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RNA CATALYSIS, THE RNA WORLD AND ITS IMPORTANCE IN THE ORIGINS OF LIFE

Abstract

Life based on proteins (as catalytic molecules) and nucleic acids (as repositories of genetic information) is too complex to have originated in that form - it provides a very real 'chicken-and-egg' paradox. An 'RNA world' where RNA acts as both catalytic and informational molecule helps solve this problem, and probably existed over 3 billion years ago. This requires that RNA molecules have the capability to act as catalytic macromolecules, despite having a small fraction of the chemical variety of proteins. Yet RNA enzymes (ribozymes) exist in contemporary biology, and arguably the most important reaction in the cell - condensation of amino acids to form peptides - is still catalysed by RNA. It is an important test of the RNA world concept to explore how efficient RNA catalysis can be.

Proteins carry out phosphoryl transfer reactions either using metal ion catalysis, or using general acid-base catalysis. The same is true for ribozymes. The group I and II intron ribozymes are clearly metalloenzymes, whereas the nucleolytic ribozymes catalyse site-specific phosphodiester cleavage and ligation transesterification reactions using general acid-base catalysis. We have made a detailed study of the VS and hairpin ribozymes, where specific adenine and guanine nucleobases perform the roles of general acid and base respectively. We present a new crystal structure of the VS ribozyme, showing the organization of the catalytic center is consistent with our mechanistic studies. The organization and mechanism of these two ribozymes appear to be closely similar. Guanine nucleotides also play a key catalytic role in the hammerhead and GlmS ribozymes. Most interestingly, GlmS appears to employ a bound glucosamine-6-phosphate molecule as general acid.

The intrinsic rate of catalysis by the VS ribozyme is comparable to that of the enzyme ribonuclease A. However, catalytic mechanisms based on nucleobase-mediated general acid-base catalysis are inherently limited by the unfavorable pKa values of the natural nucleobases, compared to that of histidine in proteins. Thus ultimately once the ribozymes evolved the capacity to carry out protein synthesis it is likely that the proteins would have rapidly taken over the catalytic function.