



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Production of electricity and reduction of high-fat diet-induced IL-6 by glucose fermentation of *Leuconostoc mesenteroides*

John Jackson Yang^a, Adelia Riezka Rahim^b, Albert Jackson Yang^b, Tsung-Hsien Chuang^c, Chun-Ming Huang^{b,*}

^a Department of Life Sciences, National Central University, Taiwan

^b Department of Biomedical Sciences and Engineering, National Central University, Taiwan

^c Immunology Research Center, National Health Research Institutes, Taiwan



ARTICLE INFO

Article history:

Received 24 August 2020

Accepted 16 September 2020

Available online 30 September 2020

Keywords:

L. mesenteroides

Electrogenic

IL-6

Fermentation

ABSTRACT

Electrogenic bacteria can mediate electron transfer to conserve energy and promote growth. To examine bacterial electrogenicity, an *L. mesenteroides* EH-1 strain was cultured in rich media in the presence and absence of 2% glucose. After 12 h incubation, glucose triggered fermentation of *L. mesenteroides* EH-1 to produce >10 mmol/l acetate and elicit electricity measured by voltage changes. The electricity production was mediated by glucose fermentation since pre-treatment of *L. mesenteroides* EH-1 with furfural, a fermentation inhibitor, completely diminished the voltage increases. The deficiency of furfural pre-treated *L. mesenteroides* EH-1 in electricity production can be restored by the external addition of acetate into the bacterial culture, suggesting the function of acetate as an electron donor. Oral administration of HFD-fed mice with *L. mesenteroides* EH-1 in the presence or absence of glucose significantly attenuated the high level of pro-inflammatory IL-6 cytokine in blood. Bacterial electricity can be elicited by fermentation. Supplementation of fermenting and electrogenic *L. mesenteroides* EH-1 may provide a novel approach for the reduction of pro-inflammatory IL-6 cytokine that increased in chronic inflammation, autoimmune diseases, cancers, and infections.

© 2021 Published by Elsevier Inc.

1. Introduction

The ingestion of high-fat diet (HFD) has been proposed as a facilitating factor to disrupt gut microbiota homeostasis and cause both intestinal and systemic inflammation [1]. Previous studies showed that HFD changed the amount of the microbiota, preferring significant levels of luminal Firmicutes and Proteobacteria and lower levels of Bacteroidetes, which can prompt an expansion in the extent of lipopolysaccharide (LPS)-containing gut bacteria and permeability of intestinal barriers, causes an increase in the concentration of circulating LPS. HFD-induced dysbiotic microbiome, which has changed intestinal microbiota and intestinal permeability, may ultimately result in the massive inflammatory response [1,2]. Circulating and adipose-derived cytokines such as interleukin 6 (IL-6) are elevated in obese people [3]. Earlier studies supported a concept that HFD-induced inflammation may result from the accumulation of activated macrophages within adipose tissues and,

particularly, surrounding enlarged adipocytes of obese organisms [4].

Supplementation of probiotic bacteria to rebalance the dysbiotic microbiome caused by HFD may be an approach to reduce inflammation. Production of short-chain fatty acids (SCFAs) as anti-inflammatory agents has been extensively studied [5]. SCFAs can activate G-coupled protein receptors (GPCRs) include free fatty acid receptors 2 and 3 (Ffar2/3) [6] and/or inhibit histone deacetylases [7] to down-regulate the inflammatory response. In inflammatory bowel disease (IBD), obesity and inflammatory disorders have been found that decreased levels of intestinal SCFA or abnormal SCFA-producing gut bacteria. This may be caused by a decreased number of probiotic bacteria forming SCFA in the intestines. Stimulating or restoring probiotic bacteria in communities will be a positive path to reducing inflammation [8]. Saputro et al. have used mixed strain probiotics including *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Streptococcus thermophilus* to reduce the production of IL-6 [9]. Other studies showed that probiotics can act as adjunctive therapy to reduce inflammation in critically ill patients [10].

Our previous studies identified a *Leuconostoc mesenteroides*

* Corresponding author.

E-mail address: chunming@ncu.edu.tw (C.-M. Huang).

(*L. mesenteroides*) EH-1 strain, which can produce butyrate to lower the production of IL-6 in type 1 diabetic mice via Ffar2 [11]. SCFAs include acetate and butyrate, which have been recognized as electron donors [12]. The addition of acetate into bacterial cultures elicited electricity production [13]. For instance, acetate is the desired electron donor for *Geobacter* bacteria; Acetate may be oxidized in the *Geobacter* bacteria's tricarboxylic acid (TCA) process to provide energy for bacterial growth and electrode reduction [14]. *L. mesenteroides*, a fermentative Gram-positive bacterium, belonging to the Firmicutes phylum and is frequently used as a probiotic bacterium in traditional fermented foods [15]. A flavin-based extracellular electron transfer (EET) mechanism has been identified in Gram-positive bacteria for electricity production [16]. Orthologs of the identified EET genes can be found in probiotic lactic acid bacteria include *Lactococci*, *Lactobacilli*, and *Tetragenococci* species [16]. In this study, we found that *L. mesenteroides* EH-1 can mediate glucose fermentation to produce SCFAs. Glucose fermentation was essential for *L. mesenteroides* EH-1 to produce electricity and down-regulate the HFD-induced IL-6 increase.

