Scientists find missing link to understand how plants make vitamin C

April 28 2007

Vitamin C is possibly the most important small molecule whose biosynthetic pathway remained a mystery. That is until now.

A group of Dartmouth and UCLA researchers, who normally work on genes involved in aging and cancer in animals, discovered the last piece of the puzzle, they report in a study published online April 26 in the *Journal of Biological Chemistry*.

Dr. Steven Clarke of the UCLA Molecular Biology Institute and the Department of Chemistry and Biochemistry explains, “We were working on an interesting gene in worms.” One insight led to another until, “We uncovered the last unknown enzyme in the synthesis of vitamin C in plants,” said Dr. Charles Brenner of Dartmouth Medical School’s Norris Cotton Cancer Center and Department of Genetics.

An essential vitamin for people, vitamin C is well known as an antioxidant and enzyme cofactor. Humans lost the ability to make vitamin C and need to take it up from dietary sources, particularly from plants.

Only in 1998 was a biosynthetic pathway proposed to explain how plants make vitamin C. Research since then has confirmed much of the pathway, although the gene responsible for the seventh step of the proposed 10-step pathway from glucose to vitamin C remained unknown.

The work began in an effort to understand the role of a gene in C. elegans, a tiny worm used as a model for aging studies by researcher Tara Gomez in Clarke's UCLA laboratory. The sequence of the gene suggested that it is related to a family of genes altered in cancer, termed HIT genes, that Brenner studies at Dartmouth.

Collaboration between the two laboratories revealed similarity of the worm gene to the product of the VTC2 gene of Arabidopis thaliana, a small roadside plant whose genetics have been well studied. Mutations in this plant gene had been previously linked to low levels of vitamin C. So the hunt was on to determine how its product would contribute to vitamin C synthesis.

The researchers, led by Brenner and Clarke, reconstituted in test tubes the long mysterious seventh step in vitamin C synthesis, a reaction they describe as the first committed step. They liken the first six steps in vitamin C synthesis to a roadmap with multiple possible routes from glucose to a variety of cellular compounds. Once the product of the sixth step, a compound called GDP-L-galactose, can take the exit marked VTC2, however, the atoms are reconfigured toward making vitamin C, specifically, and little else. The remaining three steps, like a curving driveway, require some turns but no real choices and no backing-up.

Through efforts led by UCLA postdoctoral fellow Dr. Carole Linster, the plant VTC2 enzyme was expressed and purified from bacteria. After preparing their own GDP-L-galactose, the team showed that VTC2 is responsible for the long sought seventh step in vitamin C synthesis.

Since enzymes catalyzing the first committed steps of a pathway represent sites of biological regulation, the researchers hope their discovery may lead to new strategies for increasing vitamin C levels in food crops, which could mean more nutritious foods as well as potentially higher crop yields. They still need to find out what

VTC2-related genes do in animals and how these genes may relate to aging and cancer.

Source: Dartmouth Medical School