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Worms, bacteria and micronutrients: an elegant model of our diet

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Abstract

Micronutrients are required in small proportions in a diet to carry out key metabolic roles for biomass and energy production. Humans receive micronutrients either directly from their diet or from gut microbiota that metabolize other nutrients. The nematode *Caenorhabditis elegans* and its bacterial diet provide a relatively simple and genetically tractable model to study both direct and microbe-mediated effects of micronutrients. Recently, this model has been used to gain insight into the relationship between micronutrients, physiology and metabolism. In particular, two B-type vitamins, vitamin B12 and folate, have been studied in detail. Here we review how *C. elegans* and its bacterial diet provide a powerful interspecies systems biology model that facilitates the precise delineation of micronutrient effects and the mechanisms involved.

Keywords

C. elegans; micronutrients; vitamin B; folate; gut microbiota; metabolism

Diet and micronutrients

An organism can be conceptualized as a living system that receives dietary inputs and converts these into biomass for reproduction, cell renewal or wound healing, and into energy to sustain daily tasks at the cellular and organismal levels. The diet consists of macronutrients that are consumed in large amounts and micronutrients that are much less abundant. Macronutrients, such as carbohydrates, fats and proteins are the main providers of carbon, nitrogen, and electrons/reducing power and are either incorporated into biomass or converted to energy. By contrast, the contribution of micronutrients such as vitamins, cofactors and most minerals to biomass and energy generation is more indirect. Generally, micronutrients are not metabolized except for minor modifications to acquire active molecular forms. However, they do play crucial roles in biomass synthesis and energy

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generation by activating metabolic enzymes, preventing oxidative damage as antioxidants, or by the hormonal regulation of biological processes.

Diet can affect the human body directly or indirectly (Figure 1). Direct effects involve the absorbance and utilization of nutrients from the diet itself. Indirect dietary effects are mediated by the microbial community in the digestive track, known as the gut microbiota (hereafter referred to as the microbiota) (Figure 1). The importance of such indirect effects on human health and disease is increasingly appreciated [1]. First, microbiota metabolize dietary compounds that cannot be metabolized by humans. For instance, gut bacteria break down plant-derived dietary fibers resulting in the production of the short chain fatty acids (Box 1) propionate and butyrate [2]. Second, the microbiota can provide micronutrients such as vitamin B12 and vitamin K [3]. Third, the breakdown of xenobiotics by microbial metabolism can contribute to the nutrient pool in the gut during medical treatment [4]. It is therefore perhaps not surprising that the microbiota is increasingly associated with a wide variety of human diseases, including type-2 diabetes [5], cardiovascular disease [6], obesity [7], immunity and inflammatory disease [8] and even autism [9]. Although the role of the microbiota on human health and disease is widely acknowledged, the underlying mechanisms are mostly not resolved.

Box 1

Glossary

Life history traits	Measurable physiological and phenotypic properties that affect health of an animal and the population. Examples include brood size, developmental rate and lifespan.
Postembryonic developmental rate	The rate at which *C. elegans* proceeds through the larval stages (L1, L2, L3, and L4) to the young adult stage and then to adulthood.
RNAi	RNA interference to inhibit gene expression. In *C. elegans*, double stranded RNA (dsRNA) complementary to the targeted mRNA on one strand is given to worms by feeding a bacterial strain that carries the dsRNA in a plasmid vector.
Short chain fatty acids (SCFA)	Fatty acids with five or fewer carbons: including formic- (1 carbon), acetic- (2 carbon), propionic- (3 carbon), butyric- (4 carbon) and valeric- (5 carbon) acid. SCFA are products of fatty acid beta oxidation as well bacterial fermentation, for example in human colon.
Vitamin B12 (cobalamin)	One of the water-soluble B vitamins that is important for blood formation and normal functioning of nerves. It is the most complicated vitamin, with a cobalt atom placed at the center of a tetra-pyrrole ring. Depending on the group (R) attached to this cobalt atom, it takes different forms, which include hydroxocobalamin (R=OH), adenosylcobalamin

	(R=adenosyl group), and methylcobalamin (R=methyl group).
Vitamin B9 (Folic acid)	Another water-soluble B vitamin that is important for cell division and growth. Folic acid is activated when converted to dihydrofolate, which is transformed into tetrahydrofolate, the active form in one carbon pool by folate (also known as the folate cycle; Figure 3). Different derivatives of tetrahydrofolate exist including 10-formyltetrahydrofolate, 5,10-methenyltetrahydrofolate, 5,10-methylenetetrahydrofolate, and 5-methyltetrahydrofolate.