2. Materials and methods

2.1. Ethics statement

Institute Cancer Research (ICR) female mice (8–9 weeks old) had supplied by the National Laboratory Animal Center, Taipei, Taiwan. Mice studies performed in strict accordance with a protocol authorized by Institutional Animal Care and Use Committee (IACUC) at National Central University (NCU), Taiwan with an approved protocol (NCU-106-016, 19 December 2017). Mice were sacrificed via inhalation of CO₂ anesthesia.

2.2. Bacterial culture

L. mesenteroides EH-1 strain was originally isolated from Mongolian curd cheese [11]. Bacteria were incubated overnight at 37 °C in the tryptic soy broth (TSB) (Sigma, St. Louis, MO, USA). The culture was diluted 1:100 and cultured to an optical density of 600 nm = 1.0. Bacteria were collected by centrifugation at 5,000xg for 10 min, washed with phosphate-buffered saline (PBS), and kept in PBS for further experiments.

2.3. Glucose fermentation of *L. mesenteroides* EH-1

L. mesenteroides EH-1 (10⁷ CFU/ml) was incubated at 37 °C for 24 h in rich media [11]. Phenol red [0.001% (w/v); Sigma] was added into rich media as an indicator of fermentation occurrence. Rich media and media with 2% glucose in the absence of bacteria were included as controls [17].

2.4. Gas chromatography-mass spectrometry (GC-MS) analysis

L. mesenteroides EH-1 (10⁷ CFU/ml) was incubated in TSB media (10 ml) in the presence of 2% glucose for 24 h. SCFAs in the fermentation media were done by GC-MS analysis using an Agilent 5890 Series II GC in conjunction with 5971 MS detector (Agilent Technologies, Inc., Palo Alto, CA). The levels of SCFA (acetate, propionate, butyrate, isobutyrate, and isovalerate) in the fermentation media were quantified by a calibration curve of Free Fatty Acids Test Standard (Restek Corporation, Bellefonte, PA) [18].

2.5. A chamber for detection of bacterial electricity

A laboratory-fabricated chamber equipped with cathode and anode was employed to detect bacterial electricity [19]. In brief, the

cathode was sealed with a Nafion membrane N117 as a proton exchange membrane (PEM). An external resistance (1000 Ω) were placed to connect the anode to cathode. The changes in voltage (mV) against time (min) were dynamically recorded every 10 s by a digital multimeter (Lutron, DM-9962SD, Sydney, Australia). *L. mesenteroides* EH-1 bacteria (10⁷ CFU/ml; 5 ml) in rich media in the absence or presence of 2% glucose were pipetted on the surface of the anode. In some experiments, *L. mesenteroides* EH-1 was treated at 100 °C for 30 min or pre-treated with 0.4% furfural, a fermentation inhibitor, for 12 h. Bacteria pre-treated with or without furfural in rich media contained 20 g/l glucose were cultured in the presence of acetate (0, 1, 5, 10 mmol/l) at 37 °C. Voltage changes were monitored for 300 min.

2.6. Administration of *L. mesenteroides* EH-1 to HFD-fed mice

Mice were fed with a standard vivarium-provided chow diet or 60% calorie HFD (BioLASCO Taiwan Co., Ltd.) and treated 200 µl of 2% glucose, *L. mesenteroides* EH-1 (10⁷ CFU) or *L. mesenteroides* EH-1 with glucose by oral gavage for 25 days at an interval of three days [17]. Some mice were fed with HFD and administered *L. mesenteroides* EH-1 plus glucose along with GLPG-0974 (1 mg/kg body weight) (Tocris Bioscience, Bristol, UK), a Ffar2 antagonist [11]. GLPG-0974 was dissolved in dimethylsulfoxide (DMSO). Four mice per group were used in each experiment.

2.7. IL-6 detection by enzyme-linked immunosorbent assay (ELISA)

Twenty-eight days after administration of *L. mesenteroides* EH-1, the fasting (4 h) retro-orbital sinus blood was collected in heparinized tubes and then centrifuged at 3,000xg for 15 min. Plasma was stored at –80 °C until use. A mouse IL-6 ELISA kit (R&D Systems, Minneapolis, MN, USA) was used to detect the levels of IL-6 in plasma.

2.8. Statistical analysis

Data analysis was conducted by unpaired *t*-test using GraphPad Prism® software. The *p*-values of <0.05 (*), <0.01 (**), and <0.001 (***) were considered significant. The mean ± standard deviation (SD) for at least three independent experiments was calculated.

3. Results

3.1. Production of SCFAs and electricity by glucose fermentation of *L. mesenteroides* EH-1

Incubation of media or media with glucose alone or bacteria alone for 12 h did not cause a significant change in the color of phenol red in the rich media. The phenol red in the rich media containing *L. mesenteroides* EH-1 in the presence of glucose turned yellow after 12 h incubation (Fig. 1a), indicating the occurrence of fermentation. GC-MS analysis was carried out to examine if SCFAs were produced during the glucose fermentation of *L. mesenteroides* EH-1. Five SCFAs include acetate, propionate, butyrate, isobutyrate, and isovalerate at different concentrations were detected in the fermentation media (Fig. 1b). Acetate was found to be an SCFA that was produced at the highest concentrate (>10 mmol/l) by glucose fermentation of *L. mesenteroides* EH-1.

