The Relationship Between Gut Microbiota and Inflammatory Diseases: The Role of Macrophages

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Gut microbiota, an integral part of the human body, comprise bacteria, fungi, archaea, and protozoa. There is consensus that the disruption of the gut microbiota (termed “gut dysbiosis”) is influenced by host genetics, diet, antibiotics, and inflammation, and it is closely linked to the pathogenesis of inflammatory diseases, such as obesity and inflammatory bowel disease (IBD). Macrophages are the key players in the maintenance of tissue homeostasis by eliminating invading pathogens and exhibit extreme plasticity of their phenotypes, such as M1 or M2, which have been demonstrated to exert pro- and anti-inflammatory functions. Microbiota-derived metabolites, short-chain fatty acids (SCFAs) and Gram-negative bacterial lipopolysaccharides (LPS), exert anti-inflammatory or pro-inflammatory effects by acting on macrophages. Understanding the role of macrophages in gut microbiota-inflammation interactions might provide us a novel method for preventing and treating inflammatory diseases. In this review, we summarize the recent research on the relationship between gut microbiota and inflammation and discuss the important role of macrophages in this context.

Keywords: gut microbiota, inflammatory diseases, macrophage, obesity, inflammatory bowel disease

INTRODUCTION

Gut microbes, an essential part of the microbiota ecosystem, outnumbers human cells by 10-fold (Zhang et al., 2015). The gut microbiota contains bacteria, fungi, archaea, and protozoa and can be altered by the host genetics, overuse of antibiotics, and changes in diet, as described in the accompanying review (Belkaid and Hand, 2014; Pickard et al., 2017). The most abundant phyla in human intestine were Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria (Tap et al., 2009). Firmicutes are gram-positive bacteria including the large class of Clostridia and the lactic acid bacteria. Lactic acid bacteria are marketed as probiotic which are benefit for human health. Another sort of gram-positive bacteria are Actinobacteria, which include Collinsella and Bifidobacterium spp. Bifidobacteria is the other probiotic, which has been made in functional foods. Conversely, Bacteroidetes, and Proteobacteria are gram-negative bacteria, and LPS on their surface can induce activation of macrophages toward pro-inflammatory phenotype. Both can cause infection or diseases under certain conditions. The gut microbiota plays such a critical role in human health and disease that it has been called the “forgotten organ” (O’Hara and Shanahan, 2006). During millions of years of coevolution, the gut microbiota has been living in a symbiotic relationship.
with the host and affecting the energy balance (Backhed et al., 2004). In addition, symbiotic bacteria promote the intestinal immune system maturity (Mazmanian et al., 2005) and protect against pathogen colonization (Kaiser et al., 2012). Changes in the gut microbial composition result in chronic inflammation and metabolic dysfunction, as has been reviewed elsewhere (Sommer and Backhed, 2013). It is worth noting that the microbiota metabolites, short-chain fatty acids (SCFAs), play a key role in colonic inflammation (Zeng et al., 2019). Many studies have shown that not only epithelial cells or neutrophils but also monocytes and macrophages are modulated by SCFAs (Correa-Oliveira et al., 2016).

Inflammation is a normal physiological response of the body to the foreign pathogen invasion and plays two conflicting roles in human health (Xie et al., 2013). On the one hand, inflammation is the body’s automatic defense response, which also promotes wound healing. On the other hand, excessive inflammatory response results in a series of diseases such as obesity, atherosclerosis, and cancer, which has been reviewed in elsewhere (Wellen and Hotamisligil, 2005; Galkina and Ley, 2009; Cruz and Balkwill, 2015). During acute inflammation, neutrophils are recruited to the inflamed tissue sites, while during chronic inflammation, lymphocytes, macrophages, and plasma cells accumulate and infiltrate the junction tissue (Hakansson and Molin, 2011). There is growing awareness that many prevalent diseases are linked to chronic inflammation. Thus, it is important to regulate inflammation in a timely manner to control the morbidity from disease (Tracey, 2002).