Systematically studying the effects and mechanisms of individual micronutrients is difficult in humans and other mammals, including mice. This is not only because of the long lifespans and internal complexity of these organisms, but also because genome-scale whole organism genetics is not feasible for ethical reasons or is prohibitively expensive. Further, gut microbiota are highly complex communities including many species that are yet to be cultured in the laboratory. Here, we discuss how the nematode *Caenorhabditis elegans* and its bacterial diet have been used as a genetically tractable model to gain insights into the physiological effects of micronutrients, with a focus on B-type vitamins.

C. elegans as a model organism

C. elegans is a metazoan that lives in temperate soil environments and mainly feeds on bacteria growing on rotting vegetation [10]. Since it was introduced as a genetic model organism [11], “the worm” has proven to be a powerful model that has served to provide seminal insights into a myriad of biological processes including development [12, 13], cancer [14], and aging [15]. *C. elegans* offers multiple unique advantages as a model organism, such as physiological simplicity (~1000 somatic cells), a short lifespan (~2 weeks), an early and short reproductive period, and hermaphroditic reproduction.

In the last few years the worm has also been developed as a suitable model to study the effects of diet on metabolism, physiology and gene expression. An interesting aspect of the *C. elegans* model is that bacteria serve as food, which means that bacterial biomass is the main source of macronutrients. Thus, the relationship of *C. elegans* with bacteria is different from the synergistic relationship between mammals and microbiota. However, live bacteria can also provide sufficient supplies of micronutrients to the worm as a by-product of their metabolism, absorb compounds from the environment and deliver them to the worm, or convert compounds into other molecules that are useful for the worm. Thus, the bacterial component of the *C. elegans* model can represent both direct and indirect aspects of a diet (Figure 1). In addition, *C. elegans* is able to directly absorb micronutrients and drugs from its environment or the growth medium, representing direct effects by itself.

The standard laboratory diet of *C. elegans* has been OP50, a B strain of *Escherichia coli*, although it has been fed many different types of bacteria in controlled experiments [16].

Typically, a co-culture of *C. elegans* and a bacterium is grown on solid media supplemented with peptone to promote bacterial proliferation, and this mode of growth is referred to as monoxenic. However, *C. elegans* can also be cultured in liquid with bacteria, or in an axenic medium with a well-defined set of macro- and micronutrients [17]. Thus, the direct effects of specific nutrients on *C. elegans* can be tested by the addition or omission of these factors either in axenic or monoxenic growth conditions. However, postembryonic developmental rate and fecundity are compromised in axenic medium and in monoxenic conditions with dead bacteria [18, 19]. This implies that metabolically active bacteria support optimal worm health, analogous to the microbiota that grows in the nutritionally rich environment of the human gut and supports human health by metabolic by-products. Because *C. elegans* and its bacterial diets are genetically tractable, they can both be manipulated to systematically dissect the underlying mechanisms using an “interspecies systems biology” approach.

Different bacterial diets cause significant changes in *C. elegans* physiology and gene expression when compared to the standard OP50 diet [19–22]. Changes elicited by one particular bacterial diet, *Comamonas aquatica (*hereafter referred to as *Comamonas)*, were attributed to a dilutable compound, because this species can affect worm development and gene expression even when dramatically diluted with the OP50 diet [19]. Combined genetic analyses of *E. coli*, *Comamonas* and the worm itself unveiled that this dilutable compound is the micronutrient vitamin B12 [23] (see below). This provides a powerful example of how monoxenic growth of *C. elegans* can be used as a model system to derive connections between micronutrients, gene expression and life-history traits (Box 1). We will first review studies of vitamin B12 and folate using the worm model, and then briefly discuss additional studies that focused on other micronutrients.

Vitamin B12 profoundly affects *C. elegans* physiology and metabolism

Vitamin B12, or cobalamin, occurs in different forms (Box 1) and is an essential cofactor for two enzymes in two distinct pathways. The first enzyme is methylmalonyl coenzyme A (CoA) mutase (MCM), which uses adenosylcobalamin as a cofactor and converts methylmalonyl-CoA to succinyl-CoA as part of the mitochondrial propionic acid breakdown pathway (Figure 2). This pathway receives carbon from the catabolism of propionic acid, branched chain amino acids, odd-chain fatty acids, and cholesterol. The end product succinyl-CoA then enters the tricarboxylic acid (TCA) cycle to generate energy and recycle carbon. The interruption of this pathway in humans, either due to recessive mutations in the gene encoding MCM or because of vitamin B12 deficiency, causes the devastating disease methylmalonic aciduria, which manifests itself as organ failure as a result of the accumulation of methylmalonic acid in tissues and body fluids [24–26].

