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Methanobacterium formicicum as a target rumen methanogen for the development of new methane mitigation interventions: A review

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ABSTRACT

Methanobacterium formicicum (Methanobacteriaceae family) is an endosymbiotic methanogenic Archaean found in the digestive tracts of ruminants and elsewhere. It has been significantly implicated in global CH_4 emission during enteric fermentation processes. In this review, we discuss current genomic and metabolic aspects of this microorganism for the purpose of the discovery of novel veterinary therapeutics. This microorganism encompasses a typical H_2 scavenging system, which facilitates a metabolic symbiosis across the H_2 producing cellulolytic bacteria and fumarate reducing bacteria. To date, five genome-scale metabolic models (iAF692, iMG746, iMB745, iVS941 and iMM518) have been developed. These metabolic reconstructions revealed the cellular and metabolic behaviors of methanogenic archaea. The characteristics of its symbiotic behavior and metabolic crosstalk with competitive rumen anaerobes support understanding of the physiological function and metabolic fate of shared metabolites in the rumen ecosystem. Thus, systems biological characterization of this microorganism may provide a new insight to realize its metabolic significance for the development of a healthy microbiota in ruminants. An in-depth knowledge of this microorganism may allow us to ensure a long term sustainability of ruminant-based agriculture.

1. Introduction

CH_4 is the second largest anthropogenic greenhouse gas and its global warming potential is 25 times more than that of CO_2 (Forster et al., 2007; IPCC 2007). The US-Energy Protection Agency (EPA) stated that China, India, the United States, Brazil, Russia, Mexico, Ukraine and Australia are the major CH_4 emitters in the world. CH_4 emission is projected to increase by 15% to 7904 MMT (Million Metric Ton)-CO_2Eq. by 2020 (US-EPA, 2014). About 25% of enteric CH_4 emission accounted globally from the ruminants represents a loss of 5–7% of dietary energy (Hristov et al., 2013; Thorpe, 2009).

A total CH_4 emission is estimated to be 163.3 MMT-CO_2 Eq. from enteric fermentation and 61.2 MM-TCO_2 Eq. from manure management (US-EPA, 2014). Beef (116.7 MMT-CO_2 Eq.) and dairy cattle (41.6 MMT-CO_2 Eq.) are being as main sources for enteric CH_4 emission (Table 1). The management of manure from anaerobic digester (61.2 MMT-CO_2 Eq.), dairy cattle (32.2 MMT-CO_2 Eq.) and swine (22.4 MMT-CO_2 Eq.) is also contributed to global CH_4 emission. Cattle ($77.3\,kg \times 10^6$) and buffalo ($12.1\,kg \times 10^6$) will be the major source for the projected global CH_4 emission from enteric fermentation in 2025. CH_4 emission budget ($105\,kg \times 10^6$) will be 107 times more from manure management ($12{,}849\,kg \times 10^6$) (Table 2). Hence, reducing CH_4 emissions from ruminants is not only benefits for the environment, but also to ensure the long-term sustainability of ruminant-based agriculture (Zhang et al., 2015).

1.1. Rumen microbiota

The typical rumen microbiota consists of 10–50 billion bacteria, 1 million protozoa and variable numbers of yeasts and fungi in each milliliter of rumen content (Ekarius, 2010). Anaerobic microbes are degrading polysaccharides (cellulose, hemicellulose, starch and pectin), proteins, and lipids from food/feed and of producing organic acids (formate, pyruvate, acetate, propionate, butyrate, and succinate) from which CH_4 gas is produced by rumen methanogenic archaea (Chellapandi, Prabaharan, & Uma, 2010). The rumen microbes rapidly ferment amino acids and soluble proteins and form various acidic fermentation products (NH_3, H_2 and CO_2). The turnover rate of fermentation products cannot be measured due to exchange reactions across the microorganisms (Andrade-Montemayor, Gasca, & Kawas, 2009). Pyruvate produced from anaerobes is carboxylated to form oxaloacetate and further converted to malate, fumarate and succinate. The rumen microbes that are not producing succinate can use CO_2 as a sole carbon source (Ungerfeld, 2015). Gut microbiota are able to synthesis

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Table 1
CH_4 emissions (MMT-CO_2 Eq.) from ruminant-based agriculture (US EPA report 2016).

Gas/Livestock	2005		2010		2011		2012		2013		2014	
	EF	MM	EF	MM	EF	MM	EF	MM	EF	MM	EF	MM
Beef cattle	125.2	3.3	124.6	3.3	121.8	3.3	119.1	3.2	118	3	116.7	3
Anaerobic digester*	–	56.3	–	60.9	–	61.5	–	63.7	–	61.4	–	61.2
Dairy cattle	37.6	26.4	40.7	30.4	41.1	31.1	41.7	32.6	41.6	31.8	41.9	32.2
Poultry	–	3.2	–	3.2	–	3.2	–	3.2	–	3.2	–	3.2
Horses	2.3	0.3	2.4	0.2	2.5	0.2	2.5	0.2	2.5	0.2	2.4	0.2
Sheep	1.7	0.1	1.7	0.1	1.7	0.1	1.6	0.1	1.6	0.1	1.6	0.1
Swine	1.2	22.9	1.1	23.6	1.1	23.6	1.1	24.3	1.1	23	1	22.4
Goats	0.4	–	0.4	–	0.3	–	0.3	–	0.3	–	0.3	–
American bison	0.4	–	0.4	–	0.3	–	0.3	–	0.3	–	0.3	–
Mules and asses	0.1	–	0.1	–	0.1	–	0.1	–	0.1	–	0.1	–
Gross total	168.9	56.3	171.3	60.9	168.9	61.5	166.7	63.7	165.5	61.4	164.3	61.2

*Accounts for CH_4 reductions due to capture and destruction of CH_4 at facilities using anaerobic digesters.
EF: Enteric fermentation; MM: Manure management.

Table 2
The projected CH_4 emissions (kg $\times 10^6$) in the year of 2025 from ruminant-based agriculture.

Livestock	Enteric fermentation	Manure management
Cattle	77.3	7002
Buffalo	12.1	933
Sheep	6.18	183
Goat	5.19	222
Swine	1.29	3700
Poultry	–	537
Camel	1.17	62
Horse	1.03	–
Ass	0.45	40
Mule	0.09	9
Alpaca	0.13	86
Total	105	12,849

indispensable amino acids and vitamins from the non-protein nitrogen sources and offer them as nutrient supplements to the host animal (Morowitz, Carlisle, & Alverdy, 2011). These processes clearly indicate that the rumen is a dynamic ecosystem wherein the gut microbiota may interact and support one another in a complex food web.

1.2. Rumen methanogenic archaea

Methanogenic archaea are capable of producing CH_4 from the low carbon substrates such as formate, pyruvate, methylamine, acetate, and CO_2 through methanogenesis. This process depends on the availability of ATP derived from enteric fermentation of rumen anaerobic bacteria (Balch, Fox, & Magrum, 1979; Hook, Wright, & McBride, 2010). The overall effects of methanogenic archaea play a crucial role in the physiology and health of the ruminants (Delzenne & Cani, 2011). *Methanomicrobium mobile, Methanobacterium lacus, Methanobacterium formicicum* (MFI), *Methanomicrobium bryantii, Methanobrevibacter ruminantium, Methanobrevibacter smithi, Methanosarcina barkeri* and *Methanosarcina mazei* are culturable rumen methanogenic archaea have been studied in detail (Henderson et al., 2015). Methanobacterium and Methanobrevibacter are predominant genera usually inhabited in the rumen ecosystem.

2. Methanobacterium formicicum

MFI is a representative species of methanogenic archaea found in the gut of ruminants and humans (Pimentel et al., 2012; Sirohi, Goel, & Pandey, 2012). This microorganism can utilize CO_2 with H_2, fermented by-products of the rumen bacteria, for CH_4 production in rumen gut environment. CO_2 is released by the animal into the atmosphere. MFI is a clinically important microorganism because it can cause gastrointestinal and metabolic disorders in animals and humans (Kelly et al., 2014; Mitsumori & Sun, 2008). This microorganism is able to ferment acetate, carbohydrate, amino acid, ethanol, methanol, propionate, butyrate and lactate. MFI contains all essential genes need for methanogenic process with exception of [Fe]-hydrogenase dehydrogenase (*hmd*). Both CH_4 production and formate consumption are linear functions of its growth rate. The molar growth yield of MFI for CH_4 of formate cultures is 4.8 g dry weight per mol, and that of H_2—CO_2 culture was 3.5 g dry weight per mol (Schauer & Ferry, 1980). Pseudomurein and polysaccharide biosynthesis genes are similar to those found in *M. ruminantium* (Leahy et al., 2010). MFI strain BRM9 does not have homologs of N-acylneuraminatecytidyl transferase coding genes (*neuA/neuB*) as in the strain DSM 3637 (Kandiba & Eichler, 2013). MFI consists of 3 ectoine biosynthetic genes usually existed in halo-tolerant microorganisms, but ectoine is not yet reported to be produced by methanogenic archaea (Lo, Bonner, Xie, D'Souza, & Jensen, 2009; Moe et al., 2009). The genome of this microorganism contains a large number of genes for two-component signal transduction system. This system helps to monitor the changes in the redox potential, oxygen and overall cellular energy level of MFI (Taylor & Zhulin, 1999). It has a characteristic metabolism of nitrogen, particularly in ammonium transporters and glutamine synthase/glutamate synthase pathway.