Acetate has known to be an electron donor in a microbial fuel cell system [12,20,21]. We thus examined the electrogenicity of *L. mesenteroides* EH-1 strain in the presence of glucose. Little or no voltage change was recorded over a monitoring period of 300 min in media with glucose alone (Fig. 1c). Slightly increased in voltage was detected in media with *L. mesenteroides* EH-1 alone. The

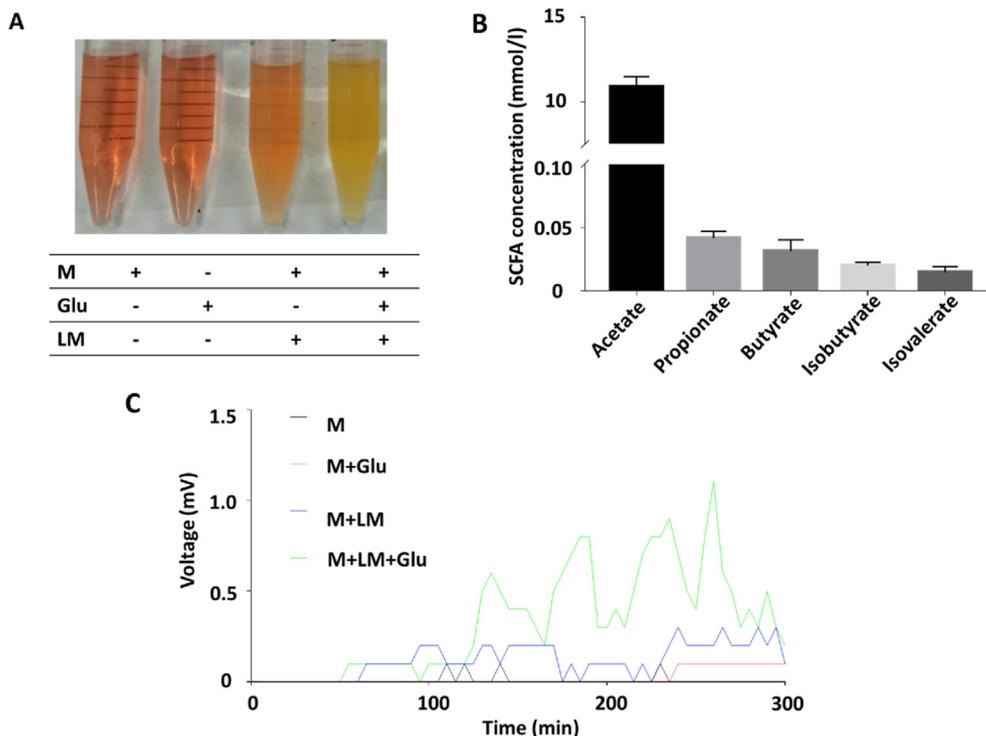


Fig. 1. Glucose fermentation of *L. mesenteroides* EH-1 produced SCFAs and electricity. (a) *L. mesenteroides* EH-1 (LM) was incubated in rich media (M) containing phenol red with and without glucose (Glu) for 12 h. The fermentation indicated by color changes of phenol red from red to yellow. (b) Five SCFAs in fermentation media were quantified by GC-MS analysis. (c) Electricity measured by voltage changes (mV) was detected for 300 min after adding media (M) or media with glucose (Glu) alone, *L. mesenteroides* EH-1 (LM) alone or *L. mesenteroides* EH-1 plus 2% glucose (M + LM + Glu) on the surface of anode. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

voltage was considerably raised to a peak of more than one mV when bacteria were placed in media in the presence of glucose. These data demonstrated that *L. mesenteroides* EH-1 is highly electrogenic when it was incubated with glucose.

3.2. Electricity production of *L. mesenteroides* EH-1 mediated by fermentation

Furfural displayed an inhibitory effect on bacterial and yeast fermentation by blocking the activities of enzymes in the pathway