Macrophages are regarded as critical effectors of inflammation. Resident tissue macrophages perform specific functions in response to their local environment (Hume et al., 2002). For example, macrophages are Kupffer cells in the liver and microglia in the central nervous system (CNS). Historically, blood monocytes exit the blood, enter tissues and undergo terminal differentiation to become tissue-resident macrophages (Geissmann et al., 2010). More recently, evidence has shown that tissue-resident macrophages, including lung macrophages and Kupffer cells, are established before birth and supplemented by recruited monocytes under inflammatory conditions (Yona et al., 2013). They express pattern recognition molecules, such as Toll-like Receptor (TLR) 4, to recognize foreign pathogens, remove foreign molecules, and protect against infection (Gordon, 2002). In addition, they respond to the inflammatory stimuli and differentiate into classically (“M1”) or alternatively (“M2”) activated macrophages. As reviewed by Hakansson and Molin (2011) macrophages infiltrate tissues during inflammation and perform major functions, including antigen presentation, phagocytosis, and production of various cytokines and growth factors to participate in immune regulation. It is worth mentioning that macrophages are pro-inflammatory under the Lipopolysaccharides (LPS) stimulation (Fujihara et al., 2003).

In this review, we summarize the current understanding of the link between gut microbiota and inflammation focusing on the roles of macrophages. In particular, we discuss two major inflammatory diseases, obesity and inflammatory bowel disease (IBD), and provide a description of the macrophages as the immune and inflammatory effector cells.

GUT MICROBIOTA AND INFLAMMATION

The gut microbiota and its metabolites may regulate the host inflammatory conditions (Yang et al., 2017; Feng et al., 2018). Numerous studies have linked the gut microbiota to inflammatory diseases. Forbes et al. (2018) have demonstrated that the immune-mediated inflammatory diseases, such as Crohn’s disease (CD), ulcerative colitis (UC), multiple sclerosis (MS), and rheumatoid arthritis (RA), change the composition of the gut microbiota. In addition, there are abundant reports highlighting the gut microbiota role in the pathogenesis of the inflammatory diseases such as asthma, type 1 and type 2 diabetes mellitus (DM), and obesity (Arrieta et al., 2015; Knip and Sijlender, 2016; Meijinkman et al., 2018).

The 16S ribosomal RNA (rRNA) sequencing paved the way for comparing the gut microbiota composition among individuals, which revealed the correlation between specific microbes and disease (Supplementary Table S1). Enterobacteriaceae, a large class of gram-negative facultative bacteria, are commonly linked to many inflammation diseases like IBD and obesity (Zeng et al., 2017). For example, adherent-invasive E. coli (AIEC) has been associated with CD, while diffusely adherent E. coli (DAEC) has been linked to UC (Mirsepasi-Lauridsen et al., 2019). In addition, the depletion of the phyla Firmicutes and the increase of the Proteobacteria populations have been linked to human IBD (Matsuoka and Kanai, 2015). Moreover, an increase in the ratio of Firmicutes to Bacteroidetes populations has been associated with obesity (Turnbaugh et al., 2006). Zhang et al. (2013) reported that the high levels of the phylum Firmicutes and the class Clostridia are found in diabetic patients. Zhu et al. (2013) found that children with non-alcoholic steatohepatitis (NASH) had a significantly higher proportion of Firmicutes. Additionally, the gut microbiota of the RA patients contained higher levels of Lactobacillus and Prevotella copri and, correspondingly, the numbers of Bifidobacteria and Bacteroides decreased (Liu et al., 2013; Scher et al., 2013; Supplementary Table S1).

