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Coenzymes as Fossils of an Earlier Metabolic State

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Summary. A metabolic system composed of nucleic acid enzymes is proposed to have existed prior to the evolution of ribosomal protein synthesis. Vestiges of these nucleic acid enzymes persist in contemporary coenzymes. This proposal rationalizes the fact that many coenzymes are nucleotides or heterocyclic bases which could be derived from nucleotides.

Key words: Coenzyme Evolution - Nucleic Acid Enzymes - Metabolic Pathways - Nucleotide-Binding Domain

Coenzymes are complex organic molecules which are essential for many enzyme-catalyzed reactions. At least 52% of the nearly 1750 enzymes recently catalogued (IUPAC-IUB, 1972) require a coenzyme for activity. Although there have been discussions of the evolution of coenzymes (Handler, 1963; Eakin, 1963), none have explained the curious fact that many coenzymes are nucleotides (NAD, NADP, FAD, coenzyme A, ATP, etc.) or contain cyclic nitrogenous bases which could be derived from nucleotides (thiamin pyrophosphate, tetrahydrofolate, pyridoxal phosphate, etc.) (Dixon & Webb, 1955). In light of the recent proposal by Kuhn (1972) on the evolution of a self-replicating genetic system, I propose that coenzymes are the surviving vestiges of nucleic acid enzymes which preceded the evolution of ribosomal protein synthesis.

The evolution of a self-replicating genetic apparatus has been depicted as a sequence of chemical events guided by natural selection (Kuhn, 1972). RNA molecules of increasing length and structural complexity eventually lead to an aggregate capable of protein synthesis. In this evolutionary scenario, nucleic acids of defined sequence precede proteins of defined sequence because they have the potential for self-replication which proteins do not. The evolution of specific protein enzymes becomes possible after the origin of the

genetic code. In the absence of specific enzymes, it has been presumed that the activated precursors for nucleic acids form spontaneously under primitive earth conditions and polymerize on an appropriate template (Orgel, 1974). The catalysts for prebiotic replication are unknown. They may have been minerals (Orgel, 1974), small peptides (Eigen, 1971) or polynucleotide enzymes (Brewin, 1972).

The absence of protein catalysts does not preclude the existence of a complex metabolic system capable of coupling chemical free energy into "bio" synthesis. Eakin (1963) has proposed that intermediary metabolism evolved by the sequential acquisition of coenzymes or coenzyme precursors. Since contemporary coenzymes by themselves are generally very poor catalysts compared to coenzyme-enzyme complexes, it is unlikely they would have been effective in primitive metabolism. If coenzymes are derived from nucleic acid enzymes, the fact that most present day coenzymes are relatively inactive catalysts in the absence of specific proteins is then not too surprising.

The nucleic acid enzymes of intermediary metabolism proposed here would probably have limited substrate specificity and would, therefore, catalyze classes of reactions rather than specific metabolic reactions. Metabolism would be much the same as today, except that one enzyme would participate in several different pathways. This view of primitive metabolism is similar to that recently proposed by Yčas (1974), except that protein enzymes are replaced here by nucleic acid enzymes. Yčas notes that the homology between essential enzymes indicates a small number of ancestral genes which must have coded for enzymes of lower specificity which catalyzed classes of reactions. Translation errors would have provided a variety of enzymes from a single gene. These two views of primitive catalysts can be considered as sequential states rather than mutually exclusive.

The appearance of coded proteins would provide new opportunities for a metabolic system composed of nucleic acid enzymes. Proteins could bind to nucleic acid enzymes and provide specific substrate binding sites not previously available. In time proteins would displace nucleic acid enzymes in all but the catalytic core of their active sites which persist as today's coenzymes. Gene duplication and independent evolution would create families of homologous enzymes.

The degree to which contemporary coenzymes reflect the proposed nucleic acid ancestry varies considerably. At one extreme are the tRNAs which Brewin (1972) has considered as polynucleotide enzymes. They also can be viewed as very

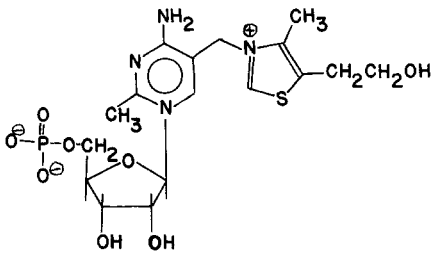

Fig.1
Thiamin mononucleotide, a hypothetical evolutionary precursor of the coenzyme thiamin pyrophosphate

large coenzymes which participate in the group transfer of amino acids. Another group of coenzymes are the mono and di-nucleotide coenzymes whose structure contains catalytically inactive portions which presumably are retained for binding to proteins. The most cryptic group of coenzymes are those which are no longer nucleotides but rather are modified cyclic nitrogenous bases which could be derived from nucleotides. One such example is the hypothetical thiamin nucleotide shown in Fig.1.

There are coenzymes such as biotin and lipoic acid which do not bear any resemblance to nucleotides or nucleotide bases.

It is conceivable that catalytic groups formerly part of nucleic acid enzymes were so important to general catalysis that the catalytic group was incorporated into specific amino acids rather than being retained as a coenzyme. In particular, the imidazole moiety of histidine may be such an example. Histidine is the only amino acid whose biosynthesis starts from a nucleotide rather than small metabolic intermediates.

In addition to rationalizing the structure of many coenzymes, the proposal outlined here suggests that the first proteins of functional significance bound to nucleic acids. Orgel (1972) and collaborators (Brack & Orgel, 1975) have proposed that the first proteins may have had an alternating sequence of hydrophobic and hydrophilic amino acids which would enable them to form ß-structures. Antiparallel ß-structures can interact in a complementary way with RNA double helices (Carter & Kraut, 1974). It is intriguing, therefore, that the nucleotide-binding domain of dehydrogenases, kinases and several other enzymes is characterized by a large sheet of parallel ß-structure (Rossmann et al., 1974; Eventoff & Rossmann, 1975). Thus, coenzymes may be fossils of nucleic acid enzymes and the coenzyme-binding sites of contemporary enzymes may be fossils of the earliest proteins.

This proposal suggests that a nucleotide binding domain will be found in many if not all enzymes that require coenzymes and that the nucleotide-binding domain will be the site of coenzyme binding.

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