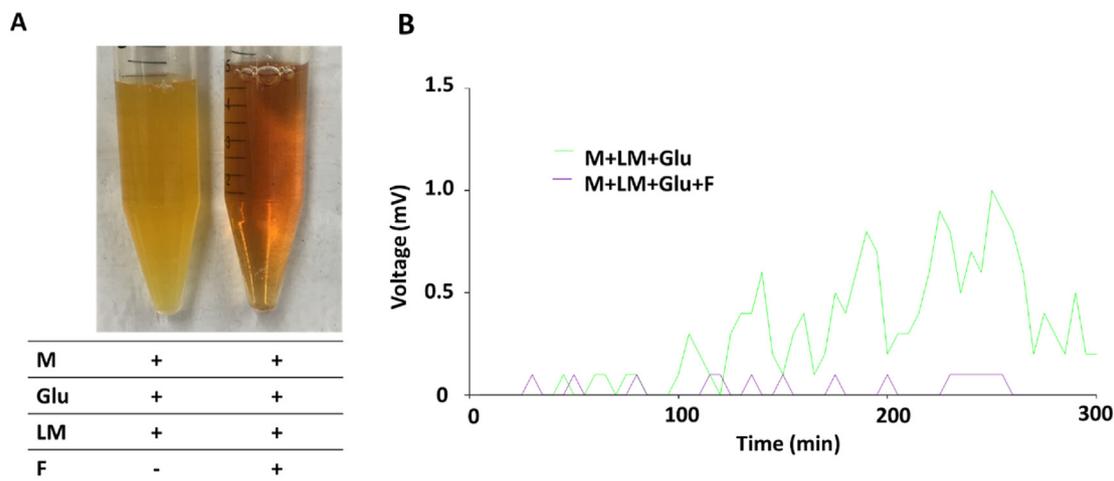


Fig. 2. Inhibition of glucose fermentation impeded electricity production of *L. mesenteroides* EH-1. (a) Media (M) with *L. mesenteroides* EH-1 (LM) plus glucose (Glu) in the presence or absence of furfural (F) were cultured for 12 h. The color change of phenol red in culture media of *L. mesenteroides* EH-1 plus glucose from red to yellow indicated the occurrence of fermentation. (b) *L. mesenteroides* EH-1 bacteria were pre-treated with or without furfural for 12 h. After pre-treatment, bacteria plus glucose were added onto the surface of anode for measurement of voltage changes (mV) for 300 min. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of fermentation [22,23]. Glucose fermentation of *L. mesenteroides* EH-1, a change in color from red to yellow, was suppressed when the 0.4% furfural was added into culture media for 12 h (Fig. 2a). To examine the essential role of glucose fermentation in electricity production, we pre-treated *L. mesenteroides* EH-1 furfural for 12 h before bacteria with 2% glucose were placed on the surface of the anode. In agreement with Fig. 1c, *L. mesenteroides* EH-1 without pre-treatment of furfural elicited more than one mV in the presence of glucose. However, the voltage change was markedly subsided when *L. mesenteroides* EH-1 was pre-treated with furfural. The result demonstrated that glucose fermentation was required for bacterial electricity production.

3.3. Induction of electrogenicity of *L. mesenteroides* EH-1 by addition of acetate

No significant voltage changes were detected in the media containing live or heat-killed *L. mesenteroides* EH-1 in the absence

of glucose. However, the voltage was provoked when *L. mesenteroides* EH-1 culture was externally added with 1, 5, or 10 mmol/l acetate (Fig. 3a). The addition of acetate at a concentration of 5 or 10 mmol/l substantially induced an elevated voltage with approximately one mV peak. The data suggested that acetate can replace glucose as an electron donor to induce bacterial electricity. Fig. 1 has shown the glucose fermentation of *L. mesenteroides* EH-1 can produce high acetate levels. Additionally, glucose fermentation can be efficiently inhibited by pre-treatment of bacteria with furfural. To investigate whether acetate can restore the deficiency of furfural pre-treated *L. mesenteroides* EH-1 in electricity production, 10 mmol/l acetate was externally added into the culture of furfural pre-treated *L. mesenteroides* EH-1 in presence of glucose. An elevated voltage was detected when acetate was added into media containing furfural pre-treated *L. mesenteroides* EH-1 and glucose (Fig. 3b). The result indicated that acetate can initiate the electrogenicity of *L. mesenteroides* EH-1.

