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Bioactive metabolites: The double-edged sword in your food

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esxM affects both types of migration and that bacteria with the truncation mutation might not spread as efficiently throughout the lungs. This could have deleterious impacts on bacterial fitness by decreasing the size of cough aerosols. How might such a defect be compensated? While the full-length gene could promote initial invasion and spread throughout the lungs, the truncated *esxM* could retain fitness by enabling bacteria to reach higher densities within individual lesions that eventually erode into the airways (Figure 1). An initial means of investigating the impact of *esxM* truncation on pulmonary disease would be to determine whether TB caused by bacteria encoding full-length *esxM* are associated with distinct patterns on chest radiography. Intriguingly, L6 has previously been associated with more extensive pulmonary disease relative to TB due to L4.¹⁰

Overall, the study by Saelens et al. demonstrates the power of approaches that integrate hypothesis generation via comparative genomics with hypothesis testing using multiple experimental and analytic modalities.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Bioactive metabolites: The double-edged sword in your food

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Food contains many different bioactive metabolites that interact with human metabolism. Many of these have health benefits, but in this issue of *Cell*, researchers show that the gut microbiome can convert a bioactive metabolite to metabolites that may elevate the risks of developing cardiovascular disease.

Ergothioneine (EGT) is a naturally occurring amino acid containing a thiol-group, which provides the molecule with anti-oxidative properties. Some bacteria and

fungi can biosynthesize EGT,¹ whereas plants and animals must acquire this molecule from the soil or their diet. Bacteria and fungi synthesize EGT by two

different pathways.² In both pathways, the free amino group of histidine is methylated, resulting in trimethyl-histidine or histidine betaine, followed by the addition



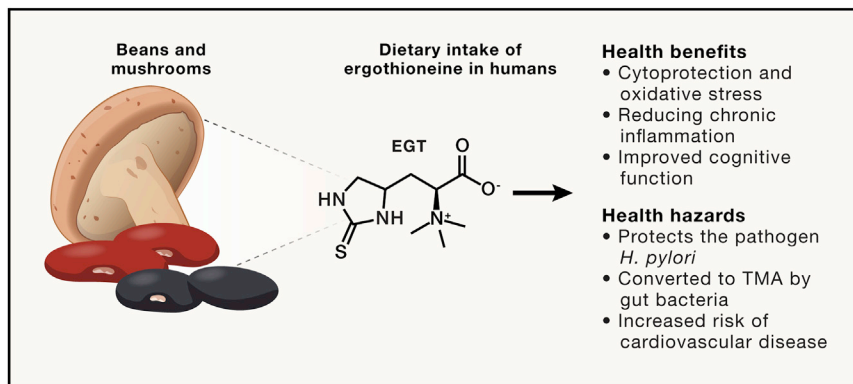


Figure 1. Bioactive metabolites in our food have both health benefits and health hazards
Humans obtain ergothioneine (EGT) through eating kidney beans, black beans, and mushrooms, which all have enriched levels of this compound. EGT has several health benefits. It is cytoprotective, protecting our cells against oxidative stress. It can reduce chronic inflammation and potentially improve cognitive function. EGT, however, also has a number of potential health hazards. Many different bacteria that live in the human gut, including *H. pylori*, can take up EGT. *H. Pylori* can use EGT for oxidative protection. Some bacteria convert EGT to trimethylamine (TMA), which increases the risk of cardiovascular disease.

of a sulfur atom from cysteine to the imidazole ring of histidine. As the sulfur is bound to the imidazole ring, EGT is a so-called tautomer, meaning that it can be present both in a thiol and thione form, which ensures that the molecule is quite stable and protected from oxidation at physiological pH. EGT has been found to have several health benefits,¹ largely ascribed to its antioxidant properties. The fact that animals have evolved a highly selective sodium symporter (OCTN1) for uptake of EGT points to its important role in animal metabolism. It is therefore a prominent example of the many different bioactive metabolites that are present in our food.

Even though EGT is synthesized by a range of different bacteria and fungi, there are still many microorganisms that do not have the capability to produce this compound. In this issue of *Cell*, Dumitrescu et al. provide a targeted metabolomics study of the human pathogen *Helicobacter pylori*.³ They search specifically for low-molecular weight thiols and find that *H. pylori* contains EGT. However, this bacterium does not have the biosynthetic capability to synthesize EGT, raising the question of how it acquires EGT. The authors show that it can take up EGT from the surrounding medium, but the *H. pylori* genome does not encode any OCTN1 orthologs. Because EGT resembles the bacterial osmolyte glycine betaine, where glycine contains three

methyl groups, the authors search for *H. pylori* genes that were annotated as hypothetical glycine betaine transporters. By analyzing the EGT content in strains with deletion of either of the two hypothetical glycine betaine transporter genes they identify here, they find that *H. pylori* requires *HPG27_777* for EGT uptake. This gene resides in a two-gene operon with the other gene in the operon (*HPG27-778*) encoding conserved motifs characteristic of ABC transporters. The authors demonstrate that *HPG27-778* is also essential for EGT transport. Thus, the EGT transporter is encoded by both genes in this operon that the authors name *EgtUV*, and it is an ABC transporter that can actively transport EGT against a concentration gradient using ATP hydrolysis to drive the process. By using this transporter, *H. pylori* can import host-derived EGT and use this molecule for oxidative protection. In fact, expression of the transporter confers *H. pylori* a competitive colonization advantage *in vivo*,³ and it is hereby an example of how *H. pylori* has evolved its metabolism to benefit from anti-oxidative metabolites that humans obtain through their diet.