2.1. Genomic features

Currently, 7 complete genome sequences are available for different species of Methanobacterium and Methanobrevibacter (Gutiérrez, 2012; Leahy et al., 2010, Leahy, Kelly, Li, 2013) (Fig. 1; Maus et al., 2013a). Researchers have identified 3 different strains (DSM3637, DSM1535 and BRM9) of MFI from the bovine rumen (Kelly et al., 2014; Maus et al., 2013, 2014). Comparison of 16S rRNA gene sequences indicate 99.8% sequence similarity between strain BRM9 and strain DSM1535 (Bryant & Boone, 1987). MFI strain KOR-1 strain isolated from an anaerobic digester using pig slurry has shown 98% rRNA gene and 97% *mcrA* gene sequence similarities to other strains (Battumur, Yoon, & Kim, 2016). The genome of strain DSM3637 (2.47 Mbp) comprises of a total of 2556 protein-coding genes in which 643 proteins assigned to be hypothetical proteins (Gutiérrez, 2012). The strain DSM1535 is 2.4 Mbp in genome size with 41.23% GC content and encoded for several adaptation genes responsible for abiotic stress (Maus et al., 2014). The BRM9 strain consists of a single 2.44 Mbp circular chromosome with 2352 protein coding genes (83%). A putative function is assigned to 1715 of the protein-coding genes, with the remainder annotated as hypothetical proteins (Kelly et al., 2014). Conserved hypothetical proteins are ranged from 413 to 736 in the genera of Methanobacterium and Methanobrevibacter.

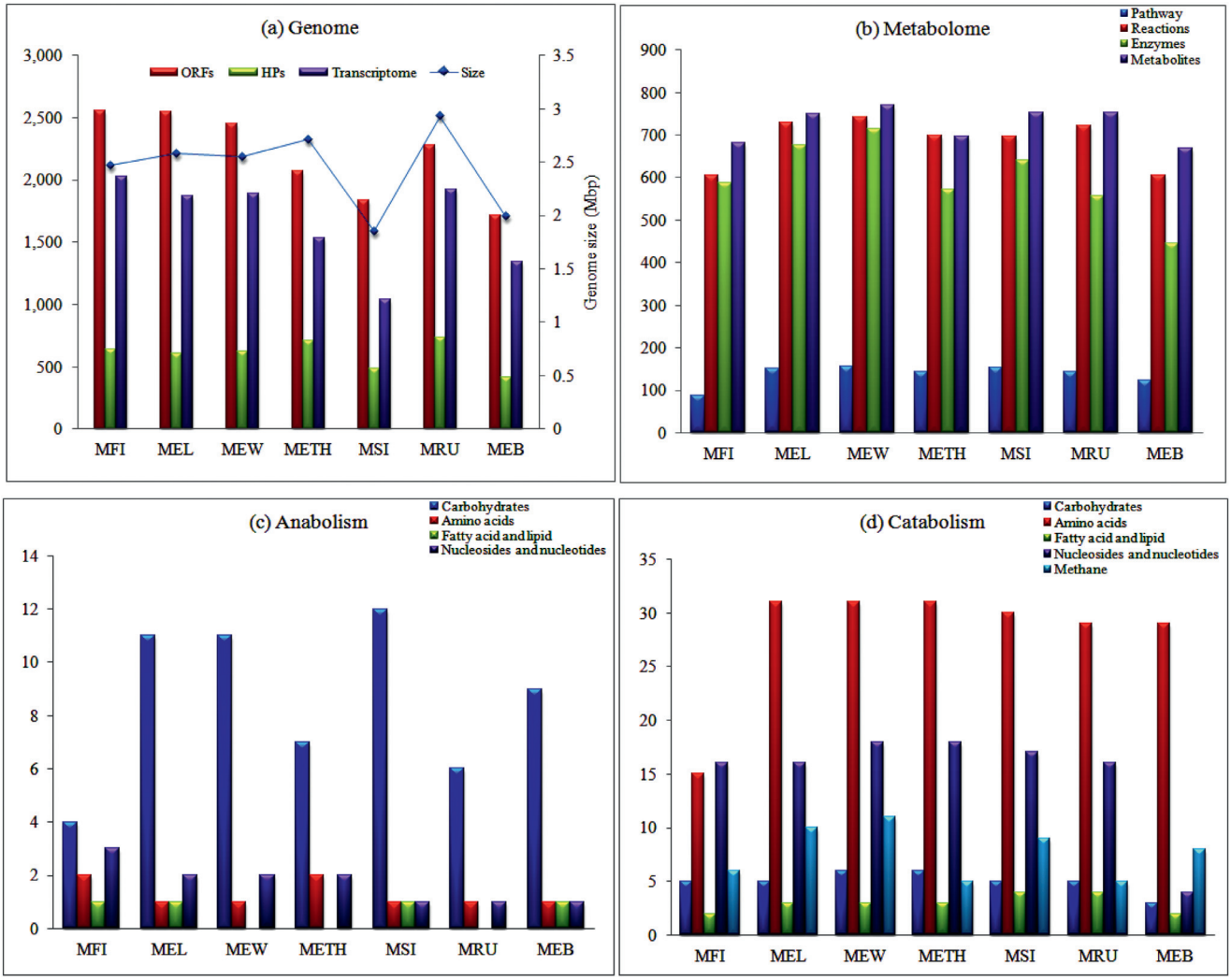

Fig. 1. Genome-scale metabolic information of MFI and related rumen methanogens, collected from the MetaCyc database (https://metacyc.org/). We compared genome (a), metabolome (b), anabolism (c) and catabolism (d) to infer genomic similarities and dissimilarities across them. (MEL: *Methanobacterium lacus*, MEW: *Methanobacterium* sp. SWAN-1, METH: *Methanobacterium* sp.MB1, MSI: *Methanobrevibacter smithii*, MRU: *Methanobrevibacter ruminantium*, MEB: *Methanobrevibacter* sp. AbM4).

2.2. Transcription regulatory systems

The MFI genome possesses a maximum number of transcription units compared to the genera of Methanobacterium and Methanobrevibacter (Kelly et al., 2014; Kern, Linge, & Rother, 2015; Worm, Stams, Cheng, & Plugge, 2011). Transcriptional regulation of coenzyme F_{420}-dependent formate dehydrogenase (*fdhCAB*) (Patel & Ferry, 1988; Schauer & Ferry, 1982; White & Ferry, 1992), glyceraldehyde-3-phosphate dehydrogenase (Fabry, Lang, Niermann, Vingron, & Hensel, 1989), archaeal histones (*hfoAB*) (Darcy, Sandman, & Reeve, 1995; Zhu, Sandman, Lee, Reeve, & Summers, 1998) has been extensively characterized in this microorganism. *NrpR* is a transcriptional regulator that represses transcription of nitrogen fixation genes, glutamine synthase and ammonium transporters. This regulator binds to inverted repeat operators in the promoter regions located upstream from the starts of *glnA,nifH, pdxT, amt1* and *amt2* (Andrade-Montemayor et al., 2009; Lie et al., 2010; Magingo & Stumm, 1991). MFI contains *nif* operon, nitrogenase and nitrogenase cofactor biosynthesis genes as similar to *Methanococcus maripaludis* (Lie et al., 2010; Magingo & Stumm, 1991). An intensive analysis of the current genomic data of MFI provided a new avenue for the development of veterinary vaccines and small-molecule inhibitors for CH_4 mitigation (Leahy, Kelly, Ronimus et al., 2013; Wedlock et al., 2010). Hence, the MFI genome is considered as a suitable candidate for studying systems biological characterization of rumen methanogens. Such systems-level information is currently useful to discover new veterinary vaccines and chemogenomic targets for new CH_4 mitigation interventions (Bharathi & Chellapandi, 2017; Sedano-Núñez, Boeren, Stams, & Plugge, 2018).

