Uncovering the mystery of DNA replication

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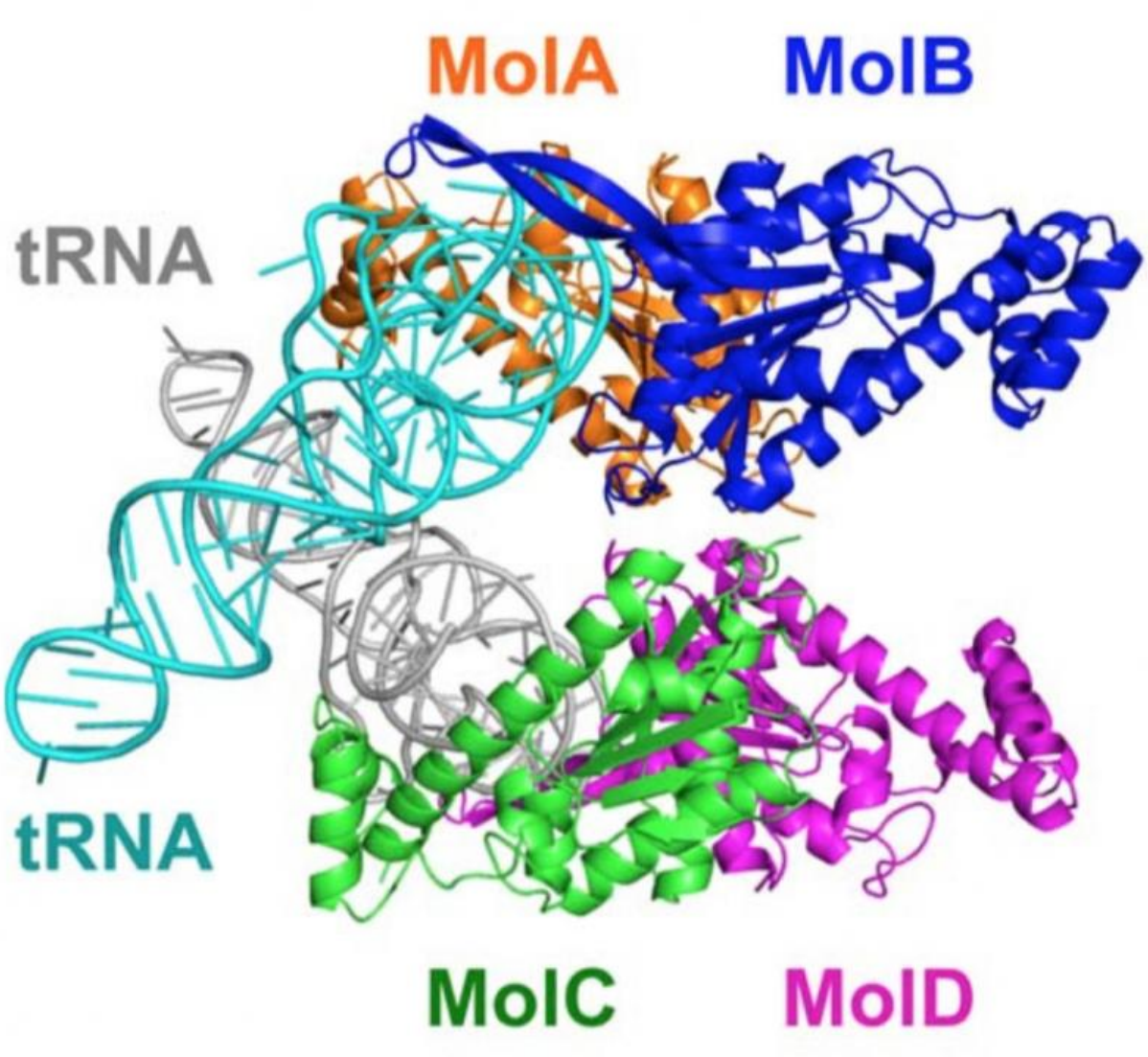

Structure of the TLP complex with tRNA revealed by X-ray crystrarography.
Credit: Kimura S. et al., Science Advances, Mar 25, 2016

By looking into the mechanism of a backward enzyme, scientists speculate why DNA replication always happens in the forward direction.

Nucleotide chains, such as DNA and RNA, are synthesized by making copies from other chains. The copying process always happens in a "forward" direction, from one particular end to the other. During the process, the two chains of a double-stranded DNA that will be copied are separated and aligned in opposite directions to each other, complicating matters. "When DNA is replicated, one of the two chains can be copied, or synthesized, in a continuous manner while the other chain is synthesized in many fragments that need to be joined later," says Min Yao from Hokkaido University. "One of the big questions in biology has been why cells don't have a reverse-direction enzyme so that both chains can be synthesized efficiently."

Recently, a group of enzymes was discovered, called Thg1-like proteins (TLPs), which were found to add nucleotides in the opposite direction. Examples of adding nucleotides in this direction are rare. TLPs are the exception and add nucleotides in the reverse direction to repair the "opposite end" of damaged RNAs. In a recently published study, Yao and her team used X-ray crystallography to uncover the structure of the TLP/RNA complex. This gave them insight into the complex mechanism that TLPs employ to add nucleotides in the reverse direction.

Their structural analysis revealed a two-step process: energy-supplying molecules are recruited and then nucleotide is added. The second step is also seen in the forward reaction. What was unique to the reverse reaction was the recruiting energy at the beginning. The enzyme apparently utilizes this energy recruitment to switch the direction from forward to reverse.

The team speculate that the reverse-direction enzyme is not used in DNA replication because it requires a structurally complicated process.

"By comparing the molecular mechanisms of forward and reverse reactions in more detail, we would like to fully understand the evolutionary context of DNA replication," says Yao.

More information: S. Kimura et al. Template-dependent nucleotide addition in the reverse (3'-5') direction by Thg1-like protein, *Science Advances* (2016). DOI: 10.1126/sciadv.1501397

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