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Previews

Evolution of Ribozymes in an RNA World

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Ribozymes (catalytic RNAs) were the center of a presumed RNA world in the early origin of life. In this issue, Lau and Unrau show evidence that an RNA world could have used a similar evolutionary pathway as most proteins do.

Among our earliest ancestors on earth were self-replicating RNA systems, according to the RNA world hypothesis. However, direct evidence of these 3billion-year-old RNA organisms is unlikely to be found. To find out how our distant past may have looked, several laboratories are attempting to recreate an RNA organism in the laboratory. Although the RNA organisms are still elusive, attempts to recreate them have taught us some aspects of the workings of an RNA world. In this issue, Lau and Unrau (2009) show evidence for a new evolutionary pathway that could have helped shape the RNA world.

There are three evolutionary pathways that can generate new ribozyme activities: (I) de novo from a random sequence, (II) from an existing ribozyme by changing its global structure, or (III) from an existing ribozyme by maintaining its global structure (Figure 1).

The first pathway would have been most important in the beginning of the RNA world, where ribozymes would have to appear de novo from more or less random sequences. The likelihood of these events depends on the information content of each ribozyme. An example for a small ribozyme is the recently discovered aminoacylating ribozyme with three conserved nucleotides (Chumachenko et al., 2009); this ribozyme would have been a frequent guest in an RNA world. However, each bit of sequence information makes the appearance of a larger ribozyme less and less likely (Carothers et al., 2004). An example for a medium-sized ribozyme is the class I ligase with 92 nucleotides. This ribozyme would appear only once in 3 x 10^{18} molecules of 220-nucleotide random RNA sequence (Ekland et al., 1995). Low probabilities like these present a major hurdle for many ribozymes to appear in an RNA world.

The second evolutionary pathway describes how an existing ribozyme evolves a different catalytic activity, with the parent and daughter ribozymes having completely different folds. Such a pathway was shown to exist by engineering all evolutionary intermediates between the self-cleaving HDV ribozyme and the class III self-ligating ribozyme (Schultes and Bartel, 2000). All of their evolutionary intermediates have either one fold and the corresponding catalytic activity, or the other fold with its corresponding activity. The intersection sequence can assume both folds. While this study showed that the pathway exists, a different study showed that this pathway is actually used by ribozymes; when an aminoacylase ribozyme was challenged to evolve into kinase ribozymes, the daughter ribozymes escaped the parent fold (Curtis and Bartel, 2005). RNA seems predestined to switch its global fold during evolution because most RNA sequences can fold into stable structures (Schultes et al., 2005). In other words, a given parental sequence has many evolutionary neighbors that contain a different catalytic activity but most of them fold into different global structures. This explains why at least some ribozymes prefer to escape their parental fold during evolution.

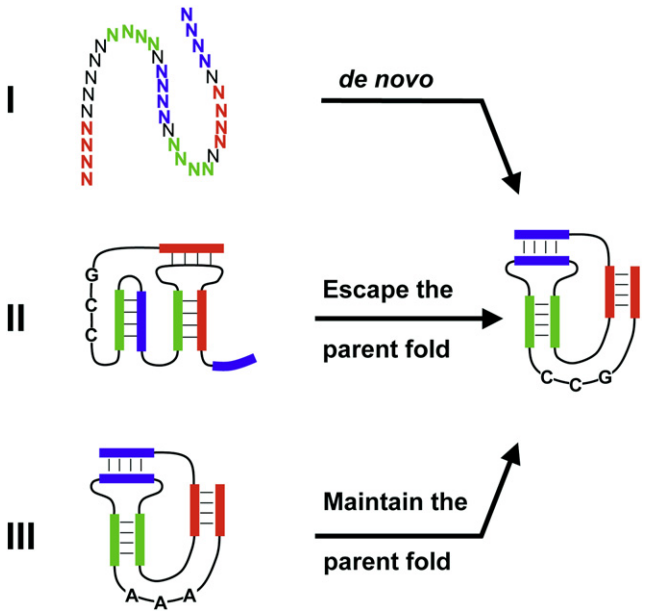

Figure 1. Three Evolutionary Pathways to Generate New Ribozymes
(I) De novo appearance: ribozymes can originate from random sequences, by amplification of the fittest.
(II) Escaping the parents: when new ribozyme activities evolve from an existing ribozyme, they tend to prefer a new global fold.
(III) Staying with the parent fold: in this issue, Lau and Unrau (2009) describe a ribozyme that could act as an evolutionary link between parent and daughter ribozymes that have maintained the same fold. Colors and letters are used to illustrate evolutionary transitions on the level of structure and sequence.

