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Capturing Mother Nature at work: seeing how plants make vitamin B6

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Vitamins are essential for life. They perform a huge variety of tasks within metabolism, with many helping to promote biochemical reactions in our bodies. In general, we cannot make vitamins from scratch, and so we must obtain them from our diet. Plants and microorganisms can make these compounds *de novo*, and are therefore a good source of vitamins for humans, which is why it's essential that we incorporate such resources within a healthy, varied diet.

The study of vitamins is important for an understanding of health but it is also crucial in combating many infectious diseases. Ideally, treatments for microbial infections are designed to target essential functions of the microbes that do not overlap with what humans and animals have, i.e. killing the microbes while leaving our bodies free from harmful side effects. For this reason, drugs that target vitamin production in pathogens would be ideal candidates for new antibiotics - a goal of growing importance in a world of increasing antibiotic resistance - as humans cannot produce vitamins.

The B vitamins are a family of eight different vitamins. One of these vitamins, vitamin B_6, is involved in hundreds of biochemical reactions—more than any other known nutrient—and so vitamin B_6 deficiency is linked to a vast range of diseases from anaemia to epileptic-like convulsions in infants and depression in adults.

Biological organisms drive chemical reactions using enzymes, miniature protein machines, which speed up reactions. Plants make vitamin B_6 with an enzyme called vitamin B_6 synthase, which coordinates a long sequence of diverse reactions, much like a biochemical version of an industrial production line. This production line is split between two locations within the physical structure of the enzyme itself (called the active sites). This is unusual: most enzymes promote just one or two kinds of reactions, before passing their products on to another enzyme to continue the biochemical manufacturing process.

As most enzymes are much too small to see by eye, even with the most powerful light microscopes, scientists use a technique called X-ray crystallography to capture snapshots of these miniature machines at work. When water evaporates from a solution, the material that is left behind may stick together in a regular arrangement, forming a crystal. This is the process that produces salt crystals on rocks along a sea-shore, or sugar crystals around the rim of a honey jar. Enzymes can crystallise out of solution in this way too. Such crystals produce patterns when illuminated with X-rays, from which the 3D architecture of the enzyme can be determined. Solving 3D models of enzymes in the presence of the compounds they use for their reactions, e.g. metabolites, allow scientists to decipher how these machines work.

Researchers at the University of Geneva purified vitamin B_6 synthase found in the plant, thale cress (*Arabidopsis thaliana*), and determined its structure by X-ray crystallography. They discovered that it forms a double ring, containing 12 copies of the enzyme, resembling two doughnuts stacked on top of one another. They were able to see the two different sites where vitamin B_6 is manufactured in the enzyme; and, where they expect raw materials are brought in, and the products released.

Vitamin B_6 synthase uses three different chemical ingredients to build vitamin B_6. The researchers found that when they added two of these chemicals to the crystals, the enzymes that make up the crystals began the process of making vitamin B_6. However, in the absence of the third chemical ingredient, the biochemical production line stops, allowing scientists to see what the enzyme looks like part way through assembling vitamin B_6. Remarkably, at this exact point on the assembly line, they saw how vitamin B_6 synthase transfers the partly processed chemical ingredients from the first to the second location in the enzyme, the latter taking advantage of a single amino acid acting as a swinging-arm. This amino acid is located between the two assembly locations in the enzyme, and swings back and forth between them, collecting the processed chemical from the first site, and carrying it across to the second site.

The Geneva study was the first time that this single amino acid swinging-arm mechanism had been observed within an enzyme. More recently, these observations were corroborated by an independent study conducted by researchers based at the Universities of Southampton in the UK and Heidelberg in Germany[1].

The novel results of this research are helping scientists understand how enzymes coordinate long sequences of complex biochemical reactions, as well as improving our understanding of the production of vitamins, essential for health and fitness, and a potential target for the development of new antibiotics.

ADDITIONAL REFERENCE:

1. Rodrigues *et* al., Lysine relay mechanism coordinates intermediate transfer in vitamin B6 biosynthesis, Nature *Chemical Biology* (2017)