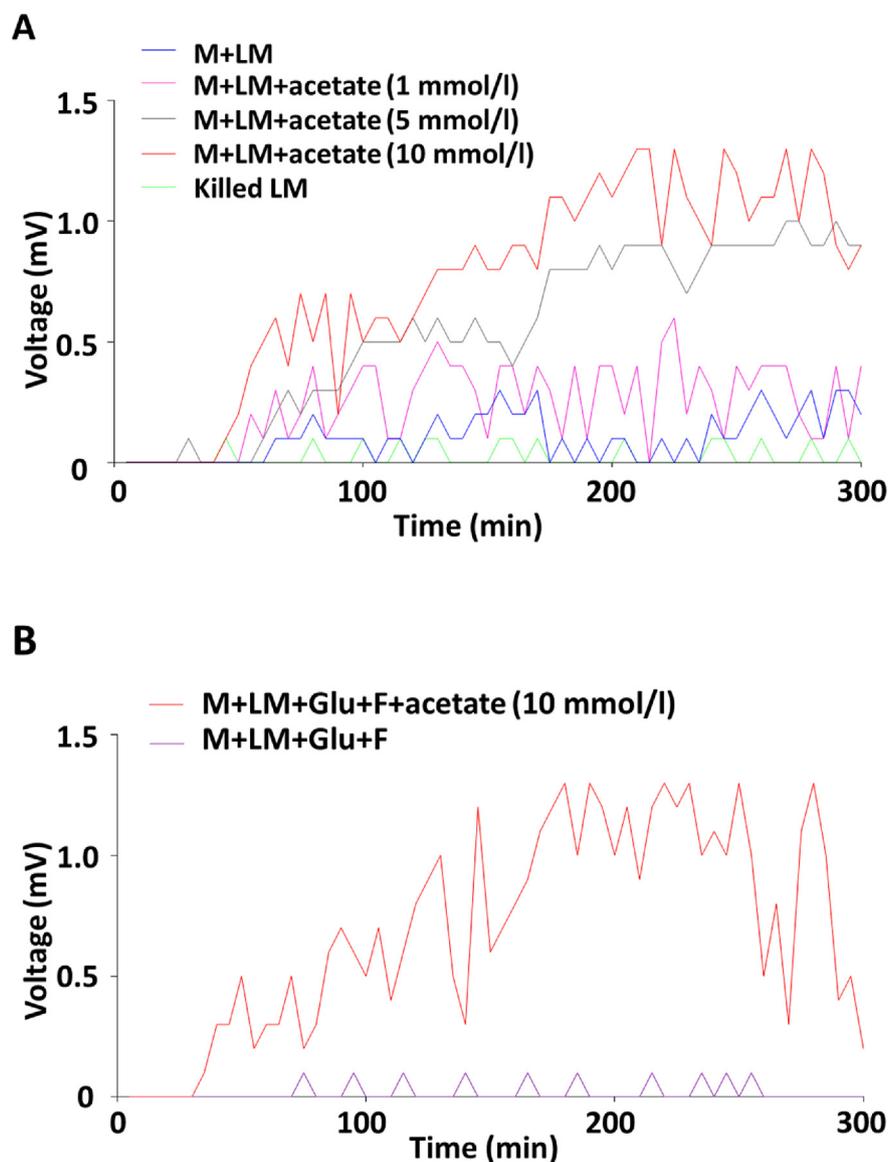


Fig. 3. Addition of acetate elicited electricity of bacteria pre-treated with furfural. (a) The surface of anode was placed with media (M) containing heat-killed (Killed LM) alone or live *L. mesenteroides* EH-1 (M + LM) plus acetate (1, 5 or 10 mmol/l). (b) The surface of anode was placed with media containing furfural pre-treated *L. mesenteroides* EH-1 in the presence or absence of 10 mmol/l acetate.

3.4. Reduction of HFD-induced IL-6 by *L. mesenteroides* EH-1

Consistent with previous findings [1], the level of IL-6 in plasma of mice fed with HFD for 25 days was significantly higher than that in mice fed with regular diet. To evaluate the probiotic activity of *L. mesenteroides* EH-1 to affect the plasma IL-6, HFD-fed mice were fed with *L. mesenteroides* EH-1 in the presence or absence of glucose. The mice treated with glucose alone did not influence the level of IL-6 in HFD-fed mice. By contrast, the level of IL-6 was decreased in HFD-fed mice treated with *L. mesenteroides* EH-1. The reduction of IL-6 was increased when HFD-fed mice were treated with *L. mesenteroides* EH-1 with glucose (Fig. 4). To examine the involvement of fermentation in HFD-induced IL-6, the mice were treated with GLPG-0974 to inhibit Ffar2 activity. The reduction of IL-6 by the administration of *L. mesenteroides* EH-1 with glucose was attenuated in HFD-fed mice administered with GLPG-0974 with *L. mesenteroides* EH-1 plus glucose (Fig. 4). The result demonstrated the requirement of *L. mesenteroides* EH-1 fermentation for the down-regulation of IL-6 induced by HFD.

4. Discussion

EET is a term about the ability of a broad range of electrogenic bacteria to transfer an electron from intercellular to extracellular space or an electron acceptor [24,25]. Recently human gut bacteria such as *Listeria monocytogenes*, *Enterococcus faecalis*, *Escherichia coli*, and many probiotic *Lactobacillus* species have been reported to express genes encoding proteins responsible for the EET process to promote bacterial growth [16,26]. Here we found that *L. mesenteroides* EH-1 can fermentatively metabolize glucose to produce SCFAs (Fig. 1). The glucose fermentation of *L. mesenteroides* EH-1 was essential for electricity production (Fig. 2) and reduction of HFD-induced IL-6 (Fig. 4). Among five identified SCFAs, acetate was most abundant in media of glucose fermentation of *L. mesenteroides* EH-1 (Fig. 1b). Previous study reported that acetate treatment had a net anti-inflammatory effect in reduction of IL-6 in

LPS-stimulated astrocytes [27]. Although mounting evidence supported the anti-inflammatory effects of SCFAs, it is not clear whether electricity produced by *L. mesenteroides* EH-1 can directly regulate the HFD-induced IL-6 increase in mice. The electrogenic *Salmonella enterica* serotype Typhimurium used the respiratory electron acceptor to promote its growth and compete with other microbiota in the lumen of inflamed gut [28]. Electrons can function as antioxidants to neutralize the positively charged free radicals, the hallmark of chronic inflammation [29]. Although inflammation induced by HFD may benefit *L. mesenteroides* EH-1 for growth, host may take advantage of electrons produced by *L. mesenteroides* EH-1 as antioxidants to quench the free radicals.

Furfural is a metabolite of bacterial fermentation, and its accumulation has been shown to inhibit fermentation by blocking the activities of multiple enzymes, including pyruvate dehydrogenase, acetolactate synthase, phosphotransacetylase, and acetate kinase in the pathway of bacterial fermentation [30–32]. It has been revealed that presence of furfural in the culture of *Clostridium thermocellum* fermentation decreased the acetate production [33]. Although acetate can serve as an electron donor [20] and produced in bacterial cytoplasm, we found that external addition of acetate into the culture of *L. mesenteroides* EH-1 triggered the bacterial electricity (Fig. 3). In fact, acetate can freely diffuse across the bacterial membrane in the protonated form [34] via the transporter acetate permease or succinate-acetate transporter protein [35]. Furfural may decrease acetate production during glucose fermentation of *L. mesenteroides* EH-1, resulting in the low level of acetate as an electron donor for electricity production. External addition of acetate into the bacterial culture may provide extra electron donors to restore electricity deficiency.