2.3. Metabolic regulatory systems

Metabolic pathway data including reactions, enzymes, and metabolites provide insight into the growth and metabolic physiology of MFI (Fig. 1b). This genome consists of abundant genes for the biosynthesis of carbohydrate and nucleotides (Fig. 1c). Genes involved in anabolism of this microorganism are considerably lower than that of other species in Methanobacterium genus, indicative of a characteristic system exists for carbohydrate biosynthesis. It has been well-established that systems for catabolism of amino acids and nucleic acids, which are relatively low to related genera (Fig. 1d). *Methanobacterium lacus* and *Methanobacterium* sp. SWAN-1 have 5 more additional genes for energetic CH_4 biosynthesis, compared to the MFI genome. MFI is a target rumen methanogen for the development of new CH_4 mitigation interventions owing to the existence of conserved nature of genes required for methanogenesis, central metabolism and Pseudomurein cell wall formation (Kelly et al., 2014).

2.4. Gut microbial symbiosis

Gut microbiota are shaped by both genetic background and lifestyle, which in turns impairs intestinal barrier function (Burcelin, 2010; Stenman, Burcelin, & Lahtinen, 2015) and modulates epithelial cell proliferation (Sommer & Bäckhed, 2013) and metabolic inflammation (Stenman et al., 2015). It is well known that healthy gut microbiota are essential one to protect against the pathogenic microorganisms in the intestine (Tremaroli & Bäckhed, 2012) and modulate gut-brain axis (Hsiao et al., 2013). Several studies have focused on the metabolic crosstalk between gut microbiota and host to reveal the metabolic disorders of human (Burcelin, 2010; Cani & Delzenne, 2009; Koeth, Wang, & Levison, 2013; Stenman et al., 2015), but none has been reported for animals. A gut microbial composition may restrict the production of certain bacterial metabolites (Heinken, Sahoo, Fleming, & Thiele, 2013). Microbial mutualism can occur through metabolic interactions between host and gut microbe and between microbe and microbe (Bath, Morrison, Ross, Hayes, & Cocks, 2012; Morgavi et al., 2015). Endo-symbiotic methanogenic archaea are usually habituated in the gastrointestinal tracts of ruminants, which are contributing in the syntrophic degradation and improved metabolic function. MFI is an endosymbiotic methanogenic archaea of free-living anaerobic flagellate *Psalteriomonas vulgaris* (Broers et al., 1993) associating syntrophically with *Syntrophomonas zehnderi* (Sousa, Smidt, Alves, & Stams, 2007).

2.5. H_2 scavenging systems

Interspecies H_2 transfer is a metabolic process occurring between hydrogenotrophic methanogenic archaea and cellulolytic/acetogenic bacteria. Hydrogenotrophic methanogenic archaea maintain the partial pressure of H_2 by utilizing H_2 produced by cellulolytic bacteria. *Ruminococcus albus* and *R. flavefaciens* are H_2-producing cellulolytic anaerobe for interspecies H_2 transfer of MFI (Chaucheyras-Durand, Masséglia, Fonty, & Forano, 2010; Joblin, Naylor, & Williams, 1990; Pavlostathis et al., 1990; Williams, Withers, & Joblin, 1994; Wolin, Miller, & Stewart, 1997). *Fibrobacter succinogenes, Wolinella succinogenes* and *Mitsuokella jalaludinii* are fumarate reducing rumen anaerobic bacteria. These microorganisms are able to reduce CH_4 production either by competing with hydrogenotrophic methanogenic archaea for H_2 as well as formate or by increasing succinate (Asanuma, Iwamoto, & Hino, 1999; Mamuad et al., 2012; Mamuad et al., 2014). Therefore, cellulolytic and fumarate reducing bacteria are extensively studied symbiotic anaerobes for interspecies H_2 transfer of MFI. Comparative metabolic analysis shows that 237 metabolic enzymes are shared across the MFI, *F. succinogens* and *R. albus* and 210 enzymes are common between *F. succinogens* and *R. albus*(Fig. 2). MFI has 126 unique enzymes across *F. succinogens* and *R. albus*, 38 enzymes shared with *R. albus* and 44 enzymes with *F. succinogens*. Hence, studying metabolic symbiosis of these genomes is important to comprehend the gut physiology and metabolic disorders of veterinary animals.

3. Systems biology paradigm

The biochemical function of individual genes and proteins of microorganisms has been investigated by traditional molecular approaches. A complexity of microbial symbiosis and metabolic crosstalk has been reconciled by recent quantitative systems biology advances. Genome-scale metabolic models are being as the promising computational platforms for studying intracellular metabolism and interspecies interactions of microbial communities and for hypotheis testing (Liu, Agren, Bordel, & Nielsen, 2010).

3.1. Genome-scale reconstructions for methanogenic archaea

Systematic analysis of methanogenic archaea and mutualistic anaerobic bacteria provides an opportunity to capture growth

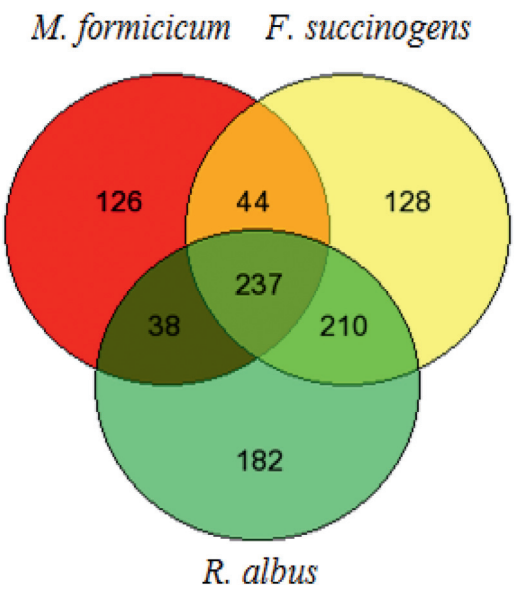

Fig. 2. Comparison of metabolic enzymes sharing across MFI, *F. succinogens* and *R. albus*. Complete metabolic enzymes (E.C.) were collected from the MetaCyc database (https://metacyc.org/), compared and then viewd in Venn diagram.

parameters and bacterial community composition (Durmus, Cakır, Özgür, & Guthke, 2015; Stolyar, Van Dien, Hillesland, & Pinel, 2007). *In silico* models for *M. barkeri* (iAF692; iMG746) (Feist, Scholten, Palsson, Brockman, & Ideker, 2006; Gonnerman, Benedict, Feist, Metcalf, & Price, 2013), *M. acetivorans* (iMB745; iVS941) (Benedict, Gonnerman, Metcalf, & Price, 2012; Kumar, Ferry, & Maranas, 2011) and *Methanococcus maripaludis* (iMM518) (Goyal, Widiastuti, Karimi, & Zhou, 2014) have been previously developed for studying their metabolic behaviors on different growth substrates. In addition to that, a metabolic flux model has been reconstructed for understanding a microbial mutualism between *M. maripaludis* (Goyal et al., 2014) and *Desulfovibrio vulgaris* (Stolyar et al., 2007).

3.2. Genome-scale reconstructions for gut-microbe interactions

Several genome-scale models have been developed for evaluating the mechanistic details of gut-microbe interactions (Ding et al., 2016; Gao, Zhao, & Huang, 2014; Sadhukhan & Raghunathan, 2014; Shoaie and Nielsen, 2014; Shoaie et al., 2013; Shoaie, Ghaffari, Kovatcheva-Datchary, & Mardinoglu, 2015) and host-microbe metabolic symbiosis (Heinken et al., 2013; Ji & Nielsen, 2015; Singer, 2010). PHIDIAS (Xiang, Tian, & He, 2007), HPIDB (Kumar & Nanduri, 2010), PHISTO (Durmus et al., 2013), PATRIC (Wattam, Gabbard, Shukla, & Sobral, 2014), PHI-base (Urban, Irvine, Cuzick, & Hammond-Kosack, 2015), CASINO (Shoaie et al., 2015), HMI™ module (Marzorati et al., 2014), and NetCooperate (Levy, Carr, Kreimer, Freilich, & Borenstein, 2015) are web-based tools and databases accessible for studying the microbe-microbe, diet-microbe and microbe-host interactions. GeoSymbio (Franklin, Stat, Pochon, Putnam, & Gates, 2012) and SymbioGenomesDB (Reyes-Prieto, Vargas-Chávez, Latorre, & Moya, 2015) are specialized computational resources developed for learning the host-microbiome interactions and microbial symbiosis (Table 3).

4. CH_4 mitigation interventions

CH_4 mitigation stratagies should ideally target features that are conserved across all rumen methanogenic archaea. Consequently, other beneficial anaerobes continue their normal digestive functions in the ruminants (Gottlieb, Wacher, Sliman, & Pimentel, 2016; Weimer, Stevenson, Mertens, & Thomas, 2008). Several CH_4 mitigation

Table 3
Systems biology tools and databases used for studying microbial mutualism in the gut environments.