Following identification of *EgtUV* in *H. pylori*, Dumitrescu et al. perform BLASTp searches for homologs in other bacteria and discover that the same operon is present in numerous bacterial phyla, including Firmicutes, Proteobacteria, and Actinobacteria.³ From this

analysis, they report putative EGT transporters in many human pathogens, including *Salmonella enterica* and *Clostridium difficile*, as well as in many members of the human gut microbiome. To evaluate if *EgtUV* homology predicts EGT transport, they test for the presence of EGT in bacteria that either contain *EgtUV* or lack *EgtUV* in their genome. Also, they note that disruption of the operon in *Escherichia coli* and *S. enterica* prevent bacterial uptake of EGT. If EGT is taken up by gut bacteria, do they convert it into other metabolites? Many dietary compounds containing quaternary amino groups, such as choline, glycine, betaine, and carnitine, can be metabolized to trimethylamine (TMA) by gut bacteria.⁴ And indeed, researchers here show that gut bacteria convert EGT to TMA.³ TMA can be oxidized by monooxygenases in the liver to trimethylamine *N*-oxide (TMAO), the presence of which in the blood is associated with increased risks of cardiovascular diseases.⁵ In fact, dietary supplementation of mice with TMAO promotes atherosclerosis, possibly through upregulation of macrophage scavenger receptors.⁵

The findings that *H. pylori* and many other bacteria, both pathogens and commensals, can take up EGT from the environment clearly points to the complex interplay between diet and metabolism in both human and bacterial cells living in the human body.⁶ Many bioactive metabolites present in our food, including EGT, can have multiple positive effects on our metabolism, either as antioxidants or regulators of human metabolism (Figure 1). This has led to an increasing market for dietary supplements containing bioactive metabolites. However, as the study from Dumitrescu et al. shows, the effect of EGT—and possibly many other bioactive metabolites—might well be more complex because it can interact with both pathogens, such as *H. pylori*, and commensals in the gut microbiome, and thereby result in negative effects (Figure 1). Specifically, EGT uptake can support *H. pylori* infection as it provides a competitive advantage for the bacterium, and it can be converted to TMAO by combined metabolism of gut bacteria and the liver, which significantly increases the risks of cardiovascular diseases. This further supports the notion that a holistic view of our metabolism is

important. Our diet affects our metabolism. So too do the myriad metabolic processes of our own cells and those of the millions of bacteria that live in our mouth, stomach, and gut.⁶ In the future, it will be important to map the metabolite interactions between food intake and the gut microbiome composition, and thereby enable prediction of how the gut microbiome can engage in converting bioactive metabolites in our food to compounds that cause increased risk of disease development. This is a complex endeavor. However, through combined blood metabolome and gut microbiome analyses of very large cohorts and standardizing data collection, we will gain greater mechanistic insight into how the gut microbiome impacts human health.

DECLARATION OF INTERESTS

J.N. is a shareholder in Chrysea, Inc. that produces bioactive metabolites through synthetic biology.

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CAR T therapy extends its reach to autoimmune diseases

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CAR T therapy has revolutionized the treatment of hematologic cancers. In their recent *Nature Medicine* paper, Mackensen et al. report the use of CAR T cells to treat systemic lupus erythematosus in five patients. This provides enthusiasm to further explore CAR T therapy beyond oncology.

Engineering chimeric antigen receptors (CARs) into T cells has been transformative for the field of oncology. This approach allows these synthetic immune cells to recognize and eliminate cancer in a powerful and precise manner. CAR T therapy has shown remarkable and lasting therapeutic effects in leukemia, lymphoma, and multiple myeloma.¹ This has resulted in multiple regulatory approvals over the last 5 years. These exciting results have incited substantial effort to expand CAR T therapy throughout cancer treatment and beyond. Recently, Mackensen et al. reported using CAR T therapy to treat five young adults diag-

nosed with systemic lupus erythematosus (SLE).²

SLE is an autoimmune disease where the body recognizes self-antigens as foreign, resulting in the activation of autoreactive B and T cells. This self-targeting can result in fatigue, inflammation, and in severe cases, death. Several clinical strategies target B cells with therapeutic effects; however, these approaches are limited as severe forms of SLE are resistant to treatment and no long-term strategy to achieve drug-free remission has been realized. CAR T cells targeting CD19 have shown ability to eliminate pathologic B cells in cancer, leading to

lasting remissions and even cures (Figure 1). We, and others, have proposed CAR T therapy may have applications in treating autoimmune diseases such as SLE.^{3,4} Building on an exciting case report from last year where CD19 CAR T products were repurposed to deplete B cells in a patient with SLE,⁵ Mackensen et al. expand on this and report this approach in five patients (Figure 1). In all five patients, these CAR T cells engrafted, expanded, and eliminated B cells. This was accompanied by a resolution of SLE symptoms in the three months following CAR T infusion. Impressively, these patients have been declared