The second vitamin B12-dependent enzyme, methionine synthase (MS), uses methylcobalamin to convert homocysteine (HCys) to methionine in the cytosolic methionine/SAM cycle (Figure 3). Because of this reaction, vitamin B12 deficiency is associated with the metabolic syndrome homocysteinemia, which results from the toxic build-up of HCys [27, 28]. MS activity is connected to DNA synthesis and amino acid interconversions via the folic acid cycle (Figure 3). Some of the methionine synthesized by MS is used for protein production, while the rest is recycled back to HCys by the generation

and subsequent conversion of S-adenosylmethionine (SAM) into S-adenosylhomocysteine (SAH). SAM acts as the major methyl donor for the methylation of nucleic acids, proteins (e.g., histones), lipids (e.g., phosphatidylcholine), and other metabolites such as neurotransmitters, creatine, carnitine and polyamines. Thus, MS activity can be linked to important cellular processes involving biomass synthesis as well as regulation. In accordance with these broad impacts of MS (Figure 3), vitamin B12 deficiency has also been associated with megaloblastic anemia [29], neuropathy [30], fetal development defects [31] and pregnancy loss [32]. Overall, vitamin B12 is a crucial micronutrient for human health because of its role in both pathways (Figures 2 and 3).

Whereas many insects and plants do not need vitamin B12, *C. elegans*, like humans, must obtain vitamin B12 from its diet. Remarkably, vitamin B12 is uniquely synthesized by bacteria and archaea [33], with the better defined bacterial pathway comprising more than 20 enzymes. It is estimated that about 1/3 of bacterial species can synthesize vitamin B12 [34]. As *E. coli* does not have this pathway, the source of vitamin B12 in the standard *C. elegans* diet is the vitamin absorbed by bacteria from culturing media.

The requirement for exogenously provided vitamin B12 for *C. elegans* was recently demonstrated. Bito et al. propagated worms for several generations on peptone-free medium with bacteria grown in the absence of vitamin B12 to establish truly vitamin B12 deficient conditions [35]. They then measured various physiological variables in the worm, as well as enzymatic activity of MS and MCM, and the concentration of key metabolites. In agreement with human and mouse studies showing fetal loss and infertility under vitamin B12 deplete conditions [32, 36, 37], the brood size of vitamin B12-deficient worms was significantly reduced. In addition, the average lifespan was reduced and animals were shorter. Not surprisingly, these observations were correlated with loss of activity in MS and MCM and a corresponding increase in methylmalonic acid and HCys levels. Because the latter can inhibit collagen biosynthesis [38], the authors hypothesized that the adverse effects of vitamin B12 deficiency on *C. elegans* morphology were due to increased HCys levels. Furthermore, the authors indicated that the SAM/SAH ratio is altered during vitamin B12 deficiency in the worm (see Figure 3). Although DNA methylation does not occur in worms, histone methylation does [39], and therefore, vitamin B12 deficiency can potentially affect gene expression via this pathway. Moreover, because SAM is a highly anabolic molecule, a reduction in vitamin B12 can also affect biomass production directly by decreasing the synthesis of essential components such as phosphatidylcholine in cellular membranes [40]. Likely because of the regulatory and metabolic roles of SAM, *sams* genes in *C. elegans* (Figure 3) have been associated with fertility [41] and aging [42].

Watson et al [23] recently discovered that the standard *E. coli* diet does not represent ample vitamin B12 conditions, although animals may not be truly vitamin B12 deficient [35]. They found that the acceleration of worm development and reduction in brood size elicited by a *Comamonas* diet could be partly explained by this bacterium's ability to provide higher levels of vitamin B12. Previously, they had generated a *C. elegans* dietary sensor strain that expresses the green fluorescent protein (GFP) under the control of the promoter of the most differentially expressed gene, the acyl-CoA dehydrogenase *acdh-1*, which serves as a proxy for the induced gene expression changes [19]. On animals fed *E. coli*, GFP expression is