Tool	Purpose	Reference
PHIDIAS	Molecular functions of pathogen and host genes	Xiang et al. (2007)
HPIDB	Microbial infections and drug targets discovery	Xiang et al. (2007)
GeoSymbio	Symbiodinium-host symbioses	Franklin et al. (2012)
PHISTO	Therapeutic targets discovery for microbial infections	Durmus et al. (2013)
PATRIC	Comparative genomic or transcriptomic analysis	Wattam et al. (2014)
HMI™ module	Mechanistic understanding of host-microbiome interactions	Marzorati et al. (2014)
PHI-base	Catalogues experimentally verified molecular virulence factors	Urban et al. (2015)
CASINO	Analysis of microbial communities through metabolic modeling	Shoaie et al. (2015)
NetCooperate	Host-microbe and microbe-microbe cooperation	Levy et al. (2015)
SymbioGenomesDB	Host-symbiont relationships	Reyes-Prieto et al. (2015)

interventions have been investigated such as change in dietary composition like use of fatty acids (Agarwal, Kamra, Chatterjee, Ravindra, & Chaudhary, 2008), tannin (Kumar et al., 2009), monensin (Weimer et al., 2008), plant extracts (Goel, Makkar, & Becker, 2008; Sirohi et al., 2012), fumarate and chemical inhibitors (Chidthaisong & Conrad, 2000; Miller & Wolin, 2001; Ungerfeld, Rust, Boone, & Liu, 2004), and anti-methanogenic vaccines (Wedlock, Janssen, Leahy, Shu, & Buddle, 2013; Williams, Popovski, & Rea, 2009). So far, only a small percentage of CH_4 mitigation has been successfully implemented by dietary changing. Some chemical inhibitors have been investigated to destroy the pathogenic bacteria, and those inhibitors may be beneficial to the host, which in turn affects the rumen microbiota. Thus, it is important to access the effect of methanogenic inhibitors on the stability of rumen healthy microbiota and also to discover new chemogenomic targets for CH_4 mitigation.

4.1. Methanogenic antibiotics and inhibitors

Chemical inhibitors or enzymes targeting essential functions of methanogenic archaea are delivered via slow-release capsules administered to the rumen. Neomycin, pseudomonic acid (Boccazzi, Zhang, & Metcalf, 2000; Jenal, Rechsteiner, & Tan, 1991), puromycin (Gernhardt, Possot, & Foglino, 1990), 8-aza-2, 6-diaminopurine (Pritchett, Zhang, & Metcalf, 2004) and 8-aza-hypoxanthine (Moore & Leigh, 2005) are methanogenic antibiotics, and inhibitors are presently used against *M. mariplaudis* and *M. barkeri*. Ethyl 2-butynoate, lovastatin, mevastatin, fluoroacetate, chloroform, 2-bromoethanesulphonate, and 2-nitroethanol are potential methanogenic inhibitors investigated to inhibit the methanogenesis of Methanobrevibacter and Methanobacterium (Chidthaisong & Conrad, 2000; Miller & Wolin, 2001; Ungerfeld et al., 2004). The growth of methanogenic archaea and persistence of 2-bromoethanesulfonate resistance increased with administration of it in bovine (Van Nevel & Demeyer, 1996). *M. ruminantium, M. mazei* and *M. mobile* found to be resistant to 3-bromopropanesulfonate up to 250 μmol/L in pure cultures (Ungerfeld et al., 2004). Therefore, it is consistent with the limited efficacy of 2-bromoethanesulfonate and 3-bromopropanesulfonate in lowering CH_4 production by rumen microbiome (Karnati, Sylvester, Ribeiro, Gilligan, & Firkins, 2009; Patra, Park, Kim, & Yu, 2017).

Monensin inhibits the methanogenesis from formate, but not from H_2—CO_2 in ruminants (Dellinger & Ferry, 1984). Bovine somatotrophin, monensin and lasalocid have been extensively used in beef and cattle farming to improve growth rates (Abrar, Kondo, Kitamura, Ban-Tokuda, & Matsui, 2016; Appuhamy et al., 2013; Etherton, 2013). Monensin affects electrolyte transport of methanogenic and propionate-producing bacteria. It also inhibits some bacteria responsible for proteolysis and deamination. A long term supplementation of monensin does not have an implementation in CH_4 reduction efficacy (Hook, Northwood, Wright, & McBride, 2009). Interestingly, Thermoplasmata archaea are methylotrophic (methylamine degrading) methanogens found in bovine rumen, which are able to mitigate methane emissions from lactating cows upon dietary supplementation with rapeseed oil (Poulsen et al., 2013). Thus, methanogenic inhibitors have been investigated in regard to their affect on the total population of Methanobacterium, Methanobrevibacter, Methanosphaera and Thermoplasmata making unbalanced microbial ecosystem in the rumen gut (Witzig, Zeder, & Rodehutscord, 2018; Zhou, Meng, & Yu, 2011; Zhu et al., 2017).

4.2. Chemogenomic targets

Generally, methanogenic antibiotics and inhibitors that target the key enzymes involved in the biosynthesis of cell wall, protein, vitamins and cofactors of MFI. Hydroxymethylglutaryl-SCoA reductase, aconitase, coenzyme M are common targets for many methanogenic inhibitors (Chidthaisong & Conrad, 2000; Miller & Wolin, 2001; Ungerfeld et al., 2004) (Table 4; Supplementary). Some of the methanogenic inhibitors have shown to decrease the proton gradient across the membrane, loss of digestible energy for ruminants, regulation of formate and H_2 oxidation, carbohydrate-fermentation and acetate metabolism (Chen & Wolin, 1979; Chidthaisong & Conrad, 2000; Liu,

Table 4
Methanogenic antibiotics and inhibitors used for reducing enteric methane emission from Methanobacterium and Methanobrevibacter genera resident in ruminants.

Compound	Conc. (mM/ml)	CH_4 inhibition (%)	Targets to be inhibited
2-Nitroethanol	0.012	99	Formate and H_2 oxidation
Sodium nitrate	0.012	70	Alternative electron acceptors
Acetylene	$7.2e^{-6}$	50	Proton gradient across the membrane
Ethylene	$1e^{-4}$	50	Proton gradient across the membrane
2-Bromoethanesulphonate	0.00025	100	Coenzyme M
Propynoic acid	0.004	96	Carbohydrate-fermentation pathway
Ethyl 2-butynoate	0.008	100	Loss of digestible energy for ruminants
Lovastatin	$1e^{-5}$	100	Hydroxymethylglutaryl-SCoAreductase
Mevastatin	$5.8e^{-6}$	100	Hydroxymethylglutaryl-SCoAreductase
Fluoroacetate	0.001	100	Aconitase
Chloroform	0.1	100	Acetate metabolism
Monensin	$5.9e^{-5}$	83	Loss of digestible energy for ruminants
lasalocid	$6.7e^{-5}$	89	Loss of digestible energy for ruminants

Table 5
Chemogenomic and vaccine targets identified in *M. formicicum* formethane mitigation.

Metabolism	Gene/Locus tag	EC	Molecular function
Amino acid metabolism	RS11100	4.2.3.4	3-Dehydroquinate synthase
	RS02945	2.5.1.19	3-Phosphoshikimate 1-carboxyvinyltransferase
	RS01470	4.1.1.20	Diaminopimelate decarboxylase
Cell cycle	RS05130| RS05135	5.99.1.3	DNA topoisomerase VI subunit AB
Cell envelop	*glmU*	2.3.1.157	Glucosamine-1-phosphate N-acetyltransferase
	glmU	2.7.7.23	UDP-N-acetylglucosaminediphosphorylase
Central carbon metabolism	*sdhA*/RS12465	1.3.5.1	Succinate dehydrogenase
	RS07380	1.5.98.2	5,10-methylenetetrahydromethanopterin reductase
	RS01770	1.5.98.1	Methylenetetrahydromethanopterin dehydrogenase
	RS10770| RS00440	2.3.1.101	Formylmethanofuran–tetrahydromethanopterinformyltransferase
	RS09605	3.5.4.27	N(5),N(10)-methenyltetrahydromethanopterincyclohydrolase
	RS09415| RS09420| RS09425| RS09430| RS09435| RS07735| RS00350| RS00355| RS00360| RS00365	2.8.4.1	Coenzyme-B sulfoethylthiotransferase
	RS09460| RS09455| RS09450| RS09445| RS09440| RS09465| RS09470| RS09475	2.1.1.86	Tetrahydromethanopterin S-methyltransferase subunit ABCDEFGH
	RS01320|RS02480	1.2.99.5	Formylmethanofuran dehydrogenase subunit E
Lipid metabolism	*ubiA*|RS11985|RS06695|RS06235|RS06250|RS02925	2.5.1.1	Dimethylallyltranstransferase
	RS05485	5.3.3.2	Isopentenyl pyrophosphate isomerase
Protein biosynthesis	RS10560|RS04105|RS04110	6.3.5.6	Asparaginyl-tRNA synthase subunit CDE
	RS01925|RS09115|RS10560|RS04105|RS04110	6.3.5.7	Glutaminyl-tRNA synthase subunit ABCDE
Vitamins and cofactors	RS10335	2.4.2.52	Triphosphoribosyl-dephospho-CoA synthase
Energy metabolism	RS06810|RS06805|RS06820|RS06800|RS06825|RS06815|RS06835|RS06830	3.6.3.14*	ATP synthase subunit ABCDFIK
	selD	2.7.9.3	Selenide, water dikinase
	bcrA, bcrB, bcrC, bcrD	1.3.7.8	Benzoyl-CoA reductase
	RS09460| RS09455| RS09450| RS09445| RS09440| RS09465| RS09470| RS09475	2.1.1.86*	Tetrahydromethanopterin S-methyltransferase subunit ABCDEFGH
Protein fate	*gspO*	3.4.23.43*	Prepilin peptidase