Short-chain fatty acids the major metabolic products of the gut microbiota digestion of the non-absorbable dietary fiber and resistant starches, included acetate, propionate, and butyrate (Kles and Chang, 2006). In addition to providing energy for the host, SCFAs exhibit anti-inflammatory effects via binding to G-protein-coupled receptor 43 (GPR43) (Maslowski et al., 2009), which is expressed in immune cells, including macrophages (Le Poul et al., 2003; Sivaprakasam et al., 2016). Butyrate is the most important SCFA due to its role in antagonizing colonic inflammation (Hamers et al., 2008) and the ability to meet 6–10% of the daily human energy requirements (Bergman, 1990). Ruminococcaceae, Eubacterium, Clostridia, and Firmicutes were identified as the main producers of butyrate (Ohira et al., 2017). Moreover, butyrate can exert an anti-inflammatory effect in part by suppressing the activation of NF-κB (Luhrs et al., 2002), a transcription factor that regulates the inflammatory and innate immune responses (Karin et al., 2002). In addition, butyrate strongly inhibits the interferon-gamma (IFN-γ) signaling to ameliorate inflammation (Klampfer et al., 2003). Butyrate also targets peroxisome proliferator-activated receptor-γ (PPARγ) to prevent colon inflammation (Kinoshita et al., 2002).
TABLE 1 | Factors that influence composition of gut microbiota.

| Factor          | Classification | Research object                          | Effects on gut microbiota                  | References                  |
|-----------------|----------------|------------------------------------------|--------------------------------------------|-----------------------------|
| Host genetics   | Twin pairs     |                                          | Heritable microbes:                        | Hansen et al., 2011;        |
|                 |                |                                          | Christensenellaceae                        | Goodrich et al., 2014;      |
|                 |                |                                          | Methanobrevibacter smithii (MZ > DZ)      | Goodrich et al., 2016       |
| Genetically obese| Mice           |                                          | ↑ Firmicutes                               | Turnbaugh et al., 2006      |
| Diet            | High-fiber diet| Children from Europe and rural Africa.   | ↑ Bacteroidetes (Prevotella)               | De Filippo et al., 2010     |
|                 | High-beef diet | Ten human volunteers                     | ↑ Bifidobacterium                           | Hentges et al., 1977        |
|                 | Human          |                                          | ↑ Bacteroides                              | Wu et al., 2011             |
|                 | Rats           |                                          | ↑ Lactobacillus                            | Lecomte et al., 2015        |
|                 | Natural sugars-fed mice (glucose, fructose) |                                          | ↑ Bacteroidetes                              | Do et al., 2018             |
|                 | Artificial sweeteners-fed mice |                                          | ↑ Bacteroides                              | Suez et al., 2014           |
| Antibiotics     | 2–7-year-old Finnish children |                                          | ↓ Actinobacteria                           | Korpela et al., 2016        |
| clindamycin     | 18–45 years healthy volunteers |                                          | ↓ Bacteroidetes                             | Rashid et al., 2015         |
| Vancomycin      | Obese males with metabolic syndrome |                                          | ↓ Proteobacteria                           | Vrieze et al., 2014         |
| Inflammation    | RA             | Human                                    | ↓ gram-positive bacteria (mainly Firmicutes) | Liu et al., 2013; Scher et al., 2013 |
|                 | IBD            | Human                                    | ↓ gram-negative bacteria (mainly Proteobacteria) | Darfeuille-Michaud et al., 2004; Frank et al., 2007; Fava and Danese, 2011; Matsuoka and Kanai, 2015 |
|                 | TRUC           | Mice                                     | ↓ Firmicutes (Clostridium)                 | Garrett et al., 2010        |

RA, Rheumatoid arthritis; IBD, inflammatory bowel disease; TRUC, T-bet-/- RAG2-/- ulcerative colitis.

MACROPHAGES AND INFLAMMATION

Macrophages have been considered to be the central effector cells in many chronic inflammatory diseases (Moore and Tabas, 2011). Macrophages have high functional plasticity (Stout and Suttles, 2004) and exhibit pro- or anti-inflammatory properties in response to various cytokines and microbial products (Mantovani et al., 2004). In the early 1990s, scientists found that interleukin (IL)-4 exerts different effects on macrophage phenotypes compared to IFN-γ and/or LPS, and the concept of alternatively activated macrophages has been proposed (Stein et al., 1992). Since then, macrophages have been divided into two groups: classically activated M1 phenotypes, which are stimulated by IFN-γ and LPS and exert pro-inflammatory effects, and alternatively activated M2 phenotypes, which are stimulated by the IL-4 or IL-13 and perform anti-inflammatory functions, as reviewed by Tang et al. (2019).