Although glucose enhanced the suppressive effect of *L. mesenteroides* EH-1 on the elevation of IL-6 in HFD-fed mice (Fig. 4), administration of *L. mesenteroides* EH-1 alone without glucose was effective to reduce the level of IL-6 in HFD-fed mice. Without glucose, *L. mesenteroides* EH-1 may utilize the various carbohydrates in mouse gut as carbon sources to produce SCFAs for suppressing the IL-6 induced by HFD. Additionally, *L. mesenteroides* EH-1 may use carbohydrates in HFD as carbon sources to produce monosaccharides such as glucose and galactose [36]. The high IL-6 in plasma of HFD-fed mice may result from an increase in the secretion of adipocytes and other cells. Hypertrophic adipocytes expressed pro-inflammatory genes and produced tremendous amounts of pro-inflammatory cytokines [37]. Furthermore, immune cells residing within the hypertrophic fat tissues can be primed toward pro-inflammatory subtypes [38]. These changes in adipose tissues may lead to elevated plasma levels of pro-inflammatory IL-6 cytokine in HFD-fed mice. IL-6 secreted by myeloid cells inhibited the accumulation of adipose tissue macrophages (ATM), but IL-6 secreted by adipocytes or muscle promotes ATM accumulation [37]. To date, macrophages or hepatocytes originating from adipose and hepatic Kupffer cells have been identified as cell targets for anti-inflammatory therapy [1]. Interactions between bacteria can promote pro-inflammatory signaling in multiple cell types of the intestine and affect the effectiveness of anti-inflammatory therapies on HFD [1]. We have previously shown that *L. mesenteroides* EH-1 exerted a probiotic activity to lower IL-6 level in type 1 diabetic mouse model [11]. In current study, we demonstrated that glucose fermentation of *L. mesenteroides* EH-1 could mediate Ffar2 to reduce HFD-induced IL-6. Besides obesity, many diseases associated with chronic inflammation or autoimmunity deficiency, and even cancers and coronavirus infection [39] can lead to high levels of IL-6 in blood [40]. Down-regulation of systemic IL-6 by administration of probiotic *L. mesenteroides* EH-1 to trigger a gut-organ axis provided a novel anti-inflammatory therapy.

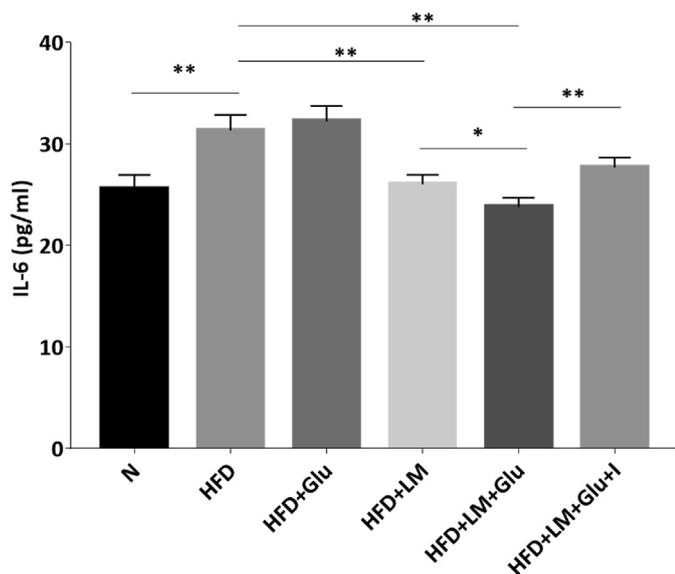


Fig. 4. Effect of *L. mesenteroides* EH-1 administration on IL-6 level in HFD-fed mice. Mice were fed with a standard vivarium-provided chow diet (N) or HFD and treated with glucose (Glu), *L. mesenteroides* EH-1 (LM) or *L. mesenteroides* EH-1 with glucose by oral gavage. Some mice were fed with HFD and treated with *L. mesenteroides* EH-1 with glucose in the presence of GLPG-0974 (I). The mean \pm SD for three separate experiments with four mice per group was calculated. * $p < 0.05$. ** $p < 0.001$. (two-tailed t-test).

Author contributions

J.J.Y., A.J.Y. and C.M.H. wrote manuscript. J.J.Y., A.J.Y. and A.R.R. performed experiments and T.H.C. assisted experimental designs. C.M.H. designed experiments and edited manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was supported by grants (108-2622-B-008-001-CC1; 108-2314-B-008-003-MY3, and 107-2923-B-008-001-MY3) awarded by the Ministry of Science and Technology (MOST), Taiwan.

