RNA as Self-replicating Genetic Material

Peter Sazani
Molecular Biology
Massachusetts General Hospital / Harvard University
Wellman 9, 50 Blossom St, Boston MA 02114
USA
sazani@molbio.mgh.harvard.edu

Jack W. Szostak
Molecular Biology
Massachusetts General Hospital / Harvard University
Wellman 9, 50 Blossom St, Boston MA 02114
USA

Ribonucleic acids have a robust functional capacity, both as ligand binders (aptamers) and as enzymes (ribozymes). This discovery has led to the "RNA world" hypothesis, which postulates that RNA could have served as both the genetic and catalytic component of life before the incorporation of DNA and proteins. For RNA to serve both functions, it must have the capacity to catalyze its own replication in a way that allows for evolution in a Darwinian fashion. Certain ribozymes are capable of catalyzing RNA polymerization, but not to the extent that the ribozyme itself could be duplicated. Toward the latter goal, we have devised and executed an *in vitro* selection scheme for the isolation of efficient RNA polymerase ribozymes from a large pool of random RNAs. This scheme takes advantage of highly activated 2-methylimidizolide nucleotide monophosphates (2-MeImpN) as substrates, which more readily polymerize on a oligonucleotide template than traditional nucleotide triphosphates (NTP). Ribozymes that use 2-MeImpN will thus have an advantage, in that a smaller catalytic rate enhancement may be sufficient to synthesize relatively long RNA polymers. We identified clones that exhibit catalytic rate enhancement of 2-MeImpN polymerization. Further characterization and optimization of these sequences is ongoing.