Many studies have been focused on applying the macrophage phenotype changes to the treatment of inflammatory diseases. For instance, atherosclerosis is a chronic inflammatory disease in which macrophages play a major role at all stages (Tabas and Bornfeldt, 2016). Ouimet et al. (2015) reported that miR-33 antagonizes atherosclerosis partly through promoting the M2 macrophage polarization. In addition, macrophages...
FIGURE 1 | Macrophages are involved in the interaction between gut microbiota and IBD or Obesity. (A) Under gut homeostasis, bone marrow derived Ly6C+ monocytes are constantly recruited to gut to replenish the intestinal macrophages (CD14− macrophages) which recognize the pathogen through TLR4 receptor and secret anti-inflammatory cytokine IL-10 to promote Treg cell expansion. (B) In IBD, the inflammatory environment lead to gut dysbiosis included increased number of AIEC which can survive and replicate in macrophages, and decreased butyrate bacteria like Ruminococcaceae, Eubacterium, Clostridia, and Firmicutes, which impairs the ability of butyrate exert anti-inflammatory role through inhibiting HDACs/NF-κB (GPR43/41) or promoting IL-10 secretion (GPR109a). Additionally, blood Ly6C+ monocytes are recruited to intestinal to become inflammatory macrophages (CX3CR1+ macrophages) and secrete pro-inflammatory cytokines such as IL-23 and TNF-α to participated in inflammatory response. (C) In Obesity, the alteration of gut microbiota composition caused by HFD-diet lead to an increase of intestinal permeability, therefore LPS enter system circulation (i.e., metabolic endotoxemia). Adipose tissue macrophages are responses to LPS activation and transform to M1 phenotype.

are associated with obesity-associated inflammatory diseases of the adipose tissue (Weisberg et al., 2003). A study by Lumeng et al. (2007) illustrated that adipose tissue macrophages (ATMs) switch from the M1 polarized macrophage to the M2 polarized macrophage, thereby reducing the adipose tissue-derived inflammatory signals (Lumeng et al., 2007). Additionally, the RA was found to be closely related to the imbalance of the M1 and M2 macrophages and could be attenuated by reestablishing the macrophage equilibrium (Li et al., 2012). Identically, IBD could be ameliorated via the M1 to M2 switch in the colitis mouse model (Zhu et al., 2016). These findings suggest a strong correlation between macrophages and the inflammatory diseases and imply that macrophages participate in the inflammatory process mainly by shifting from the pro-inflammatory (M1) to anti-inflammatory (M2) phenotype (Porcheray et al., 2005).

MACROPHAGES ARE INVOLVED IN THE INTERACTION BETWEEN THE GUT MICROBIOTA AND OBESITY

Obesity is a state of low-grade chronic inflammation, characterized by the expanded adipose tissue (AT) in which macrophages account for 1–30% of its composition (Hauner, 2005). As reviewed by Russo and Lumeng (2018), adipose tissue macrophages (ATMs) include tissue-resident and monocyte-derived macrophages, and the increased number of ATMs in AT is mainly due to the recruitment of blood-macrophages and proliferation of resident macrophages. ATMs are the major effectors of the adipose tissue inflammation; ATMs accumulate in AT to participate in the inflammatory pathways, such as increasing the adipose tissue production of pro-inflammatory cytokines (Weisberg et al., 2003). Since scientists have found that the composition of the gut microbiota is significantly different between the lean mice and the obese mice, the latter showing lower Bacteroidetes and higher Firmicutes bacteria (Ley et al., 2005) levels, people began to realize the close connection between the gut microbiota and obesity. Subsequently, the gut microbiota has been found not only responsible for the weight gain and energy harvest (Samuel et al., 2008), but also involved in the development of the low-grade inflammation associated with obesity (Cani and Delzenne, 2009).