high, whereas on *Comamonas* it is barely detectable. By transposon-based mutagenesis in *Comamonas*, Watson et al. identified mutations in the vitamin B12 biosynthesis pathway that lead to a failure of *C. elegans* to repress GFP expression [23]. In addition, a genome-scale screen of the *E. coli* deletion collection [43] showed that a deletion in the *tonB* gene further activates GFP expression in the worm. This gene encodes an outermembrane siderophore transporter that is important for the uptake of vitamin B12 by *E. coli*. Furthermore, RNAi silencing of two worm genes involved in the conversion of cobalamin to its active forms, *mttr-1* and Y76A2B.5 (Figure 2 and Table 1), repressed the response of the dietary sensor. Also, genes encoding the enzymes that directly use vitamin B12 as a cofactor, *metr-1* and *mmcm-1*, were both uncovered during prior genome-scale genetic screens in the worm using the dietary sensor [44]. Consistent with all the genetic evidence, direct supplementation of the standard *E. coli* diet with extra vitamin B12 both repressed the dietary sensor and, importantly, mimicked the effects of the *Comamonas* diet on developmental rate and egg laying. However, the negative effect of *Comamonas* on *C. elegans* lifespan [19] was not reproduced by vitamin B12, demonstrating that other bacterial factors are responsible for this effect.

To determine the mechanism of developmental acceleration, Watson et al. tested the effect of vitamin B12 on animals that harbor mutations in either of the two pathways that require this vitamin (Figures 2 and 3). While the developmental rate of animals harboring mutations in *mce-1* or *pcca-1* (propionic acid breakdown, Table 1, Figure 2) could be accelerated by vitamin B12 supplementation, mutations in *sams-1* or *metr-1* (methionine/SAM cycle, Table 1, Figure 3) rendered the animal unresponsive to vitamin B12. The effects of these mutations on egg laying were similar. Thus, the vitamin B12 phenotypes related to biomass production occur via the methionine/SAM cycle, which is in agreement with the central anabolic role of this pathway (Figure 3).

A major function of the propionic acid breakdown pathway (Figure 2) is to prevent buildup of this toxic metabolite, which can be produced by central metabolism or obtained from the diet. In propionic acid toxicity assays [23], vitamin B12 supplementation significantly improved the animal's ability to withstand high doses of propionic acid, presumably by enhancing the catabolism of propionyl-CoA (Figure 2). Interestingly, a Δ*metr-1* mutant (Table 1, Figure 3) had improved survival rates under vitamin B12-limiting conditions as compared to wild type animals, implicating that the two vitamin B12 reactions may compete with each other for this cofactor, and that blockage of one pathway may increase the flux in the other. In humans, propionic acid is produced by the microbiota from the digestion of dietary fibers [2] as well as by endogenous metabolism from propionyl-CoA. Although propionic acid has positive roles in human metabolism such as serving as an energy source [2], high levels of propionate have been associated with toxicity, leading to neurological disorders and gingival inflammation [45]. The inborn metabolic disorder propionic aciduria/acidemia is an extreme case of toxicity where mutations in the *PCCA* gene (Table 1) render the enzyme inactive thereby causing the build-up of propionate and other toxic compounds resulting in damage to various organs and eventually death [46]. The worm results indicate that this animal is also a good model to study propionic acid toxicity [23].

Vitamin B9, or folate, greatly affects *C. elegans* biology by direct or microbe-mediated mechanisms

Folic acid (or folate) is another water-soluble B vitamin (Box 1). The active forms of folate act as donors or acceptors of one-carbon groups in amino acid and nucleic acid metabolism (Figure 3). Due to its role in the biosynthesis of thymine and purines, as well as in amino acid conversions, folate levels are critical for fast-dividing cells. Accordingly, folate deficiency in humans has been associated with anemia [47], fetal growth retardation [48], and neural tube defects during embryonic development [49]. Folate and vitamin B12 metabolism intersect in the methionine/SAM cycle (Figure 3). Likely because of this intersection these two vitamins can have similar effects [50]. For instance, vitamin B12 deficiency can mimic folate deficiency because of the so-called methyl trap [51], where 5-methyltetrahydrofolate (5mTHF) cannot be converted back to tetrahydrofolate (THF) due to lowered activity of MS, and therefore, active folate forms cannot be replenished.

Similar to humans, *C. elegans* obtains folate from its diet. Earlier studies with the worm focused on folate transport: the *folt-1* gene was found to encode the major folate uptake system [52]. This resembles the corresponding protein in mammals, the reduced folate carrier (RFC; Figure 3, Table 1), in multiple ways. First, both proteins are able to transport not only folate but also its derivatives. Secondly, FOLT-1 and mammalian RFC are both developmentally regulated. The expression of *folt-1* is highest in earlier larval stages [52]. Similarly, in rats, RFC is expressed at higher levels during earlier stages of postembryonic development [53]. Finally, drugs that inhibit folate uptake by targeting RFC in humans also do so in the worm [52].