References

- [1] S. Ding, M.M. Chi, B.P. Scull, R. Rigby, N.M. Schwerbrock, S. Magness, C. Jobin, P.K. Lund, High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse, *PLoS One* 5 (2010), e12191.
- [2] P.J. Turnbaugh, R.E. Ley, M.A. Mahowald, V. Magrini, E.R. Mardis, J.I. Gordon, An obesity-associated gut microbiome with increased capacity for energy harvest, *Nature* 444 (2006) 1027.
- [3] P.A. Kern, S. Ranganathan, C. Li, L. Wood, G. Ranganathan, Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance, *Am. J. Physiol. Endocrinol. Metab.* 280 (2001) E745–E751.
- [4] S.P. Weisberg, D. McCann, M. Desai, M. Rosenbaum, R.L. Leibel, A.W. Ferrante, Obesity is associated with macrophage accumulation in adipose tissue, *J. Clin. Invest.* 112 (2003) 1796–1808.
- [5] S. Tedelind, F. Westberg, M. Kjerrulf, A. Vidal, Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease, *World J. Gastroenterol.* 13 (2007) 2826.
- [6] S.P. Mishra, P. Karunakar, S. Taraphder, H. Yadav, Free fatty acid receptors 2 and 3 as microbial metabolite sensors to shape host health: pharmacophysiological view, *Biomedicines* 8 (2020) 154.
- [7] K. Nishitsuji, J. Xiao, R. Nagatomo, H. Umemoto, Y. Morimoto, H. Akatsu, K. Inoue, K. Tsuneyama, Analysis of the gut microbiome and plasma short-chain fatty acid profiles in a spontaneous mouse model of metabolic syndrome, *Sci. Rep.* 7 (2017) 1–10.
- [8] R. Nagpal, S. Wang, S. Ahmadi, J. Hayes, J. Gagliano, S. Subashchandrabose, D.W. Kitzman, T. Becton, R. Read, H. Yadav, Human-origin probiotic cocktail increases short-chain fatty acid production via modulation of mice and human gut microbiome, *Sci. Rep.* 8 (2018) 1–15.
- [9] I. Saputro, O. Putra, S. H Pebriantoro, Effects of probiotic administration on IGA and IL-6 level in severe burn patients: a randomized trial, *Ann. Burns Fire Disasters* 32 (2019) 70.
- [10] S. Sanaie, M. Ebrahimi-Mameghani, H. Hamishehkar, M. Mojtahedzadeh, A. Mahmoodpoor, Effect of a multispecies probiotic on inflammatory markers in critically ill patients: a randomized, double-blind, placebo-controlled trial, *J. Res. Med. Sci.: Off. J. Isfahan Univ. Med. Sci.* 19 (2014) 827.
- [11] S. Traisaeng, A. Batsukh, T.-H. Chuang, D.R. Herr, Y.-F. Huang, B. Chimeddorj, C.-M. Huang, *Leuconostoc mesenteroides* fermentation produces butyric acid and mediates Ffar2 to regulate blood glucose and insulin in type 1 diabetic mice, *Sci. Rep.* 10 (2020) 1–10.
- [12] N. Finke, V. Vandiekens, B.B. Jørgensen, Acetate, lactate, propionate, and isobutyrate as electron donors for iron and sulfate reduction in Arctic marine sediments, Svalbard, *FEMS (Fed. Eur. Microbiol. Soc.) Microbiol. Ecol.* 59 (2007) 10–22.
- [13] L. He, Y. Zhong, F. Yao, F. Chen, T. Xie, B. Wu, K. Hou, D. Wang, X. Li, Q. Yang, Biological perchlorate reduction: which electron donor we can choose? *Environ. Sci. Pollut. Control Ser.* (2019) 1–17.
- [14] T.H. Yang, M.V. Coppi, D.R. Lovley, J. Sun, Metabolic response of *Geobacter sulfurreducens* towards electron donor/acceptor variation, *Microb. Cell Factories* 9 (2010) 90.
- [15] J.Y. Jung, S.H. Lee, H.J. Lee, H.-Y. Seo, W.-S. Park, C.O. Jeon, Effects of *Leuconostoc mesenteroides* starter cultures on microbial communities and metabolites during kimchi fermentation, *Int. J. Food Microbiol.* 153 (2012) 378–387.
- [16] S.H. Light, L. Su, R. Rivera-Lugo, J.A. Cornejo, A. Louie, A.T. Iavarone, C.M. Ajo-Franklin, D.A. Portnoy, A flavin-based extracellular electron transfer mechanism in diverse Gram-positive bacteria, *Nature* 562 (2018) 140–144.
- [17] J.J. Yang, M.T. Pham, A.R. Rahim, T.-H. Chuang, M.-F. Hsieh, C.-M. Huang, Mouse abdominal fat depots reduced by butyric acid-producing *Leuconostoc mesenteroides*, *Microorganisms* 8 (2020) 1180.
- [18] M.S. Kao, S. Huang, W.L. Chang, M.F. Hsieh, C.J. Huang, R.L. Gallo, C.M. Huang, Microbiome precision editing: using PEG as a selective fermentation initiator against methicillin-resistant *Staphylococcus aureus*, *Biotechnol. J.* 12 (2017).
- [19] A. Balasubramaniam, P. Adi, T.M. Do Thi, J.-H. Yang, A.S. Labibah, C.-M. Huang, Skin bacteria mediate glycerol fermentation to produce electricity and resist UV-B, *Microorganisms* 8 (2020) 1092.
- [20] C. Chen, Y. Shen, D. An, G. Voordouw, Use of acetate, propionate, and butyrate for reduction of nitrate and sulfate and methanogenesis in microcosms and bioreactors simulating an oil reservoir, *Appl. Environ. Microbiol.* 83 (2017).
