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LETTER TO THE EDITOR

# On the road to a DNA–protein world

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Following the RNA world and the appearance of ribonuclease reductase activity, it is proposed that the progression of genetic templates from single-stranded RNA to DNA occurred gradually via an increasing deoxyribonucleotide content in the RNA molecules coupled to an increased polymerase stringency, rather than in one step corresponding to a major polymerase evolution (Lazcano et al., 1992). This hypothesis is supported by both DNA (Lazcano et al., 1992) and RNA polymerase data (Conrad et al., 1995) that indicate that the early polymerases possessed rather broad substrate and template specificities (ribose versus deoxyribose). This hypothesis envisions mixed RNA–DNA molecules (M-molecules) composed of randomly interspersed ribo- and deoxyribonucleotides. The obvious question is whether such M-molecules served exclusively template functions or also served catalytic functions.

With the development of chemical synthesis strategies for RNA compatible with those for DNA, M-molecules can now be prepared (Usman & Cedergren, 1992) and this question properly addressed. Synthetic M-molecules possess several conspicuous characteristics, as illustrated by the following examples. Predominantly deoxyribonucleotide-containing "hammerhead" ribozymes (i.e., nucleozymes) exhibit a significant level of cleavage, showing that ribozyme-type catalysis is not restricted solely to pure RNA (Bratty et al., 1993). Furthermore, DNA molecules with catalytic functions (i.e., deoxyribozymes) have been developed using the powerful in vitro selection approach. Breaker and Joyce (1994) synthesized a deoxyribozyme with the ability to cleave RNA molecules, and Cuenoud and Szostak (1995) developed a deoxyribozyme that catalyzes the ligation of DNA substrates. In addition, several reports have shown that both M-molecules and pure DNA molecules of sequences corresponding to RNA substrates may act as ribozyme substrates (Cech et al., 1992; Bratty et al., 1993; Perreault & Altman, 1992). Moreover, the presence of the deoxyribonucleotides in ribozymes confers greater stability toward both aqueous hydrolysis, which is promoted by the 2′-hydroxyl groups, and ribonuclease degradation (Bratty et al., 1993). Thus, the introduction of several deoxyribonucleotides into RNA molecules does not necessarily result in a severe reduction in either their catalytic properties or their substrate efficiency. Hence, M-molecules appear to fold in a manner analogous to pure RNA. This point is also illustrated by the introduction of a single ribonucleotide into a DNA helix driving the conformation to the A-type helix characteristic of RNA, as observed in three-dimensional studies of some Okazaki fragments (Egli et al., 1993).

The initial incorporation of deoxyribonucleotides into RNA was totally at random due to the indiscriminate nature of the existing polymerases. The different nucleotides within the resulting M-molecules were distinguished solely by their base-pairing properties and not by their sugar moieties. As a result, catalytically inactive products lacking a ribonucleotide at a critical position may have existed; however, whether all M-molecules required a ribonucleotide at a given position is not clear, because mutant sequences could conceivably have released these molecules from the ribonucleotide requirement. Additionally, catalytically inactive products might have been replicated, and their descendants either re-established catalytic properties or became specialized for the carrying of genetic information.

Thus, M-molecules are not only polymerized by enzymes but also possess catalytic activities analogous to those of RNA and may be more stable than pure RNA. Clearly they satisfy all the requirements for early genetic material, and, when coupled with the concurrent evolution of polymerase stringency, provide the likely vehicle for the bridge from the ancestral RNA world to the modern DNA–protein world.

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