Accumulating evidence indicates that alterations in the gut microbiota are responsible for the progression of obesity. There are two possible pathways of the gut microbiota affecting obesity and the obesity-related diseases, such as diabetes and cardiovascular diseases: the circulation of bacterial components (e.g., LPS) and metabolites SCFAs (Harris et al., 2012) (Figure 1).
The obesity-associated decrease in the *Bifidobacterium* levels leads to the reduced production of GLP-2, a key molecule that promotes the intestinal barrier function, eventually destroying the tight junction integrity of the epithelial barrier and enhancing the intestinal permeability (Cani et al., 2009). Under these circumstances, LPS enters circulation through passive diffusion across the intestinal mucosa (Harris et al., 2012). In addition, Caesar et al. (2012) found that the conventionally raised (CONVR) mice showed increased plasma LPS concentrations compared with the germ-free (GF) mice, both mildly obese. Moreover, gut-derived LPS promoted macrophage accumulation in the adipose tissue (Caesar et al., 2012) and increased the proliferation of the ATMVs via a CD14-dependent pathway (Luche et al., 2013). In AT, macrophages recognized LPS through the TLR4 receptor, which is expressed on the cell surface, thereby converting from the M2 phenotype to the M1 phenotype and subsequently secreting pro-inflammatory cytokines, such as IL-1β and TNF-α, to participate in the inflammatory response (Weisberg et al., 2003; Park et al., 2009; Harford et al., 2011). Similarly, some reports reveal that the lack of TLR4 attenuates the adipose tissue inflammation by shifting the ATM polarization toward the M2 phenotype (Orr et al., 2012). In addition, the level of SCFAs was found to be higher in the obese compared with the normal-weight children due to the differences in the gut microbiota (Rahat-Rozenbloom et al., 2014; Riva et al., 2017). Conversely, the HFD-fed mice displayed decreased SCFAs levels (Lu et al., 2016). Abundant reports indicate that macrophages are involved in the SCFA-mediated anti-inflammatory effects in obesity. For example, propionic acid, a major SCFA, prevents the obesity-inflammation by regulating the function of colonic T cells (Tregs) (Smith et al., 2013). In a word, the inflammation-related disruption of the host-microbe interactions and decrease in the SCFA levels are involved in the development of IBD (Figure 1).

Intestinal macrophages, which reside in the lamina propria, are among the most abundant immune cells in the gut (Lee et al., 1985) and the first line of defense against the invasion of foreign pathogens (Smythies et al., 2005). Unlike blood monocytes or other tissue-resident macrophages, intestinal macrophages do not respond to LPS due to the absence of CD14, a surface receptor that plays a key role in the LPS-induced cell activation; hence, the LPS-induced pro-inflammatory cytokine production (IL-1, IL-6, IL-8, and TNF-α) is markedly reduced (Ulevitch and Tobias, 1995; Smith et al., 2001; Smythies et al., 2005). Moreover, intestinal macrophages produce anti-inflammatory cytokines like IL-10 and further regulate T-cell differentiation to prevent mucosal auto-inflammation (Denning et al., 2007). Although human intestinal macrophages exhibit profound “inflammatory anergy,” they retain strong phagocytic activity and perform defense functions (Smythies et al., 2005). Since intestinal macrophages perform such essential functions, they are integral to maintaining intestinal homeostasis. Kamada et al. (2008) identified a unique CD-specific macrophage subset that expresses high levels of CD14 and produces pro-inflammatory cytokines, such as IL-23 and TNF-α, leading to the accumulation of pro-inflammatory macrophages. In other words, there are “resident” and “inflammatory” macrophages in the gut that share the same Ly6Chi monocyte precursors under different conditions (Bain et al., 2013).