- [21] D.Y. Sorokin, E. Detkova, G. Muyzer, Propionate and butyrate dependent bacterial sulfate reduction at extremely haloalkaline conditions and description of *Desulfobotulus alkaliphilus* sp. nov., *Extremophiles* 14 (2010) 71–77.
- [22] N. Banerjee, R. Bhatnagar, L. Viswanathan, Inhibition of glycolysis by furfural in *Saccharomyces cerevisiae*, *Eur. J. Appl. Microbiol. Biotechnol.* 11 (1981) 226–228.
- [23] B. Sanchez, J. Bautista, Effects of furfural and 5-hydroxymethylfurfural on the fermentation of *Saccharomyces cerevisiae* and biomass production from *Candida guilliermondii*, *Enzym. Microb. Technol.* 10 (1988) 315–318.
- [24] L. Shi, H. Dong, G. Reguera, H. Beyenal, A. Lu, J. Liu, H.-Q. Yu, J.K. Fredrickson, Extracellular electron transfer mechanisms between microorganisms and minerals, *Nat. Rev. Microbiol.* 14 (2016) 651–662.
- [25] X. Liu, S. Wang, A. Xu, L. Zhang, H. Liu, L.Z. Ma, Biological synthesis of high-conductive pili in aerobic bacterium *Pseudomonas aeruginosa*, *Appl. Microbiol. Biotechnol.* 103 (2019) 1535–1544.
- [26] W. Wang, Y. Du, S. Yang, X. Du, M. Li, B. Lin, J. Zhou, L. Lin, Y. Song, J. Li, Bacterial extracellular electron transfer occurs in mammalian gut, *Anal. Chem.* 91 (2019) 12138–12141.
- [27] M.L. Soliman, C.K. Combs, T.A. Rosenberger, Modulation of inflammatory cytokines and mitogen-activated protein kinases by acetate in primary astrocytes, *J. Neuroimmune Pharmacol.* 8 (2013) 287–300.
- [28] S.E. Winter, P. Thiennimitr, M.G. Winter, B.P. Butler, D.L. Huseby, R.W. Crawford, J.M. Russell, C.L. Bevins, L.G. Adams, R.M. Tsolis, Gut inflammation provides a respiratory electron acceptor for *Salmonella*, *Nature* 467 (2010) 426–429.
- [29] J.L. Oschman, Can electrons act as antioxidants? A review and commentary, *J. Alternative Compl. Med.* 13 (2007) 955–967.
- [30] S. Keshari, A. Balasubramaniam, B. Myagmardoolonjin, D.R. Herr, I.P. Negari, C.-M. Huang, Butyric acid from probiotic *staphylococcus epidermidis* in the skin microbiome down-regulates the ultraviolet-induced pro-inflammatory IL-6 cytokine via short-chain fatty acid receptor, *Int. J. Mol. Sci.* 20 (2019) 4477.
- [31] M. Kumar, B. Myagmardoolonjin, S. Keshari, I.P. Negari, C.-M. Huang, 5-Methyl furfural reduces the production of malodors by inhibiting sodium l-lactate fermentation of *Staphylococcus epidermidis*: implication for deodorants targeting the fermenting skin microbiome, *Microorganisms* 7 (2019) 239.
- [32] M.H. Thomsen, A. Thygesen, A.B. Thomsen, Identification and characterization of fermentation inhibitors formed during hydrothermal treatment and following SSF of wheat straw, *Appl. Microbiol. Biotechnol.* 83 (2009) 447.
- [33] C.M. Wilson, S. Yang, M. Rodriguez, Q. Ma, C.M. Johnson, L. Dice, Y. Xu, S.D. Brown, Clostridium thermocellum transcriptomic profiles after exposure to furfural or heat stress, *Biotechnol. Biofuels* 6 (2013) 131.
- [34] J.M. Grime, M.A. Edwards, N.C. Rudd, P.R. Unwin, Quantitative visualization of passive transport across bilayer lipid membranes, *Proc. Natl. Acad. Sci. Unit. States Am.* 105 (2008) 14277–14282.
- [35] J. Sá-Pessoa, S. Paiva, D. Ribas, I.J. Silva, S.C. Viegas, C.M. Arraiano, M. Casal, SATP (YaaH), a succinate–acetate transporter protein in *Escherichia coli*, *Biochem. J.* 454 (2013) 585–595.
- [36] I. Kimura, K. Ozawa, D. Inoue, T. Imamura, K. Kimura, T. Maeda, K. Terasawa, D. Kashiwara, K. Hirano, T. Tani, The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43, *Nat. Commun.* 4 (2013) 1–12.
- [37] M.S. Han, A. White, R.J. Perry, J.-P. Camporez, J. Hidalgo, G.I. Shulman, R.J. Davis, Regulation of adipose tissue inflammation by interleukin 6, *Proc. Natl. Acad. Sci. Unit. States Am.* 117 (2020) 2751–2760.
- [38] H.S. Schipper, B. Prakken, E. Kalkhoven, M. Boes, Adipose tissue-resident immune cells: key players in immunometabolism, *Trends Endocrinol. Metabol.* 23 (2012) 407–415.
- [39] H. Han, Q. Ma, C. Li, R. Liu, L. Zhao, W. Wang, P. Zhang, X. Liu, G. Gao, F. Liu, Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors, *Emerg. Microb. Infect.* 9 (2020) 1123–1130.
- [40] W.T. Peppler, L.K. Townsend, D.C. Wright, Recent advances in the role of interleukin-6 in health and disease, *Curr. Opin. Pharmacol.* 52 (2020) 47–51.