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Chemistry World

The mother of all enzymes

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Scientists have uncovered the three-dimensional structure of what might be biology's first enzyme. This sheds light on the chemistry at a key moment in the origin of life, they argue.

The biggest challenge for origin-of-life scientists is to account for the first self-replicating molecule. Genes are needed to make proteins and proteins are needed to make genes, so which came first? The answer, some think, is ribozymes, RNA molecules capable of both coding and catalysis.

The discovery of such RNA enzymes in the 1980s led to the suggestion of an 'RNA World' that preceded the DNA and protein machinery that dominates life today. A few ribozymes still live on, perhaps relics of this bygone evolutionary era, but they are only capable of fairly feeble chemistry and certainly nothing like that required for self-replication.

This hasn't stopped molecular biologists from playing around in the laboratory, creating 'artificial' ribozymes to demonstrate that these molecules might have been up to more interesting chemistry. So far, researchers have managed to come up with several ribozymes that can join two fragments of RNA, the sort of fundamental reaction that would have been required of any self-respecting self-replicator.

One of these putative RNA World enzymes - the L1 ligase ribozyme - exclusively produces the 3' to 5' phosphodiester linkage that is characteristic of all biologically relevant nucleic acid polymers, says William Scott of the Center for the Molecular Biology of RNA at the University of California, Santa Cruz.

He and a colleague have solved the three-dimensional structure of the product of this reaction. This, they report in *Science*, suggests how the L1 ligase ribozyme carries out its catalytic trickery. The tertiary structure stabilizes a fold in the ribozyme, creating a pocket in which a magnesium ion can bind and coordinate three phosphates, says Scott. Interestingly, the ribozyme appears to use biochemical strategies that are well known in naturally occurring ribozymes.

The crystal structure reveals 'what may have been the first enzyme of biology, or at least the central enzyme of the RNA world,' said Gerald Joyce, professor of chemistry and molecular biology at The Scripps Research Institute in California. 'In the years ahead, we can expect to see the structure of other ligases, and eventually of polymerase and replicase RNA enzymes,' he predicts in a supporting paper.

The x-ray structure is 'very interesting', agrees Leslie Orgel of the Salk Institute in San Diego and one of three visionary thinkers who independently proposed the existence of ribozymes in the 1960s. 'It suggests one mechanism by which a relatively simple ribozyme could have facilitated RNA replication.'

Henry Nicholls

References

M P Robertson and W G Scott, *Science*, 2007, **315**, 1552
G F Joyce, *Science*, 2007, **315** 1507

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