Control of metabolism in changing conditions

Andrew D Hanson, Professor at the University of Florida, USA, is investigating the metabolic biochemistry of plants, with a particular emphasis on B vitamin metabolism. His current project uses maize and exploits cutting-edge genetic, genomic, biochemical, and metabolic modelling approaches to gain a thorough understanding of the metabolic pathways involved in B vitamin synthesis and how these pathways interact with environmental stresses.The results will inform synthetic plant biology and determine how plant vitamin metabolism might be improved.

The word vitamin originates from the term 'vitamine', meaning vital amine, and was first coined in 1912 following the discovery of thiamin as an essential human nutrient found in rice. However, vitamins are a much more diverse group of organic molecules than first thought and their name suggests. In fact, most are not even amines. Some, such as vitamin E, are fat-soluble and act as vital antioxidants, while other water-soluble vitamins (the B vitamins) play crucial roles facilitating biochemical reactions.

GOOD FOR PLANTS, GOOD FOR PEOPLE

The presence of B vitamins in plants is not only essential for the plants themselves, but also to humans. This is because, unlike plants, humans cannot make their own vitamins, and therefore need to rely on dietary sources.

Crucial to our health, plants provide the ultimate source of much of the human B vitamin supply. These vitamins are essential as they provide the building blocks for the cofactors of enzymes that are central to our metabolic processes. Without a healthy supply of these cofactors, metabolism begins to malfunction and organism vigour and viability decline. Hanson's current project focuses on the B vitamin/cofactor network, investigating how B vitamins are made and how B vitamin deficiency affects gene expression and metabolism in plants. His team are also exploring how B vitamin deficiency may be triggered by environmental stresses, discovering key insights that could inform synthetic biology – potentially enhancing both crop stress tolerance and human vitamin supply.

As vitamins are usually synthesised by plants in such small amounts, the associated biochemical pathways and enzyme reactions used to be very difficult to study. Now, with the advent of increasingly powerful biological tools, Hanson and other researchers are finally able

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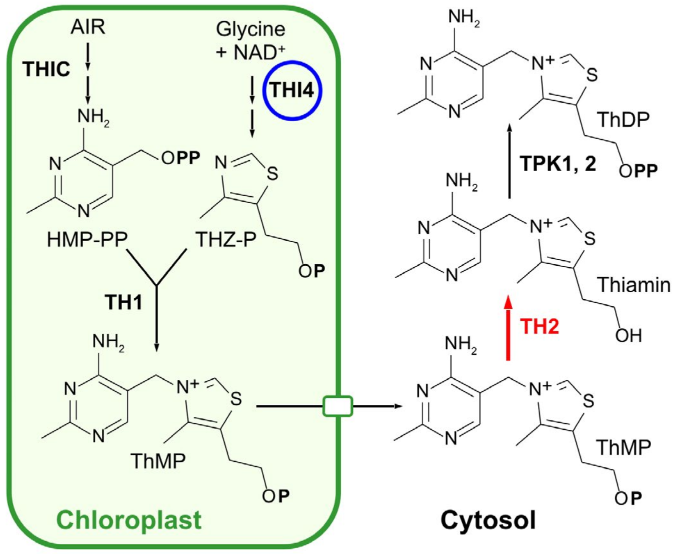
to dissect vitamin biosynthesis in plants at a molecular level. The type of knowledge gained is of crucial importance for informing crop improvement and eradicating widespread human malnutrition.

DEVELOPING A PARTS LIST

The first step in establishing a sufficient supply of B vitamins in both plants and humans is to discover exactly how plants produce B vitamins. Hanson and his team have been precisely mapping the metabolic pathways and genes involved, uncovering components that had, until now, remained hidden. Part of this effort was to create a set of vitamin B-deficient maize lines, from which they obtained transcriptome and metabolome data through a systems approach. The researchers are now using the information to build – for the first time in plants – metabolic models that include all B vitamins and their cofactors as functional components. Such models will be able to predict – and to help understand – the impact of vitamin deficiency on the entire plant metabolic network.

Through this work, Hanson and his team discovered one of the key genes essential for the synthesis of vitamin B1 (thiamin) which gives rise to a cofactor crucial for a wide variety of metabolic enzymes. This enzyme had remained undiscovered for so long that many scientists doubted that an enzyme specific to this step existed at all. However, Hanson and his team have now established that plants possess a ThMP (thiamin monophosphate) phosphatase enzyme, encoded by the *TH2* gene, dedicated specifically to the hydrolysis of ThMP to thiamin. Their experiments have also revealed that a depletion of this enzyme can lead to severe symptoms of vitamin deficiency in plants.