Because studies with RFC in mammals had been limited to the cellular level, Balamurugan et al. proposed that *C. elegans* may provide a suitable model to study unknown aspects of folate uptake at the whole animal level [52]. Austin et al. [54] found that loss of *folt-1* reduces *C. elegans* lifespan by 44%, and greatly reduces fertility by attenuating spermatogenesis and decreasing oogenesis likely due to a reduction in germline nuclei [54]. In addition, the defecation rate of Δ*folt-1* animals is lower than that of wild type animals, which suggests an overall reduced metabolic rate. Thus folate uptake seems to play an important role in both reproduction and metabolism of *C. elegans*. However, since the deletion allele used in this study was not outcrossed, in the absence of complementation tests to rescue the mutation and additional RNAi tests, there is also the possibility that unknown linked mutations explain the observed phenotypes.

Other recent studies on *C. elegans* folate metabolism emphasized the indirect effects of diet (Figure 1). For instance, Virk et al. serendipitously discovered that impairment of folate synthesis in *E. coli* extends *C. elegans* lifespan by more than 30% [55]. This can occur genetically by mutating a key bacterial gene (*aroD)* that is involved in the biosynthesis of aromatic compounds such as precursors of folate, or by inhibiting folate synthesis with bacteriostatic antibiotic sulfamethoxazole. Supplementation with folate precursors overrides the effect of *aroD* mutants and restores lifespan. Analytical measurements showed that the folate cycle in the worm was functional even when bacterial biosynthesis of folate is blocked. While reduction of bacterial folate synthesis delays aging, lifespan is reduced in

folt-1 mutant animals [54] (see above). Thus, there must be an optimal level of folate in the worm to support long lifespan as both limited and excess folate can reduce lifespan.

Although bacterial growth was not affected by drug treatment under the conditions tested [55], it is still not clear if the observed changes are due to broader impacts of folate metabolism in the bacterium, or simply to a decrease in the amount of dietary folate [56]. Experiments with axenic medium where bacterial metabolism is eliminated will be helpful to directly test the effect of dietary folate on the worm. An interesting observation in support of bacterial folate synthesis being the main effector is that sulfo drugs that inhibit microbial folate biosynthesis also extend lifespan in rats [57]. Taken together, *C. elegans* is a suitable model to derive hypotheses for the effects of folate metabolism status in microbiota on human health [55, 56].

A surprising microbe-mediated effect on worm physiology and metabolism was recently discovered [58] during the studies with the anti-diabetic drug metformin, which had been known to extend lifespan in *C. elegans* [59] and mice [60]. Cabreiro et al. showed that this occurs through bacterial folate and methionine metabolism [58]. Remarkably, metformin increases the lifespan of *C. elegans* when fed live bacteria, but reduces it when animals are fed dead bacteria or are grown in axenic medium. Analysis of active bacteria showed that metformin changed the relative abundance of folate derivatives: meTHF was increased, while methionine was decreased, which is consistent with a possible inhibition of MS (Figure 3). The authors proposed that decreased methionine levels in the diet reduced SAM/SAH ratio in the worm (as can be inferred from Figure 3), which mimics dietary restriction (DR). Glucose supplementation suppressed the effects of metformin in *C. elegans*, suggesting that a high sugar diet might offset the benefits of metformin [58]. Taken together, bacteria may mediate some of the effects of metformin, which has implications for human treatment as well since it may affect or be metabolized by the microbiota. This is supported by the observation that the composition of microbiota is sensitive to metformin treatment in rats [61, 62] and type-2 diabetes patients [63].

Other micronutrients

Micronutrients other than B vitamins have also been studied for their direct or bacteria-mediated effects on *C. elegans*, particularly on aging. Based on the mitochondrial theory of aging [64], antioxidants such as vitamin C and vitamin E may be expected to increase lifespan, but studies with these compounds disagree on their effects on humans as well as *C. elegans* [65, 66]. Because the bacterial diet of *C. elegans* is not a source of these vitamins, they are to be tested by dietary supplementation. However, worms cannot efficiently uptake these compounds [65, 66]. Recently, Nishikawa and colleagues developed methods to orally deliver to *C. elegans* both hydrophilic compounds such as vitamin C derivatives [67] and hydrophobic compounds such as vitamin E derivatives [68] by vehicles that act as bacteria-like particles. For both families of vitamins, they were able to demonstrate an increase in lifespan, thus demonstrating the direct effect of these antioxidants for the worm model.

