

MIT biologists solve vitamin puzzle

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Solving a mystery that has puzzled scientists for decades, MIT and Harvard researchers have discovered the final piece of the synthesis pathway of vitamin B12-the only vitamin synthesized exclusively by microorganisms.

B12, the most chemically complex of all vitamins, is essential for human health. Four Nobel Prizes have been awarded for research related to B12, but one fragment of the molecule remained an enigma-until now.

The researchers report that a single enzyme synthesizes the fragment, and they outline a novel reaction mechanism that requires cannibalization of another vitamin.

The work, which has roots in an MIT undergraduate teaching laboratory, "completes a piece of our understanding of a process very fundamental to life," said Graham Walker, MIT professor of biology and senior author of a paper on the work that will appear in the March 22 online edition of *Nature*.

Vitamin B12 is produced by soil microbes that live in symbiotic relationships with plant roots. During the 1980s, an undergraduate research course taught by Walker resulted in a novel method for identifying mutant strains of a soil microbe that could not form a symbiotic relationship with a plant.

Walker's team has now found that one such mutant has a defective form of an enzyme known as BluB that leaves it unable to synthesize B12.

BluB catalyzes the formation of the B12 fragment known as DMB, which joins with another fragment, produced by a separate pathway, to form the vitamin. One of several possible reasons why it took so long to identify BluB is that some bacteria lacking the enzyme can form DMB through an alternate pathway, Walker said.

One of the most unusual aspects of BluB-catalyzed synthesis is its cannibalization of a cofactor derived from another vitamin, B2. During the reaction, the B2 cofactor is split into more than two fragments, one of which becomes DMB.

Normally, the B2-derived cofactor would assist in a reaction by temporarily holding electrons and then giving them away. Such cofactors are not consumed in the reaction.

Cannibalization of a cofactor has very rarely been observed before in vitamin synthesis or any type of biosynthetic pathway, says Michiko Taga, an MIT postdoctoral fellow in Walker's lab and lead co-author of the Nature paper.

"There are almost no other examples where the cofactor is used as a substrate," she said.

One early clue to BluB's function was that a gene related to it is located near several other genes involved in B12 synthesis in a different bacterium. Still, the researchers were not convinced that one enzyme could perform all of the complicated chemistry needed to produce DMB.

"It looked like a number of things had to happen in order to make the DMB," said Walker. "We originally thought that BluB might be just one of several enzymes involved in DMB synthesis."

Therefore, it came as a surprise when Taga isolated the BluB protein and showed that it could make DMB all by itself.

Nicholas Larsen, lead co-author and a former college classmate of Taga's now at Harvard Medical School, did a crystallographic analysis of the protein after Taga told him about her research over coffee one day. The protein structure he developed clearly shows the "pocket" of BluB where the DMB synthesis reaction takes place.

Still to be explored is the question of why soil bacteria synthesize B12 at all, Walker said. Soil microorganisms don't require B12 to survive, and the plants they attach themselves to don't need it either, so he speculates that synthesizing B12 may enable the bacteria to withstand "challenges" made by the plants during the formation of the symbiotic relationship.

More than 30 genes are involved in vitamin B12 synthesis, and "that's a lot to carry around if you don't need to make it," Walker said.

The full implications of the new research will probably not be known for some years, which is often the case with basic research, Walker said. "I've been in many other situations in research where we did something very basic and did not immediately realize the importance of it, and subsequently the implications were found to be much more broad-reaching," he said.

Other authors on the paper are Annaleise Howard-Jones, a postdoctoral fellow at Harvard Medical School, and Christopher Walsh, professor of biological chemistry and molecular pharmacology at Harvard Medical School.

Source: MIT

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