Trends in **Parasitology**



Spotlight

Cross-kingdom vitamin B5 biosynthesis and cvst nematode susceptibility

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Vitamin deficiencies are known to cause disorders in human beings. Siddique et al. discovered that vitamin B5 biosynthesis in cyst nematodes requires steps in their host plants. Disruption of an Arabidopsis thaliana 'susceptibility gene', which is involved in the production of vitamin B5 precursors, results in reduced parasitism.

Plant parasitic nematodes pose a major threat to global food security. Over 4100 species of plant parasitic nematodes collectively cause an annual crop loss of more than US\$80 billion globally [1]. As obligate biotrophs, cyst nematodes make huge negative impacts on crop production by causing severe disease in a wide range of plant species. A cyst, which is produced from the body wall of a dead female and contains hundreds of eggs, can help cyst nematodes to survive in the soil, even in the absence of host plants, for up to 20 years, making it extremely difficult to control these sedentary endoparasites.

History has already told us repeatedly that one of the most efficient ways to control plant diseases is to use resistant crops. Resistance can be obtained not only through the expression of a resistance gene but also through the loss of a susceptibility gene. Although transgenic plants that overexpress plant resistance genes are likely to offer robust immunity to plants, constitutive activation of plant

defense could compromise crop yield. Moreover, the expression of these genes may also be unstable due to gene silencing. In contrast, loss of a disease susceptibility gene is known to provide plants with durable and broad-spectrum resistance against infection by pathogens [2].

Recently, Siddique et al. found that knocking out an Arabidopsis thaliana susceptibility gene AtPANB1, which is involved in vitamin B5 biosynthesis, makes A. thaliana more resistant to cyst nematodes [3]. This paper is a product of collaborative studies from a large consortium of 33 scientists from 18 different units. The authors focused on beet cyst nematode Heterodera schachtii because it infects sugar beets and brassicaceous plants, including the model plant A. thaliana, and it is a close relative of soybean cyst nematode, which results in an annual loss of more than US \$1 billion in the USA alone [4]. Siddique et al. assembled a high-quality genome sequence of H. schachtii, which serves as a platform for a reference transcriptome resource covering the entire life cycle of H. schachtii on its host plant A. thaliana (Figure 1A) [3].

To analyze the host and nematode gene expression over time during different stages of an infection cycle, the authors focused on five discrete expression clusters at different time points from 10 h to 24 days post infection (Figure 1A) [3]. Through large-scale analyses, the authors identified 'lineagespecific' nematode genes such as effector genes that modulate the expression of 'widely conserved' plant genes such as genes involved in the development of cyst nematode feeding sites (Figure 1A). Siddique et al. then used KEGG Automatic Annotation Server to annotate host and parasite metabolic pathways and identified 1998 KEGG Orthology (KO) terms that are shared by the host and the parasite [3]. They further manually surveyed pathways that are incomplete in the parasite but completed by the host plants.

The authors found only two genes in the genome of H. schachtii that are involved in the last step of vitamin B5 (pantothenate) production (Figure 1B) [3]. Therefore, the production of vitamin B5 in the beet cyst nematodes requires several steps in the host plant. These two putative H. schachtii PANC genes are different from their plant counterparts. Instead, they share similarity with bacterial genes, suggesting that they are acquired by H. schachtii through horizontal gene transfer from a bacterium. This type of trans-kingdom vitamin B5 biosynthesis helps to avoid feedback or feedforward inhibition and makes sure that the rapidly developing cyst nematodes receive sufficient vitamin B5.

Vitamin B5, also called pantothenic acid, is the precursor of coenzyme A, which is essential in all microorganisms [5]. In Arabidopsis plants, AtPANB1 and AtPANB2 convert α-ketolsovalerate to α-ketopantoate in the penultimate pathway, which is the last upregulated step in vitamin B5 biosynthesis during beet cyst nematode infection [3]. Due to a reduced supply of vitamin B5 precursors, T-DNA knockout plants of the AtPANB1 gene, which is highly induced during cyst nematode infection, show reduced susceptibility to this parasite (Figure 1B) [3]. The authors observed smaller syncytia, smaller females, and smaller cysts, which support a reduced number of eggs, in atpanb1-1 mutant plants compared with the wild-type plants [3]. Overexpression of AtPANB1 in atpanb1-1 mutant plants restores susceptibility to beet cyst nematodes. Importantly, there were no major growth defects in the atpanb1-1 mutant plants with the exception of a slight delay in flowering time. The cyst nematode gene HsPANC is required for the cyst nematode parasitism while the A. thaliana gene AtPANC is not, indicating that cyst nematodes indeed carry a functional PANC gene, which catalyzes the last step of vitamin B5 production in cyst nematodes.