*Vaccine targets

Wang, Wang, & Chen, 2011; Zhou et al., 2011; Ungerfeld et al., 2004). However, the inhibitory effect is lost or reverted following long term administration in ruminants. It suggests the discovery of new therapeutic targets to be intended to resolve such crises.

4.3. Veterinary vaccination

Immunization is one of the novel CH_4 mitigation stratagies in which the animals acquire immunity against a particular rumen methanogenic Archaean (Iqbal, Cheng, Zhu, & Zeshan, 2008; Mitsumori & Sun, 2008; Ulyatt, Lassey, Shelton, & Walker, 2002). When animals are vaccinated, salivary antibodies are produced in the animal against rumen methanogenic archaea. A vaccine developed against *Streptococcus bovis* and *Lactobacillus* species causes a lactic acidosis, which elicits an immune response against rumen methanogenic archaea (Gill, Shu, & Leng, 2000; Shu et al., 2000). Using VF3 and VF7 antigens, anti-methanogenic vaccines have been investigated for the reduction of CH_4 emission from enteric fermentation (Williams et al., 2009; Wright et al., 2004). Vaccination of sheep with methanogenic archaeal fractions has been developed for effective CH_4 mitigation (Wedlock et al., 2010). Genome sequence of *M. ruminantium* M1 was compared with closely related methanogenic archaea to identify conserved methanogen surface proteins as suitable candidates for the development of vaccines (Leahy et al., 2010). Energy metabolism (EC 2.1.1.86, 3.6.3.14), protein fate (EC 3.4.23.43) and adhesion/cell surface proteins are identified as vaccine targets for MFI (Table 5; Supplementary). Yet, new CH_4 mitigation interventions should be addressed in the development of alternative veterinary vaccines against MFI. Any veterinary vaccine should be targeted methanogen-specific proteins and should not affect the growth of other beneficial microorganisms, which can be resolved by systems-biology approach.

5. Conclusions

Grazing ruminant animals are important contributors to the CH_4 pool and account for 25% of greenhouse gas emission in the world. A genome-scale metabolic network of MFI could be reconstructed to elucidate its metabolic symbiosis across the gut microbiota and host. The mechanisms underlying syntrophic and competitive behaviors of this microorganism can be explored with experiment-driven molecular hypotheses. Metabolic modeling process may serve as a platform to discover and prioritize the potential chemogenomic and vaccine targets from MFI for CH_4 mitigation interventions. To resolve this issue effectively at the systems-scale, we should address the following questions; 1. What are the key metabolites to be produced from MFI to ensure its growth and methanogenesis in a rumen ecosystem? 2. How does the core metabolic network of MFI determined its symbiotic behavior across the physiologically distinct anaerobes? and 3. How is MFI interacting with gut microbiota via metabolic crosstalk in response to microbial symbiosis, drugs and nutrients?

The development of CH_4 mitigation interventions is a great concern for improving animal production efficiency because of the demand for increased meat and milk products. The H_2 scavenging action of MFI is an essential function, since it prevents accumulation of H_2 produced as a result of enteric fermentation. Moreover, it is imperative for us to know that if the rumen methanogenic archaea are inhibited, what would be the alternate ways in which to reduce the accumualtion of H_2. Metabolic symbiosis of MFI in response to different environmental stimuli has resulted from the action of syntrophic and competitive bacteria in the ruminants, and it is important to understand its growth physiology in the gut environment. CH_4 mitigation strategies should be developed, but without affecting the beneficial rumen microbiome and microbiota, and without compromise to the digestive function of ruminants. Methanogenic antibiotics, inhibitors and vaccines have been narrow spectrum and species-specific activity, reflecting the demand for the potential target discovery for wide-range of methanogenic archaea.

Conflict of interest

The authors declare that this article's content has no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.vas.2018.09.001.

References

Abrar, A., Kondo, M., Kitamura, T., Ban-Tokuda, T., & Matsui, H. (2016). Effect of supplementation of rice bran and fumarate alone or in combination on in vitro rumen fermentation, methanogenesis and methanogens. *Animal Science Journal, 87*, 398–404.

Agarwal, N., Kamra, D. N., Chatterjee, P. N., Ravindra, K., & Chaudhary, L. C. (2008). In vitro methanogenesis, microbial profile and fermentation of green forages with buffalo rumen liquor as influenced by 2-bromoethanesulphonic acid. *Asian-Australasian Journal of Animal Sciences, 21*, 818–823.

Andrade-Montemayor, H., Gasca, T. G., & Kawas, J. (2009). Ruminal fermentation modification of protein and carbohydrate by means of roasted and estimation of microbial protein synthesis. *Revista Brasileira de Zootecnia, 38*.

Appuhamy, J. A., Strathe, A. B., Jayasundara, S., Wagner-Riddle, C., Dijkstra, J., France, J., et al. (2013). Anti-methanogenic effects of monensin in dairy and beef cattle: A meta-analysis. *Journal of Dairy Science, 96*, 5161–5173.

Asanuma, N., Iwamoto, M., & Hino, T. (1999). Effect of the addition of fumarate on methane production by ruminal microorganisms in vitro. *Journal of Dairy Science, 82*, 780–787.

Balch, W. E., Fox, G. E., & Magrum, L. J. (1979). Methanogens: Reevaluation of a unique biological group. *Microbiological Reviews, 43*, 260–296.

Bath, C., Morrison, M., Ross, E. M., Hayes, B. J., & Cocks, B. G. (2012). The symbiotic rumen microbiome and cattle performance: A brief review. *Animal Production Science, 53*, 876–881.

Battumur, U., Yoon, Y. M., & Kim, C. H. (2016). Isolation and characterization of a new *Methanobacterium formicicum* KOR-1 from an anaerobic digester using pig slurry. *Asian-Australasian Journal of Animal Sciences, 29*, 586–953.

Benedict, M. N., Gonnerman, M. C., Metcalf, W. W., & Price, N. D. (2012). Genome-scale metabolic reconstruction and hypothesis testing in the methanogenic archaeon Methanosarcina acetivorans C2A. *Journal of Bacteriology, 194*, 855–865.

Bharathi, M., & Chellapandi, P. (2017). Intergenomic evolution and metabolic cross-talk between rumen and thermophilic autotrophic methanogenic archaea. *Molecular Phylogenetics and Evolution, 107*, 293–304.

Boccazzi, P., Zhang, J. K., & Metcalf, W. W. (2000). Generation of dominant selectable markers for resistance to pseudomonic acid by cloning and mutagenesis of the ileS gene from the archaeonMethanosarcina barkerifusaro. *Journal of Bacteriology, 182*, 2611–2618.

Broers, C. A., Meijers, H. H., Symens, J. C., Stumm, C. K., Vogels, G. D., & Brugerolle, G. (1993). Symbiotic association of Psalteriomonas vulgaris n. spec. with *Methanobacterium formicicum*. *European Journal of Protistology, 29*, 98–105.

Bryant, M. P., & Boone, D. R. (1987). Isolation and characterization of *Methanobacterium formicicum* MF. *International Journal of Systematic and Evolutionary, 37*, 171.

Burcelin, R. (2010). Regulation of metabolism: A cross-talk between gut microbiota and its human host. *Physiology, 27*, 300–307.

Cani, P. D., & Delzenne, N. M. (2009). The role of the gut microbiota in energy metabolism and metabolic disease. *Current Pharmaceutical Design, 15*, 1546–1558.

Chaucheyras-Durand, F., Masséglia, S., Fonty, G., & Forano, E. (2010). Influence of the composition of the cellulolytic flora on the development of hydrogenotrophic microorganisms, hydrogen utilization, and methane production in the rumens of gnotobiotically reared lambs. *Applied and Environmental Microbiology, 76*, 7931–7937.