Another micronutrient that may affect aging in *C. elegans* is Coenzyme Q (Q), which has diverse functions including its major role in the electron transport chain and as an

antioxidant [69]. *C. elegans* produces its own specific form (Q9) [70], but can also use Q8 from its *E. coli* diet [71]. When fed mutant *E. coli* that do not produce Q8, the lifespan of the worm increases [72]. Remarkably, this effect was the result of altered bacterial metabolism, and not due to direct dietary contribution [73], as supplemented Q10 did not reverse the lifespan extension. Further, the lifespan extension with Q-less *E. coli* was not due to lowered caloric intake because of compromised bacterial growth. One possibility for the mechanism is the production of fermentation metabolites such as ethanol and lactic acid that may be the actual causes of lifespan extension in the worm [73]. However, more recently, Gomez et al. [74] showed that lactic acid produced by Q-less *E. coli* was not responsible for the life-span extension. Instead, they suggested that the survival rate of worms may be improved due to the delay in the colonization of the worm gut by respiratory-deficient bacteria as compared to the wild type bacteria.

Finally, a surprising compound that was recently shown to delay aging in *C. elegans* is alpha-ketoglutarate (AKG) [75], an intermediate in the TCA cycle. Direct supplementation of AKG extended lifespan by more than 25% irrespective of bacterial metabolic activity. Rather, AKG acts by binding and suppressing ATP synthase to reduce energy generation in the worm. This effect is dependent on the target of rapamycin pathway, whose inactivation delays aging [76]. Overall, AKG supplementation creates DR-like conditions. Interestingly, AKG concentrations also increase during starvation, suggesting the presence of a feedback mechanism responding to nutrient availability [75]. Thus the common metabolite AKG also acts as a signaling molecule.

Concluding remarks

Altogether, the studies we discussed firmly establish the nematode *C. elegans* and its bacterial diet as a model for both direct and microbe-mediated effects of diet on health and longevity. Since micronutrients obtained from the diet or supplied by the microbiota affect human health by complicated mechanisms that are difficult to systematically characterize, it is likely that studies using the interspecies worm system will greatly illuminate basic physiological responses and underlying mechanisms.

The worm/bacteria system will not be a suitable model for all aspects of human diet and metabolic diseases. First, *C. elegans* and the co-cultured bacteria do not represent a case of mutualism as in human and microbiota, but have a trophic relationship. Thus, the *C. elegans*/bacteria model is limited to a simplified conceptual model of direct and indirect effects as in Figure 1. Second, whereas human microbiota is a complex community, *C. elegans* interacts with a pure culture during monoxenic growth in the laboratory. However, monoxenically grown *C. elegans* does offer the possibility of testing different bacterial species individually for their role on indirect dietary effects, as long as they can be cultured in the laboratory. In any case, pathway-level mechanisms discovered in the worm can serve as hypotheses for further testing in mammalian model systems or humans.

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HIGHLIGHTS

- Micronutrients affect human health either directly or indirectly via gut microbiota
- *Caenorhabditis elegans* and its bacterial diet can be used as a model for both effects
- The worm and its bacterial diet provide a powerful interspecies systems biology model
- The worm/bacteria model connects vitamins B9 and B12 to animal physiology and metabolism