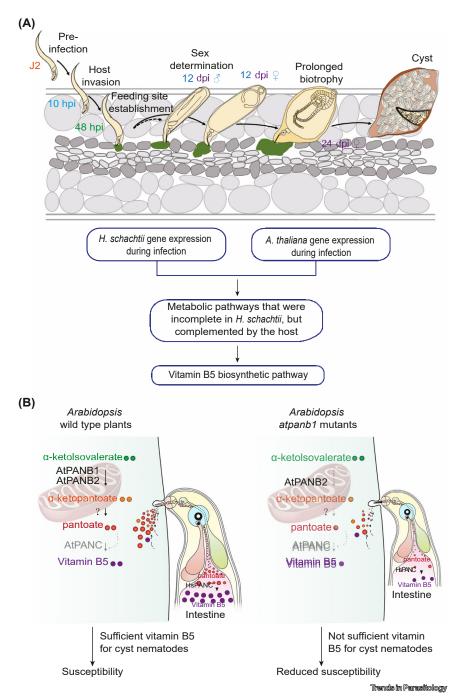


Figure 1. Cross-kingdom vitamin B5 biosynthesis and generation of cyst nematode resistant Arabidopsis thaliana through the loss of a susceptibility gene. (A) By analyzing the transcriptome of the beet cyst nematode Heterodera schachtii and A. thaliana in the infection site covering all major stages of the infection cycle, Siddique et al. identified differentially expressed 'lineage-specific' parasitic genes and 'widely conserved' host genes. By examining metabolic pathways that are incomplete in the nematodes but complemented by the host, the vitamin B5 biosynthetic pathway was identified. (B) The biosynthesis of vitamin B5 in H. schachtii requires precursors in A. thaliana. H. schachtii only harbors two PANC genes involved in the last step of vitamin B5 biosynthesis. The PANB1 and PANB2 genes, which are required for the early steps in (Figure legend continued at the bottom of the next page.)

This paper represents an excellent example that knowledge generated through big data analysis can guide us to develop effective strategies for reducing crop yield losses [3,6]. Vitamin B1, B5, and B7 biosynthetic genes were found in the soybean cyst nematode Heterodera glycines [7]. In addition, vitamin B1, B5, and B6 biosynthetic genes have been reported in yellow potato cyst nematodes [8]. Furthermore, vitamin B5 biosynthetic gene PANC has been found in the southern root-knot nematode Meloidogyne incognita and in a pathogenicity island in the northern rootknot nematode Meloidogyne hapla [7]. These genes are also likely to be acquired by horizontal gene transfer from a bacterium. Similar to H. schachtii, H. glycines carries only the last key step of the vitamin B5 and B7 biosynthetic pathway, suggesting that H. glycines requires precursors from its host plants to produce vitamin B5 and B7. Both vitamin B5 and B7 are essential for all life. Vitamin B7, also known as biotin, functions as a carboxyl carrier for biotin-dependent carboxylases, which catalyze key reactions in carbohydrate, fats, and amino acid metabolism. It would be interesting to find out whether it is possible to knockout a vitamin B1, B5, B6, or B7 biosynthetic gene in their host plants to enhance the resistance to the parasitic nematodes. Gene editing through CRISPR-Cas9 technology could be used as a powerful tool for generating these mutants. It will also be important to find out whether the deletion of these vitamin B5 or B7 biosynthetic genes affects the growth and yield of these plants or crops.

The protozoan parasites Toxoplasma gondii, Cryptosporidium parvum, Perkinsus marinus, and the notorious malaria parasite Plasmodium falciparum also contain vitamin B1, B5, and B6 biosynthetic genes [9], while human beings obtain these vitamins through diets. Therefore, molecules that target these vitamin biosynthetic pathways could be used as drugs to specifically interfere with

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the development of these parasites without major side effects on human beings.

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Declaration of interests

The authors declare no competing interests.

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References

- 1. Jones, J.T. et al. (2013) Top 10 plant-parasitic nematodes in molecular plant pathology. Mol. Plant Pathol.
- 2. Pavan, S. et al. (2010) Loss of susceptibility as a novel breeding strategy for durable and broad-spectrum resistance. Mol. Breed. 25, 1-12
- 3. Siddique, S. et al. (2022) The genome and lifestage-specific transcriptomes of a plant-parasitic nematode and its host

- reveal susceptibility genes involved in trans-kingdom synthesis of vitamin B5. Nat. Commun. 13, 6190
- 4. Wrather, J.A. and Koenning, S.R. (2006) Estimates of disease effects on soybean yields in the United States 2003 to 2005. J. Nematol. 38, 173-180
- 5. Gheita, A.A. et al. (2020) The potential role of B5: a stitch in time and switch in cytokine. Phytother. Res. 34, 306-314
- 6. Piquerez, S.J. et al. (2014) Improving crop disease resistance: lessons from research on Arabidopsis and tomato. Front. Plant Sci. 5, 671
- 7. Craig, J.P. et al. (2009) Evidence for horizontally transferred genes involved in the biosynthesis of vitamin B(1), B(5), and B(7) in Heterodera glycines. J. Nematol. 41, 281-290
- 8. Eves-van den Akker, S. et al. (2016) The genome of the yellow potato cyst nematode, Globodera rostochiensis, reveals insights into the basis of parasitism and virulence. Genome Biol. 17, 124
- 9. Muller, S. and Kappes, B. (2007) Vitamin and cofactor biosynthesis pathways in Plasmodium and other apicomplexan parasites. Trends Parasitol. 23, 112-121