The plant thiamin biosynthesis pathway is split between chloroplasts and cytosol. The step catalysed by TH2 is shown in red. The suicide enzyme THI4 is circled in blue

Corn fields scorched by drought in Castroville, Texas during the 2011 drought

MAINTAINING VITAMIN CONTENT AND CROP PRODUCTIVITY DURING WEATHER CHALLENGES

B vitamin deficiency affects millions of people worldwide. Although the problem persists even in developed countries, it is the five billion people in developing countries who are most affected. This is primarily due to suboptimal levels of vitamins in most staple crops (including wheat, rice, maize, potato and cassava), combined with a heavy reliance on a single staple crop by many populations. Vitamin losses due to crop processing following harvesting make the situation even worse. Solving these problems remains one of the greatest challenges for human nutrition across the globe.

It has long been suspected that the efficiency with which plants make their essential vitamins depends on environmental factors. More specifically, that when exposed to climatic stresses such as heat, high salinity and drought, plants can fail to make B vitamins. This would lead to metabolic defects that result in severe loss of crop yield and quality. However, prior to Dr Hanson's project, the hypothesis that stress causes B vitamin deficiency had never been thoroughly investigated.

Dr Hanson's team has been looking deeper, trying to answer whether – and how – environmental stresses cause B vitamin deficiency. Taken with other information, their work points to maintaining thiamin levels as being especially troublesome. Thiamin biosynthesis is extraordinarily energy intensive. Enzymes all have finite life-spans; however, these can vary greatly in length. One of the enzymes now identified to play a key role in thiamin synthesis (THI4) is a so-called "suicide enzyme".

Synthetic biology has great potential to accurately install modified pathways with unrivalled specificity, far superior to conventional genetic engineering methods

A suicide enzyme is permanently inactivated when it carries out its catalytic role, so that each enzyme molecule catalyses only one reaction before needing to be replaced. Another of the enzymes in the pathway (THIC) can probably achieve only a maximum of five catalytic turnovers during its life-span. Therefore, plants must constantly invest in the replacement of these enzymes, requiring the production and breakdown of more than one whole protein molecule per molecule of thiamin.

This can quickly become problematic when a plant is under stress – research has shown that one of the responses to stress is to shut down protein production. This, combined with the fact that a dozen absolutely central metabolic enzymes require a thiamin-derived cofactor, leads to a multitude of problems. If just one single enzyme begins to run out of cofactor, all the corresponding reactions slow down, leading to a domino-like cascade of effects that further exacerbate any stress-derived injury. The dependence on protein synthesis would explain why the thiamin pathway, in particular, may be so sensitive to environmental stresses, resulting in a high susceptibility to thiamin deficiency and its detrimental impacts.

These findings are driving Hanson's team to explore alternative, more stable and efficient pathways to produce thiamin – in other words, to rethink how thiamin could be made and then replace the natural pathway with the rethought one. Synthetic biology has great potential to accurately install such modified pathways with unrivalled specificity, far superior to conventional genetic engineering methods. Although the application of synthetic biology in plants is in its relative infancy, the first plant synthetic circuits for metabolite production have been successfully created. This shows great promise for engineering pathways, with far reaching potential benefits for human health.

Q&A

What inspired you to work on unravelling the details of the B vitamin pathway in plants in particular?

B vitamins are at the heart of metabolism; without them metabolism would grind to a halt. But they are also easily destroyed, so cells have to be extraordinarily good at maintaining their levels under all circumstances. This combination of centrality and fragility is fascinating – and crucial for agricultural productivity.

What do you think is the greatest accomplishment of your project thus far?

Realising that thiamin is a special case among the B vitamins, because it is at the same time very susceptible to being destroyed and takes an exceptional amount of precious energy to make.

How is the data you are gathering being made available for the benefit of plant science research across the globe?

We publish our work in widely read scientific journals and present talks and posters at international conferences, as well as getting the message out on social media.

What do you think is the biggest challenge you still face in achieving the aims of your project?

Securing adequate funding and finding the right human resources.

What are your hopes for the future of your research?

That it will lay the groundwork needed to use synthetic biology to reconfigure plant metabolism in radical new ways that will benefit agriculture.

B vitamins' combination of centrality and fragility is fascinating – and crucial for agricultural productivity

Detail

RESEARCH OBJECTIVES

Andrew Hanson's research interests include metabolic biochemistry, plant vitamin metabolism, comparative genomics, and synthetic biology. His latest research is laying the groundwork for synthetic biology approaches to manipulate B vitamin synthesis.

FUNDING

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COLLABORATORS

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BIO

After BSc and PhD degrees (University of London), working in industry, and postdoctoral training in France and the USA, Andrew pursued research in plant and microbial metabolic biochemistry in the USA and Canada. He holds the CV Griffin Sr. Eminent Scholar Chair in the Horticultural Sciences Department, University of Florida.

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