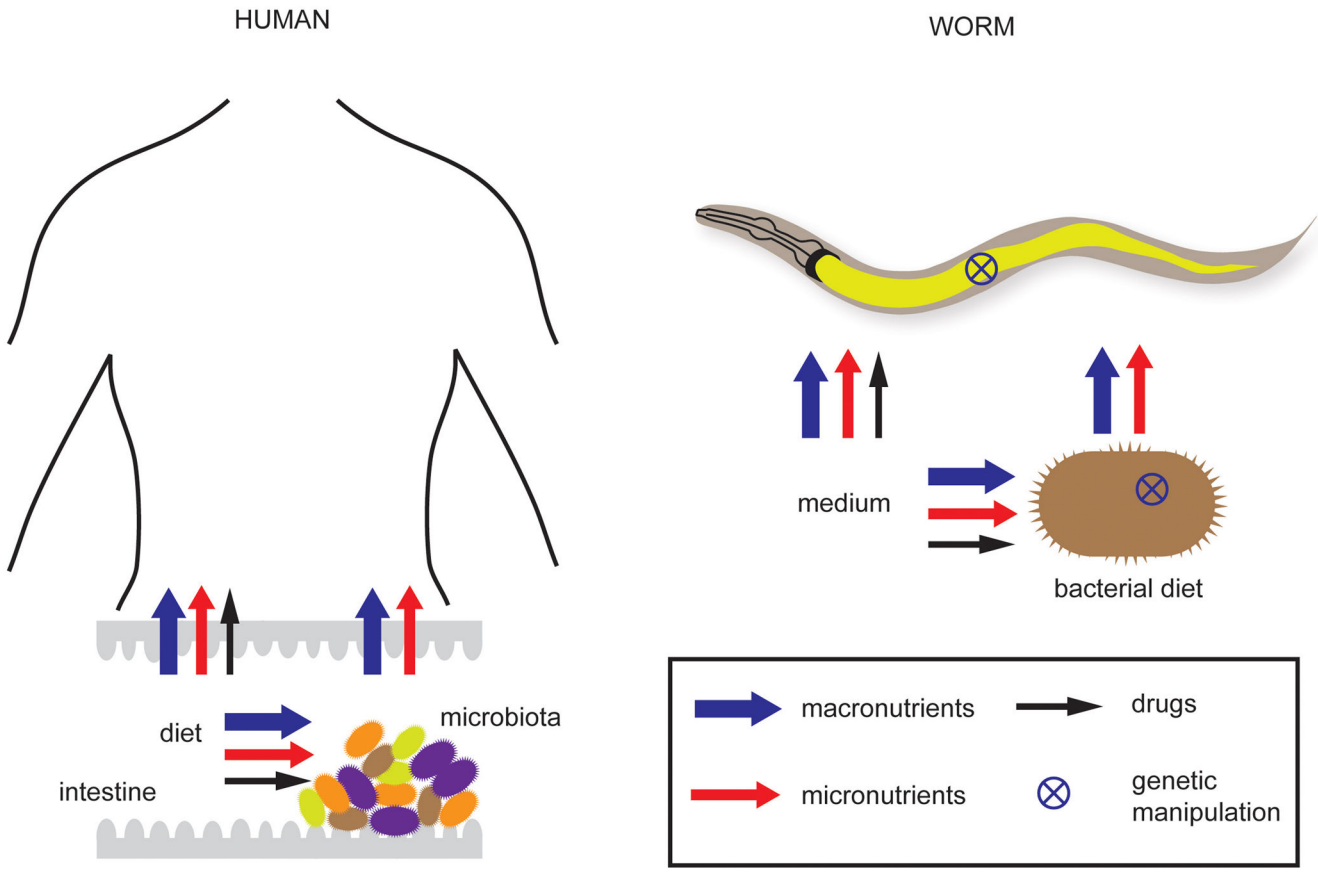

Figure 1.
C. elegans as a model organism to study the direct and microbiota-mediated effects of diet.

