, and transmethylation reactions, as well as porphyrin biosynthesis, catalyzed by RNA. To the best of our knowledge, no mechanisms have been suggested at the molecular level for these processes, all of which involve carbon-carbon bond formation.

In this memoir, a catalytic mechanism for polyketide and, by extension, fatty acid and polyprenoid biosynthesis using an RNA template is proposed. The first step is the (mis)acylation of t-RNA with acetyl and malonyl equivalents. Alignment of the charged t-RNA on a short segment (10-20 mer) of RNA complementary to the t-RNA would then enable the propinquity of the 3'-esters to engage in the necessary Claisen chemistry of polyketide synthesis using Mg^{2+} as cofactor as illustrated below.

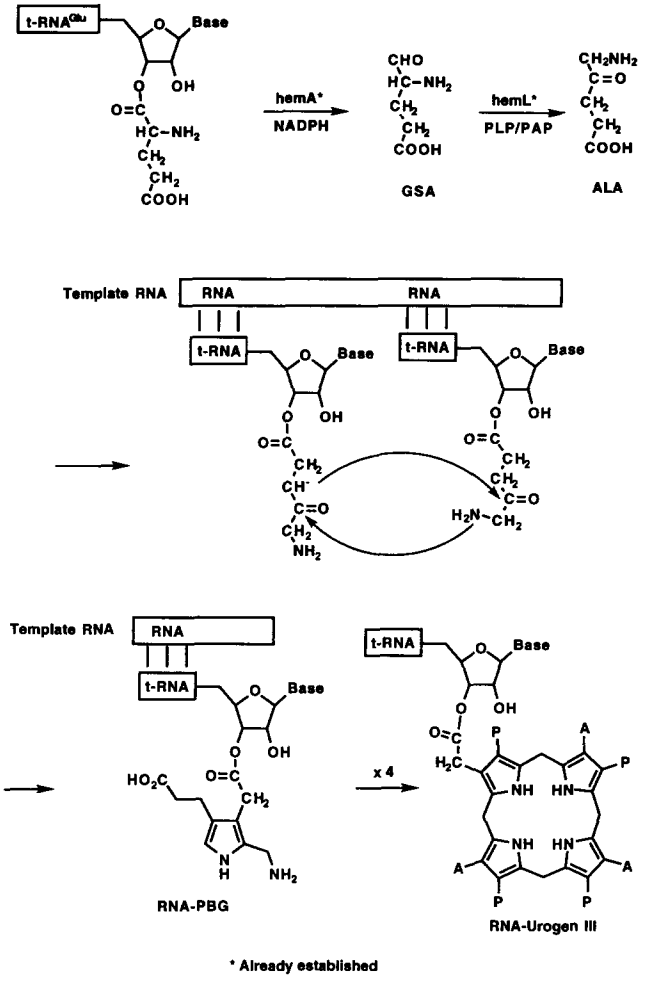


The chemistry of this system has been developed in an intramolecular model using the two phenolic hydroxyls of catechol, one loaded with acetate and the second with malonate, to effect the net synthesis of acetoacetate, the diketide progenitor of fatty acids.[3] A second, more primitive scenario embodying aminoacylated mononucleosides aligned on an oligomeric template, was used to model oligopeptide synthesis *in vitro*.[4] If the monomeric nucleosides were charged instead with acetate and malonate units, the same chemistry would allow polyketide synthesis. Extrapolation to polyprenoid synthesis using 3'-phosphorylated RNA as the adapter rationalizes the formation of the terpenoid motif as suggested below, thereby providing a second avenue for production of lipids in the primitive organism. The more sophisticated fidelity of protein biosynthesis, dependent on the presence of DNA and triplet coding, presumably evolved from the above mechanisms catalyzed by RNA and has been assigned a role in the "breakthrough" organism[1] which followed the most primitive form of life.



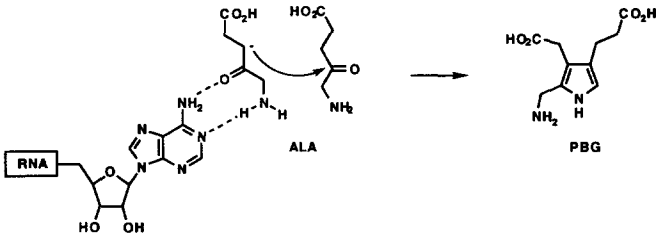
Finally, as an example of the aldol reaction necessary for the second step of porphyrin biosynthesis, catalyzed today by aminolevulinic acid dehydratase, and the carbon-carbon bond formation necessary for the third and fourth steps (performed by PBG deaminase, and uroporphyrinogen III synthase) it is proposed that the primitive organism could effect these processes[5] on the substrates bound either covalently or non-covalently to t-RNA. The suggestion is based on the fact that the first step of tetrapyrrole biosynthesis in most bacteria and plants is the

reduction of glutamyl-t-RNA^{glu} to glutamate semialdehyde[6] followed by rearrangement to 5-aminolevulinic acid, ALA, as shown below.



The proposed ribozymatic counterparts for ALA dehydratase, porphobilinogen deaminase and uroporphyrinogen synthase, which have evolved to the appropriate enzymes, might have shared with glutamyl-t-RNA reductase a mechanism dependent on interaction with RNA. Interestingly, of those steps catalyzed by HemA-HemD, only the contemporary reductase (HemA)

actually uses the aminoacylated $tRNA^{glu}$ as substrate. The bonding of ALA to t-RNA would provide a template to enable the unsymmetrical aldol reaction to occur with the desired regiochemistry. It has been shown[7] that, in the absence of polymeric material, such as an ion exchange resin, the self condensation of ALA produces the 3-aminopyrrole (pseudo-PBG) via the alternative aldol condensation. Similarly, although models exist[8] for the deaminase/cosynthase (*hemC, D*) sequence (via acid-catalyzed oligomerization and cyclization of PBG), the attachment of PBG to RNA would provide the template for directing the reaction towards urogen III. The covalent version is illustrated, but the hydrogen bonded structure shown below would rationalize the necessary activation of ALA at C-3 (rather than C-5) to effect PBG synthesis.



The long term goal of experiments (now under way) to test the above hypotheses is to develop *Genetically Programmed* organic synthesis as a logical extension to the current repertoire of synthetic methodology, using the template control already in place for ribosomal protein synthesis.

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