A5. Abiotic Synthesis of Genetic Polymers

Abiological synthesis of polymer precursors is a long way from creating genetic polymers like RNA and DNA. These genetic polymers have one property that at first glance seems not conducive to a genetic molecule. Both are polyanions, which must be packed into a cell and folded onto itself to form the classic dsDNA helix and many different RNA structures. This problem is solved to some degree by the presence of counterions that help mask the charge on the negative backbone of the nucleic acids. The presence of phosphate in the phosphodiester backbone linkage does confer an important advantage over other possible links (carboxylic acid esters, amides and anhydrides). The electrophilic phosphorous atom is hindered from nucleophilic attack by the negative O attached to the phosphorous. Also, the phosphorous is sp3 hybridized compared to the sp2 hybridization of the electrophilic carbon atom in anhydrides, esters, and amides, and hence is less accessible to nucleophilic attack. Most people now believe that RNA, which can act both as an enzyme and genetic template, preceded DNA as the genetic carrier. The evolution of DNA as the primary genetic carrier required an enzyme to convert ribose to deoxyribose. This would make the nucleic acid less likely to cleave at the phosphodiester bond with the replacement of a nucleophilic 2’ OH with an H, and make the genetic molecule more stable. Other types of genetic carriers might have preceded the RNA world, especially if the monomer required could be more readily synthesized from abiological sources. One such alternative are threose nucleic acids (TNA).Synthetics ssTNA can base pair with either RNA, DNA, or itself to form duplexes.
Other possible candidate include peptide nucleic acids (PNA). These can also form double stranded structures with DNA, RNA, or PNA single strands. They were initially designed to bind to dsDNA in the major grove forming a triple-stranded structure. Binding could alter DNA activity, possibly by inhibiting transcription, for example. The structure of a single-stranded PNA is shown. Note that the backbone, a polymer of N-(2-aminoethyl)glycine (AEG) which can be made in prebiotic soups, is not charged, making it easier to bind to dsDNA. AEG polymerizes at 100°C to form the backbone.

In addition to changing the backbone, additional bases other than A, C, T, G, and U can be accommodated into dsDNA and ssRNA molecules (Brenner, 2004).

In a recent extension, Pinheiro et al have shown that 6 different foreign backbone architectures can produce xeno-nucleic acids (XNAs) that can be replicated by engineered polymerases which make XNAs from a complementary DNA strand, and a polymerase that can make a complementary copy of DNA from an XNA. XNAs can also be evolved as aptamers to bind specific target molecules. The investigators replaced the deoxyribose and ribose backbone sugar with xenoanalogs (congeners) including 1,5-anhydrohexitol (HNAs), cyclohexene (CeNA), 2′-O,4′-C-methylene-b-D ribose (locked nucleic acids - LNA), L-arabinose (LNA), 2′-fluoro-L-arabinose (FANAs) and threose (TNAs) as shown in the figure below.

**Figure: Xeno-nucleic acid sugar congeners**
Polymers of these XNA can bind to complementary RNA and DNA and as such act as nuclease-resistant inhibitors of translation and transcription.

Von Kiedrowski, in an experiment similar to the self-replication of peptides described above, has shown that a single stranded 14 mer DNA strand, when immobilized on a surface, can serve as a template for the binding of complementary 7 mers and their conversion to 14 mers. When released by base, this process can occur with exponential growth of the complementary 14 mers. (von Kiedrowski Nature, 396, Nov 1998). Ferris has shown that if the clay montmorillonite is added to an aqueous solution of diadenosine pyrophosphate, polymerization occurs to produce 10 mers which are 85% linked in a 5' to 3' direction.

Contributors

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