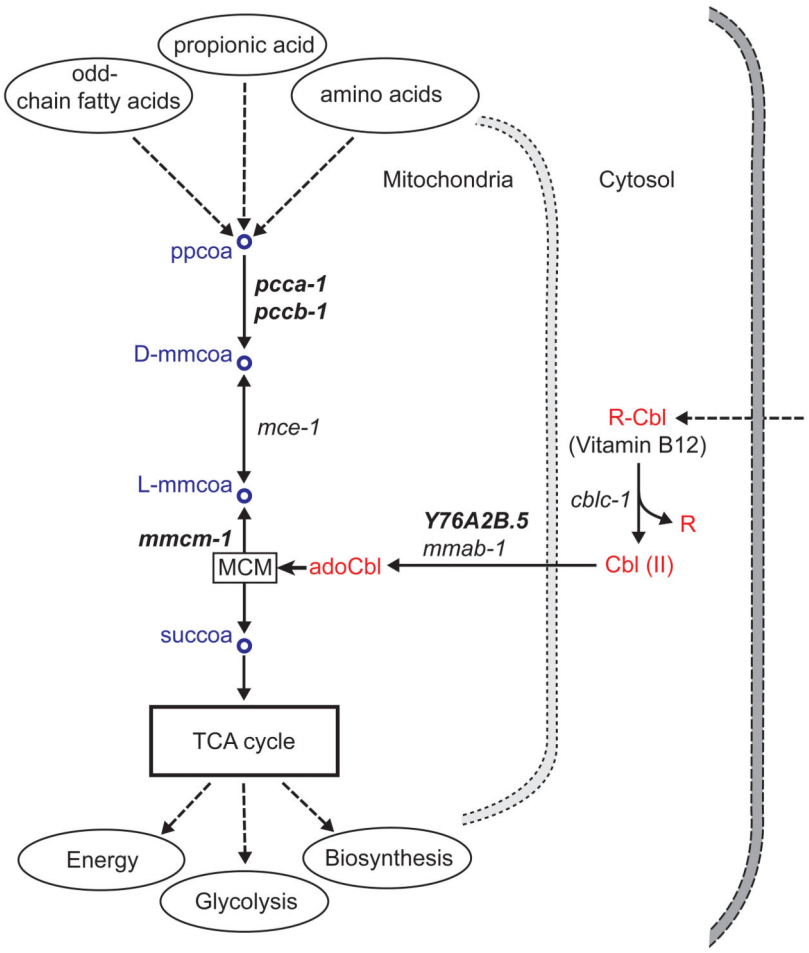

Figure 2.

Propionic acid breakdown pathway and Vitamin B12. *C. elegans* genes that are associated with each reaction are shown in italics. Human orthologs of selected genes (bold italics) are provided in Table 1. Dashed arrows indicate pathways not shown in detail. MCM, Methylmalonyl-CoA mutase; ppcoa, propionyl CoA; mmcoa, methylmalonyl CoA; succoa, succinyl CoA; Cbl, cobalamin; adoCbl, adonesylcobalamine.

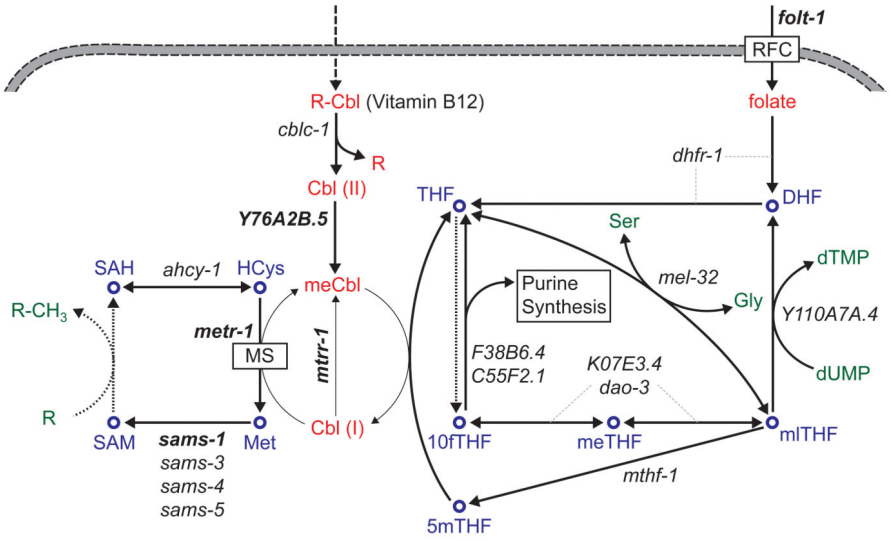

Figure 3.

Methionine and folic acid cycles. *C. elegans* genes that are associated with each reaction are shown in italics. Human orthologs of selected genes (bold italics) are provided in Table 1. Dotted arrows indicate multiple reactions with multiple genes. MS, methionine synthase; RFC, reduced folate carrier; DHF, dihydrofolate; THF, tetrahydrofolate; 10fTHF, 10-formyltetrahydrofolate, meTHF, 5,10-methenyltetrahydrofolate; mlTHF, 5,10-methylenetetrahydrofolate; 5mTHF, 5-methyltetrahydrofolate; HCys, homocysteine; Met, methionine; SAM, S-adenosyl methionine; SAH, S-adenosyl homocysteine; Cbl, cobalamin; meCbl, methylcobalamine; Ser, serine; Gly, glycine.

Table 1

Selected genes in Vitamin B12- and folic acid-related pathways[a].

Pathway Figure	Protein Name	*H. sapiens*	*C. elegans*
Figure 2	Propionyl-CoA carboxylase alpha subunit	PCCA	*pcca-1*
	Propionyl-CoA carboxylase beta subunit	PCCB	*pccb-1*
	Methylmalonyl-CoA epimerase	MCEE	*mce-1*
	Methylmalonyl-CoA mutase	MCM	*mmcm-1*
Figure 3	Methionine synthase reductase	MTRR	*mtrr-1*
	Methionine synthase	MTR	*metr-1*
	S-adenosylmethionine synthetase	MAT1A	*sams-1*
	Reduced folate carrier	SLC19A1	*folt-1*
Both	Methylmalonic aciduria and homocystinuria type D protein	MMADHC	Y76A2B.5

[a] see Figures 2 and 3 for the function of genes in these pathways.