Chellapandi, P., Prabaharan, D., & Uma, L. (2010). Evaluation of methanogenic activity of biogas plant slurry for monitoring codigestion of ossein factory wastes and cyanobacterial biomass. *Applied Biochemistry and Biotechnology, 162*, 524–535.

Chen, M., & Wolin, M. J. (1979). Effect of monensin and lasalocid-sodium on the growth of methanogenic and rumen saccharolytic bacteria. *Applied and Environmental Microbiology, 38*, 72–77.

Chidthaisong, A., & Conrad, R. (2000). Pattern of non-methanogenic and methanogenic degradation of cellulose in anoxic rice field soil. *FEMS Microbiology Ecology, 31*, 87–94.

Darcy, T. J., Sandman, K., & Reeve, J. N. (1995). *Methanobacterium formicicum*, a mesophilic methanogen, contains three HFo histones. *Journal of Bacteriology, 177*, 858–860.

Dellinger, C. A., & Ferry, J. G. (1984). Effect of monensin on growth and methanogenesis of *Methanobacterium formicicum*. *Applied and Environmental Microbiology, 48*, 680–682.

Delzenne, N. M., & Cani, P. D. (2011). Interaction between obesity and the gut microbiota: Relevance in nutrition. *Annual Review of Nutrition, 31*, 15–31.
Ding, T., Case, K. A., Omolo, M. A., Reiland, H. A., Metz, Z. P., Diao, X., et al. (2016). Predicting essential metabolic genome content of Niche-Specific enterobacterial huma4n pathogens during simulation of host environments. *PLoS One, 11*, e0149423.
Durmus, S., Cakır, T., Özgür, A., & Guthke, R. (2015). A review on computational systems biology of pathogen–host interactions. *Front Microbiology, 6*, 235.
Durmus, S., Tekir, S., Cakır, T., Ardic, E., Sayılırbas, A. S., Konuk, G., et al. (2013). PHISTO: Pathogen-host interaction search tool. *Bioinformatics, 29*, 1357–1358.
Ekarius, C. (2010). *Small-Scale livestock farming: A grass-based approach for health, sustainability, and profit.* Storey Publishing 192.
Etherton, T. D. (2013). Clinical review 21: The efficacy and safety of growth hormone for animal agriculture. *The Journal of Clinical Endocrinology & Metabolism, 72*, 957.
Fabry, S., Lang, J., Niermann, T., Vingron, M., & Hensel, R. (1989). Nucleotide sequence of the glyceraldehyde-3-phosphate dehydrogenase gene from the mesophilic methanogenic archaebacteria Methanobacterium bryantii and *Methanobacterium formicicum*. Comparison with the respective gene structure of the closely related extreme thermophile Methanothermusfervidus. *European Journal of Biochemistry, 179*, 405–413.
Feist, A. M., Scholten, J. C. M., Palsson, B. O., Brockman, F. J., & Ideker, T. (2006). Modeling methanogenesis with a genome-scale metabolic reconstruction of Methanosarcina barkeri. *Molecular Systems Biology, 2* 2006.0004.
Forster, P. V., Ramaswamy, P., Artaxo, T., Berntsen, R., Betts, D. W., Fahey, J., et al. (2007). Changes in atmospheric constituents and in radiative forcing. In Miller (Ed.). *Climate change 2007: The physical basis. contribution of working group I to the fourth assessment report of the intergovernmental panel on climate change* (pp. 129–234). Cambridge, UK, and New York: Cambridge University Press.
Franklin, E. C., Stat, M., Pochon, X., Putnam, H. M., & Gates, R. D. (2012). GeoSymbio: A hybrid, cloud-based web application of global geospatial bioinformatics and ecoinformatics for Symbiodinium-host symbioses. *Molecular Ecology Resources, 12*, 369–373.
Gao, Y. D., Zhao, Y., & Huang, J. (2014). *Metabolic modeling of common Escherichia coli strains in human gut microbiome.* BioMed Research International694967.
Gernhardt, P., Possot, O., Foglino, M., et al. (1990). Construction of an integration vector for use in the archaebacteriumMethanococcus voltae and expression of a eubacterial resistance gene. *Molecular Genetics and Genomics, 221*, 273–279.
Gill, H. S., Shu, Q., & Leng, R. A. (2000). Immunization with Streptococcus bovis protects against lactic acidosis in sheep. *Vaccine, 18*, 2541–2548.
Goel, G., Makkar, H. P., & Becker, K. (2008). Changes in microbial community structure, methanogenesis and rumen fermentation in response to saponin-rich fractions from different plant materials. *Journal of Applied Microbiology, 105*, 770–777.
Gonnerman, M. C., Benedict, M. N., Feist, A. M., Metcalf, W. W., & Price, N. D. (2013). Genomically and biochemically accurate metabolic reconstruction of Methanosarcina barkeriFusaro, iMG746. *Biotechnology Journal, 8*, 1070–1079.
Gottlieb, K., Wacher, V., Sliman, J., & Pimentel, M. (2016). Review article: Inhibition of methanogenic archaea by statins as a targeted management strategy for constipation and related disorders. *Alimentary Pharmacology & Therapeutics, 43*, 197–212.
Goyal, N., Widiastuti, H., Karimi, I. A., & Zhou, Z. (2014). A genome-scale metabolic model of Methanococcus maripaludis S2 for CO_2 capture and conversion to methane. *Molecular BioSystems, 10*, 1043–1054.
Gutiérrez, G. (2012). Draft genome sequence of *Methanobacterium formicicum* DSM 3637, an archaebacterium isolated from the methane producer amoeba Pelomyxapalustris. *Journal of Bacteriology, 194*, 6967–6968.
Heinken, A., Sahoo, S., Fleming, R. M., & Thiele, I. (2013). Systems-level characterization of a host-microbe metabolic symbiosis in the mammalian gut. *Gut Microbes, 4*, 28–40.
Henderson, G., Cox, F., Ganesh, S., Jonker, A., Young, W., & Janssenb, P. H. (2015). Rumen microbial community composition varies with diet and host, but a core microbiome is found across a wide geographical range. *Scientific Reports, 5*, 14567.
Hook, S. E., Wright, A. D., & McBride, B. W. (2010). Methanogens: Methane producers of the rumen and mitigation strategies. *Archaea*945785.
Hook, S. E., Northwood, K. S., Wright, A. D., & McBride, B. W. (2009). Long-term monensin supplementation does not significantly affect the quantity or diversity of methanogens in the rumen of the lactating dairy cow. *Applied and Environmental Microbiology, 75*, 374–380.
Hristov, A. N., Oh, J., Firkins, J. L., Dijkstra, J., Kebreab, E., Waghorn, G., et al. (2013). Special topics—Mitigation of methane and nitrous oxide emissions from animal operations: I. A review of enteric methane mitigation options. *Journal of Animal Sciences, 91*, 5045–5069.
Hsiao, E. Y., McBride, S. W., Hsien, S., Sharon, G., Hyde, E. R., McCue, T., et al. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell, 155*, 1451–1463.
IPCC (2007). Climate Change 2007: Mitigation. In B. Metz, O. R. Davidson, P. R. Bosch, R. Dave, & L. A. Meyer (Eds.). *Contribution of Working Group III to the Fourth Assessment Report of the IntergovernmentalPanel on Climate Change* (pp. xxx). Cambridge, United Kingdom and New York, NY, USA: Cambridge University Press.
Iqbal, M. F., Cheng, Y., Zhu, W., & Zeshan, B. (2008). Mitigation of ruminant methane production: Current strategies, constraints and future options. *World Journal of Microbiology and Biotechnology, 24*, 2747–2755.