In the third pathway, a new ribozyme activity is generated from an existing ribozyme but the daughter ribozyme maintains the fold of the parent ribozyme. This evolutionary behavior has been known for proteins (Soding and Lupas, 2003): catalytic promiscuity allows the parent protein to catalyze a second reaction to a low extent, then evolution can improve the efficiency of this second activity (O'Brien and Herschlag,

1999). However, the only example of a ribozyme that indicates such an evolutionary path is the self-splicing group I intron, which is able to catalyze several closely related reactions (Forconi and Herschlag, 2005). A ribozyme was now found that catalyzes two very different reaction chemistries, both of which are coupling ribose and guanine covalently (Lau and Unrau, 2009). One reaction creates the N-glycosidic bond as seen in today's nucleotides, the other creates a stable connection via Schiff base chemistry and Amadori rearrangement. Therefore, this ribozyme could act as an evolutionary intermediate between two ribozymes, each specific for one reaction. Because this ribozyme probably has the same global fold for both catalytic activities, it is the best available evidence for ribozyme evolution via the third pathway. Future research may elucidate the evolutionary neighbors of this intersection sequence, and in vitro selection experiments could show that this evolutionary pathway actually takes place.

In contrast to RNAs, protein enzymes appear unable or unlikely to walk the first or the second evolutionary pathway because only very few amino acid sequences specify a stable fold. Therefore, the first peptides probably evolved using the third pathway by building onto an RNA scaffold before being able to fold independently (Soding and Lupas, 2003). Later evolutionary steps would have used these independently folding protein scaffolds to develop new catalytic activities (Seelig and Szostak, 2007).

Which of the pathways would have been dominant in an RNA world? Currently, the numbers of identified ribozymes are on the side of "escaping the parent fold" (Curtis and Bartel, 2005). However, the discovery of the promiscuous nucleotide synthase ribozyme (Lau and Unrau, 2009) shows that this picture is still emerging. Further in vitro evolution experiments are needed to determine when a ribozyme follows a specific evolutionary pathway. For example, the evolutionary decision could hinge on the reaction mechanisms or the evolutionary plasticity of an RNA structure. However, only after self-replicating and evolving ribozyme systems are found (Lincoln and Joyce, 2009) that are capable of generating ribozymes with new activities will we be able to pose these burning questions face-to-face with our strange RNA ancestors.

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REFERENCES

Carothers, J.M., Oestreich, S.C., Davis, J.H., and Szostak, J.W. (2004). J. Am. Chem. Soc. *126*, 5130–5137.

Chumachenko, N.V., Novikov, Y., and Yarus, M. (2009). J. Am. Chem. Soc. *131*, 5257–5263.

Curtis, E.A., and Bartel, D.P. (2005). Nat. Struct. Mol. Biol. *12*, 994–1000.

Ekland, E.H., Szostak, J.W., and Bartel, D.P. (1995). Science *269*, 364–370.

Forconi, M., and Herschlag, D. (2005). J. Am. Chem. Soc. *127*, 6160–6161.

Lincoln, T.A., and Joyce, G.F. (2009). Science *323*, 1229–1232.

Lau, M.W., and Unrau, J.P. (2009). Chem. Biol. *16*, this issue, 815–825.

O'Brien, P.J., and Herschlag, D. (1999). Chem. Biol. *6*, R91–R105.

Schultes, E.A., and Bartel, D.P. (2000). Science *289*, 448–452.

Schultes, E.A., Spasic, A., Mohanty, U., and Bartel, D.P. (2005). Nat. Struct. Mol. Biol. *12*, 1130–1136.

Seelig, B., and Szostak, J.W. (2007). Nature *448*, 828–831.

Soding, J., and Lupas, A.N. (2003). Bioessays *25*, 837–846.

Putative Fat Fighter Hits the Middle Man

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In this issue, Kamisuki and colleagues characterize fatostatin. This compound inhibits the activity of SREBPs, the master transcription factors of lipid homeostasis. This useful laboratory tool also improved the lipid profile of obese mice; does this have clinical implications?

Obesity is a growth industry, with no prospect of downsizing anytime soon. Associated with cardiovascular disease, hypertension, and diabetes, obesity has become a major health burden in the developed world and is becoming an increasingly prominent issue in developing countries as well. Despite the stigma often attached to lipids in the public consciousness, they are crucial for growth and development. For instance, fatty acids and cholesterol are essential for the synthesis of cell membranes and various signaling molecules.

At the molecular level, lipid levels are tightly regulated by the family of sterol-regulatory element binding proteins (SREBPs) (Goldstein et al., 2006). These transcription factors initially reside in the endoplasmic reticulum (ER), tethered to SREBP cleavage activating protein (SCAP). SCAP escorts SREBP to the Golgi apparatus, where SREBP is processed by site-1-protease (S1P) and site-2-protease (S2P) (Figure 1A). This releases the mature form of SREBP, which migrates into the nucleus to target the genes involved in