Jenal, U., Rechsteiner, T., Tan, P. Y., et al. (1991). Isoleucyl-tRNAsynthetase of Methanobacterium thermoautotrophicum Marburg. Cloning of the gene, nucleotide sequence, and localization of a base change conferring resistance to pseudomonic acid. *The Journal of Biological Chemistry, 266*, 10570–10577.
Ji, B., & Nielsen, J. (2015). From next-generation sequencing to systematic modeling of the gut microbiome. *Frontiers in Genetics, 6*, 219.
Joblin, K. N., Naylor, G. E., & Williams, A. G. (1990). Effect of Methanobrevibacter smithii on xylanolytic activity of anaerobic ruminal fungi. *Applied and Environmental Microbiology, 56*, 2287–2295.
Kandiba, L., & Eichler, J. (2013). Analysis of putative nonulosonic acid biosynthesis pathways in Archaea reveals a complex evolutionary history. *FEMS Microbiology Letters, 345*, 110–120.
Karnati, S. K., Sylvester, J. T., Ribeiro, C. V., Gilligan, L. E., & Firkins, J. L. (2009). Investigating unsaturated fat, monensin, or bromoethanesulfonate in continuous cultures retaining ruminal protozoa. I. Fermentation, biohydrogenation, and microbial protein synthesis. *Journal of Dairy Science, 92*, 3849–3860.
Kelly, W. J., Leahy, S. C., Li, D., Perry, R., Lambie, S. C., Attwood, G. T., et al. (2014). The complete genome sequence of the rumen methanogen *Methanobacterium formicicum* BRM9. *Standards in Genomic Sciences, 8*, 9–15.
Kern, T., Linge, M., & Rother, M. (2015). Methanobacterium aggregans sp. nov., a hydrogenotrophic methanogenic archaeon isolated from an anaerobic digester. *International Journal of Systematic and Evolutionary Microbiology, 65*, 1975–1980.
Koeth, R. A., Wang, Z., Levison, B. S., et al. (2013). Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature Medicine, 19*, 576–585.
Kumar, R., & Nanduri, B. (2010). HPIDB–a unified resource for host-pathogen interactions. *BMC Bioinformatics, 7*, 11.
Kumar, S., Puniya, A., Puniya, M., Dagar, S., Sirohi, S., Singh, K., et al. (2009). Factors affecting rumen methanogens and methanemitigation strategies. *World Journal of Microbiology and Biotechnology, 25*, 1557–1566.
Kumar, V. S., Ferry, J. G., & Maranas, C. D. (2011). Metabolic reconstruction of the archaeon methanogen Methanosarcina acetivorans. *BMC Systems Biology, 5*, 28.
Leahy, S. C., Kelly, W. J., Altermann, E., Ronimus, R. S., Yeoman, C. J., Pacheco, D. M., et al. (2010). The genome sequence of the rumen methanogen Methanobrevibacter ruminantium reveals new possibilities for controlling ruminant methane emissions. *PLoS One, 5*, e8926.
Leahy, S. C., Kelly, W. J., Li, D., Li, Y., Altermann, E., Lambie, S. C., et al. (2013a). The complete genome sequence of Methanobrevibacter sp. AbM4. *Standards in Genomic Sciences, 8*, 215–227.
Leahy, S. C., Kelly, W. J., Ronimus, R. S., Wedlock, N., Altermann, E., & Attwood, G. T. (2013b). Genome sequencing of rumen bacteria and archaea and its application to methane mitigation strategies. *Animal, 7*, 235–243.
Levy, R., Carr, R., Kreimer, A., Freilich, S., & Borenstein, E. (2015). NetCooperate: A network-based tool for inferring host-microbe and microbe-microbe cooperation. *BMC Bioinformatics, 16*, 164.
Lie, T. J., Hendrickson, E. L., Niess, U. M., Moore, B. C., Haydock, A. K., & Leigh, J. A. (2010). Overlapping repressor binding sites regulate expression of the Methanococcus maripaludis glnK1 operon. *Molecular Microbiology, 75*, 755–762.
Liu, H., Wang, J., Wang, A., & Chen, J. (2011). Chemical inhibitors of methanogenesis and putative applications. *Applied Microbiology and Biotechnology, 89*, 1333–1340.
Liu, L., Agren, R., Bordel, S., & Nielsen, J. (2010). Use of genome-scale metabolic models for understanding microbial physiology. *FEBS Letters, 584*, 2556–2564.
Lo, C. C., Bonner, C. A., Xie, G., D'Souza, M., & Jensen, R. A. (2009). Cohesion group approach for evolutionary analysis of aspartokinase, an enzyme that feeds a branched network of many biochemical pathways. *Microbiology and Molecular Biology Reviews, 73*, 551–594.
Magingo, F. S. S., & Stumm, C. K. (1991). Nitrogen fixation by *Methanobacterium formicicum*. *FEMS Microbiology Letters, 81*, 273–278.
Mamuad, L., Kim, S. H., Jeong, C. D., Choi, Y. J., Jeon, C. O., & Lee, S. S. (2014). Effect of fumarate reducing bacteria on in vitro rumen fermentation, methane mitigation and microbial diversity. *The Journal of Microbiology, 52*, 120–128.
Mamuad, L. L., Kim, S. H., Lee, S. S., Cho, K. K., Jeon, C. O., & Lee, S. S. (2012). Characterization, metabolites and gas formation of fumarate reducing bacteria isolated from Korean native goat (Capra hircuscoreanae). *The Journal of Microbiology, 50*, 925–931.
Marzorati, M., Vanhoecke, B., De Ryck, T., Sadabad, M. S., Pinheiro, I., Possemiers, S., et al. (2014). The HMI™ module: A new tool to study the Host-Microbiota Interaction in the human gastrointestinal tract in vitro. *BMC Microbiology, 14*, 133.
Maus, I., Stantscheff, R., Wibberg, D., Stolze, Y., Winkler, A., Pühler, A., et al. (2014). Complete genome sequence of the methanogenic neotype strain *Methanobacterium formicicum* MF (T.). *Journal of Bacteriology, 20*, 192.
Maus, I., Wibberg, D., Stantscheff, R., Cibis, K., Eikmeyer, F. G., König, H., et al. (2013). Complete genome sequence of the hydrogenotrophic archaeonMethanobacterium sp. Mb1 isolated from a production-scale biogas plant. *Journal of Bacteriology, 168*, 734–736.
Miller, T. L., & Wolin, M. J. (2001). Inhibition of growth of methane-producing bacteria of the ruminant forestomach by hydroxymethylglutaryl-SCoAreductase inhibitors. *Journal of Dairy Science, 84*, 1445–1448.
Mitsumori, M., & Sun, W. (2008). Control of rumen microbial fermentation for mitigating methane emissions from the rumen. *Asian-Australasian Journal of Animal Sciences, 21*, 144–154.
Moe, W. M., Yan, J., Nobre, M. F., da Costa, M. S., & Rainey, F. A. (2009). Dehalogenimonaslykanthroporepellens gen. nov., sp. nov., a reductively dehalogenating bacterium isolated from chlorinated solvent-contaminated groundwater. *International Journal of Systematic and Evolutionary, 59*, 2692–2697.
Moore, B. C., & Leigh, J. A. (2005). Markerless mutagenesis in Methanococcus maripaludis demonstrates roles for alanine dehydrogenase, alanine racemase, and alanine permease. *Journal of Bacteriology, 187*, 972–979.
Morgavi, D. P., Rathahao-Paris, E., Popova, M., Boccard, J., Nielsen, K. F., & Boudra, H. (2015). Rumen microbial communities influence metabolic phenotypes in lambs. *Frontiers in Microbiology, 6*, 1060.
Morowitz, M. J., Carlisle, E., & Alverdy, J. C. (2011). Contributions of intestinal bacteria to nutrition and metabolism in the critically ill. *The Surgical Clinics of North America, 91*, 771–785.

Patel, P. S., & Ferry, J. G. (1988). Characterization of the upstream region of the formate dehydrogenase operon of *Methanobacterium formicicum*. *Journal of Bacteriology, 170*, 3390–3395.
Patra, A., Park, T., Kim, M., & Yu, Z. (2017). Rumen methanogens and mitigation of methane emission by anti-methanogenic compounds and substances. *Journal of Animal Science and Biotechnology, 8*, 13.
Pavlostathis, S. G., Miller, T. L., & Wolin, M. J. (1990). Cellulose fermentation by continuous cultures of Ruminococcusalbus and Methanobrevibacter smithii. *Applied Microbiology and Biotechnology, 33*, 109–116.
Pimentel, M., Gunsalus, R. P., Rao, S. S. C., & Zhang, H. (2012). Methanogens in Human Health and Disease. *American Journal of Gastroenterology Supplements, 1*, 28–33.
Poulsen, M., Schwab, C., Jensen, B. B., Engberg, R. M., Spang, A., Canibe, N., et al. (2013). Methylotrophic methanogenic Thermoplasmata implicated in reduced methane emissions from bovine rumen. *Nature Communications, 4*, 1428.
Pritchett, M. A., Zhang, J. K., & Metcalf, W. W. (2004). Development of a markerless genetic exchange method for Methanosarcina acetivorans C2A and its use in construction of new genetic tools for methanogenic archaea. *Applied and Environmental Microbiology, 70*, 1425–1433.
Reyes-Prieto, M., Vargas-Chávez, C., Latorre, A., & Moya, A. (2015). *SymbioGenomesDB: A database for the integration and access to knowledge on host–symbiont relationships.* Database (Oxford) bav109.
Sadhukhan, P. P., & Raghunathan, A. (2014). Investigating host-pathogen behavior and their interaction using genome-scale metabolic network models. *Methods in Molecular Biology, 1184*, 523–562.
Schauer, N. L., & Ferry, J. G. (1980). Metabolism of formate in *Methanobacterium formicicum*. *Journal of Bacteriology, 142*, 800–807.
Schauer, N. L., & Ferry, J. G. (1982). Properties of formate dehydrogenase in *Methanobacterium formicicum*. *Journal of Bacteriology, 150*, 1–7.
Sedano-Núñez, V. T., Boeren, S., Stams, A. J. M., & Plugge, C. M. (2018). Comparative proteome analysis of propionate degradation by Syntrophobacterfumaroxidans in pure culture and in coculture with methanogens. *Environmental Microbiology*. https://doi.org/10.1111/1462-2920.14119.
Shoaie, S., & Nielsen, J. (2014). Elucidating the interactions between the human gut microbiota and its host through metabolic modeling. *Frontiers in Genetics, 5*, 86.
Shoaie, S., Ghaffari, P., Kovatcheva-Datchary, P., Mardinoglu, A., Sen, P., Pujos-Guillot, E., de Wouters, T., et al. (2015). Quantifying diet-induced metabolic changes of the human gut microbiome. *Cell Metabolism, 22*, 320–331.
Shoaie, S., Karlsson, F., Mardinoglu, A., Nookaew, I., Bordel, S., & Nielsen, J. (2013). Understanding the interactions between bacteria in the human gut through metabolic modeling. *Scientific Reports, 3*, 2532.
Shu, Q., Hillard, M. A., Bindon, B. M., Duan, E., Xu, Y., Bird, S. H., et al. (2000). Effects of various adjuvants on efficacy of a vaccine against Streptococcus bovis and Lactobacillus spp. In cattle. *American Journal of Veterinary Research, 61*, 839–843.
Singer, M. (2010). Pathogen-pathogen interaction: A syndemic model of complex biosocial processes in disease. *Virulence, 1*, 10–18.
Sirohi, S. K., Goel, N., & Pandey, P. (2012). Efficacy of different methanolic plant extracts on anti-methanogenesis, rumen fermentation and gas production kinetics in vitro. *Open Veterinary Journal, 2*, 72–77.
Sommer, F., & Bäckhed, F. (2013). The gut microbiota - masters of host development and physiology. *Nature Reviews Microbiology, 11*, 227–238.
Sousa, D. Z., Smidt, H., Alves, M. M., & Stams, A. J. (2007). Syntrophomonaszehnderi sp. nov., an anaerobe that degrades long-chain fatty acids in co-culture with *Methanobacterium formicicum*. *International Journal of Systematic and Evolutionary, 57*, 609–615.
Stenman, L. K., Burcelin, R., & Lahtinen, S. (2015). Establishing a causal link between gut microbes, body weight gain and glucose metabolism in humans – towards treatment with probiotics. *Beneficial Microbes, 7*, 11–22.
Stolyar, S., Van Dien, S., Hillesland, K. L., Pinel, N., et al. (2007). Metabolic modeling of a mutualistic microbial community. *Molecular Systems Biology, 3*, 92.
Taylor, B. L., & Zhulin, I. B. (1999). PAS domains: Internal sensors of oxygen, redox potential, and light. *Microbiology and Molecular Biology Reviews, 63*, 479–506.
Thorpe, A. (2009). Enteric fermentation and ruminant eructation: The role (and control?) of methane in the climate change debate. *Climate Change, 93*, 407–431.
Tremaroli, V., & Bäckhed, F. (2012). Functional interactions between the gut microbiota and host metabolism. *Nature, 489*, 242–249.
Ulyatt, M. J., Lassey, K. R., Shelton, I. D., & Walker, C. F. (2002). Methane emission from dairy cows and wether sheep fed subtropical grass-dominant pastures in midsummer in New Zealand. *New Zealand Journal of Agricultural Research, 45*, 227–234.
Ungerfeld, E., Rust, S., Boone, D., & Liu, Y. (2004). Effects of several inhibitors on pure cultures of ruminal methanogens. *Journal of Applied Microbiology, 97*, 520–526.
Ungerfeld, E. M. (2015). Shifts in metabolic hydrogen sinks in the methanogenesis-inhibited ruminal fermentation: A meta-analysis. *Frontiers in Microbiology, 6*, 37.
Urban, M., Irvine, A. G., Cuzick, A., & Hammond-Kosack, K. E. (2015). Using the pathogen-host interactions database (PHI-base) to investigate plant pathogen genomes and genes implicated in virulence. *Frontiers in Plant Science, 6*, 605.
U.S. Environmental Protection Agency. (2014). Climate change indicators in the United States,2014. Third edition. EPA 430-R-14-004.
Van Nevel, C., & Demeyer, D. (1996). Control of rumen methanogenesis. *Environmental Monitoring and Assessment, 42*, 73–97.
Wattam, A. R., Gabbard, J. L., Shukla, M., & Sobral, B. W. (2014). Comparative genomic analysis at the PATRIC, a bioinformatic resource center. *Methods in Molecular Biology, 1197*, 287–308.
Wedlock, D. N., Pedersen, G., Denis, M., Dey, D., Janssen, P. H., & Buddle, B. M. (2010). Development of a vaccine to mitigate greenhouse gas emissions in agriculture: Vaccination of sheep with methanogen fractions induces antibodies that block methane production in vitro. *New Zealand Veterinary Journal, 58*, 29–36.
Wedlock, N., Janssen, P. H., Leahy, S., Shu, D., & Buddle, B. M. (2013). Progress in the development of vaccines against rumen methanogens. *Animal, 7*, 244–252.
Weimer, P. J., Stevenson, D. M., Mertens, D. R., & Thomas, E. E. (2008). Effect of monensin feeding and withdrawal on populations of individual bacterial species in the rumen of lactating dairy cows fed high-starch rations. *Applied Microbiology and Biotechnology, 80*, 135–145.
White, W. B., & Ferry, J. G. (1992). Identification of formate dehydrogenase-specific mRNA species and nucleotide sequence of the fdhC gene of *Methanobacterium formicicum*. *Journal of Bacteriology, 174*, 4997–5004.
Williams, A. G., Withers, S. E., & Joblin, K. N. (1994). The effect of co cultivation with hydrogen-consuming bacteria on xylanolysis by Ruminococcusflavefaciens. *Current Microbiology, 29*, 133–138.
Williams, Y. J., Popovski, S., & Rea, S. M. (2009). A vaccine against rumen methanogens can alter the composition of archaeal populations. *Applied and Environmental Microbiology, 75*, 1860–1866.
Witzig, M., Zeder, M., & Rodehutscord, M. (2018). Effect of the ionophoremonensin and tannin extracts supplemented to grass silage on populations of ruminalcellulolytics and methanogens in vitro. *Anaerobe, 50*, 44–54.
Wolin, M., Miller, T., & Stewart, C. (1997). Microbe–microbe interactions. In P. N.. Hobson, & C. S.. Stewart (Eds.). *The rumen microbial ecosystem* (pp. 467–491). London, UK: Blackie Academic & Professional.
Worm, P., Stams, A. J., Cheng, X., & Plugge, C. M. (2011). Growth- and substrate-dependent transcription of formate dehydrogenase and hydrogenase coding genes in Syntrophobacterfumaroxidans and Methanospirillumhungatei. *Microbiology, 157*, 280–289.
Wright, A. D. J., Kennedy, P., O'Neill, C. J., Troovey, A. F., Popovski, S., Rea, S. M., et al. (2004). Reducing methane emissions in sheep by immunization against rumen methanogens. *Vaccine, 22*, 3976–3985.
Xiang, Z., Tian, Y., & He, Y. (2007). PHIDIAS: A pathogen-host interaction data integration and analysis system. *Genome Biology, 8*, R150.
Zhang, Y., Huang, D., Badgery, W. B., Kemp, D. R., Chen, W., Wang, X., et al. (2015). Reduced grazing pressure delivers production and environmental benefits for the typical steppe of north China. *Scientific Reports, 5*, 16434.
Zhou, Z., Meng, Q., & Yu, Z. (2011). Effects of methanogenic inhibitors on methane production and abundances of methanogens and cellulolytic bacteria in in vitro ruminal cultures. *Applied and Environmental Microbiology, 77*, 2634–2639.
Zhu, W., Sandman, K., Lee, G. E., Reeve, J. N., & Summers, M. F. (1998). NMR structure and comparison of the archaeal histone hfoB from the mesophile*Methanobacterium formicicum* with hmfB from the hyperthermophileMethanothermusfervidus. *Biochemistry, 37*, 10573–10580.
Zhu, Z., Noel, S. J., Difford, G. F., Al-Soud, W. A., Brejnrod, A., Sørensen, S. J., et al. (2017). Community structure of the metabolically active rumen bacterial and archaeal communities of dairy cows over the transition period. *PLoS One, 12*, e0187858.