Although there is a current consensus that gut dysbiosis is closely linked to IBD, it should not be concluded that there is a direct causal relationship between them (Ni et al., 2017). However, it is clear that intestinal inflammation can alter the composition of the gut microbiota, which further exacerbates inflammation (Pickard et al., 2017). Macrophages are well established as the innate immune system cells that recognize invading microbiota using pattern recognition receptors and exhibit efficient phagocytic and bactericidal activity (Janeway and Medzhitov, 2002). Under normal conditions, intestinal macrophages rely on the commensal microbiota for the immune response, while in IBD, inflammatory macrophages are recruited to the inflamed tissue (Grainger et al., 2017). Moreover, the impaired acute inflammatory response in CD leads to the delayed clearance of bacteria (Smith et al., 2009). Adherent-invasive *E. coli* (AIPEC), the aggressive functionally altered resident strains in IBD, have the ability to invade intestinal epithelial cells (IEC) (Sartor and Wu, 2017; Palmela et al., 2018). Subsequently, AIEC is swallowed by macrophages and replicates inside them due to the defect in autophagy (Lapaquette et al., 2010), which is involved in the pathogenesis of IBD. Additionally,
the SCFA butyrate can exert anti-inflammatory effects via regulating the intestinal macrophage function as a histone deacetylase (HDAC) inhibitor (Chang et al., 2014) or suppressing the NF-κB activation (Luhrs et al., 2002). Furthermore, butyrate has the ability to exhibit anti-inflammatory activity on intestinal macrophages, which express Gpr109a by inducing the expression of IL-10 (Singh et al., 2014), while these functions are attenuated in IBD due to the decrease of butyrate concentration.

CONCLUSION

This review provides current understanding of the role of macrophages in gut microbiota and inflammation interactions. On the one hand, the polarization of macrophages, mediated by gut-derived LPS and its metabolites SCFA, plays a key role in the regulation of inflammatory diseases. On the other hand, macrophages are the main players in ensuring intestinal homeostasis through pathogen recognition and elimination and production of anti-inflammatory cytokines. Besides, a recent report by Earley et al. (2018) revealed that a loss of intestinal macrophages influenced the establishment of the gut microbiota in zebrafish, which suggests a critical role of macrophages in shaping the gut microbiota. Taking into account the important role of macrophages in the relationship between gut microbiota and inflammation, developing macrophage-targeting approaches in the prevention and therapy of inflammatory diseases is an appealing strategy. However, the related molecular signaling pathways involved in the roles of macrophages between gut microbiota and inflammation diseases are remained to be defined. Further work is needed to apply macrophages as a perspective target in the treatment of gut microbiota-related inflammatory diseases, like obesity and non-alcoholic fatty liver.

AUTHOR CONTRIBUTIONS

JW wrote the manuscript. Y-DW and W-DC initiated the idea for writing, revised the manuscript, and secured the funding for this work.

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SUPPLEMENTARY MATERIAL

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REFERENCES

Agace, W. W., and McCoy, K. D. (2017). Regionalized development and maintenance of the intestinal adaptive immune landscape. Immunity 46, 532–548. doi: 10.1016/j.immuni.2017.04.004

Al-Lahham, S., Roelofs, H., Rezaee, F., Weening, D., Hoek, A., Vonk, R., et al. (2012). Propionic acid affects immune status and metabolism in adipose tissue from overweight subjects. Eur. J. Clin. Invest. 42, 357–364. doi: 10.1111/j.1365-2362.2011.02590.x

Arrieta, M. C., Stiensma, L. T., Dimitriu, P. A., Thorson, L., Russell, S., Yurist-Dutsch, S., et al. (2015). Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci. Transl. Med. 7:307ra152. doi: 10.1126/scitranslmed.aab2271

Backhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Ngy, A., et al. (2004). The gut microbiota as an environmental factor that regulates fat storage. Proc. Natl. Acad. Sci. U.S.A. 101, 15718–15723. doi: 10.1073/pnas.0407071101

Bain, C. C., Scott, C. L., Uronen-Hansson, H., Gudjonsson, S., Jansson, O., Grip, O., et al. (2013). Resident and pro-inflammatory macrophages in the colon represent alternative context-dependent fates of the same Ly6Chi monocyte precursors. Mucosal Immunol. 6, 498–510. doi: 10.1038/mi.2012.89

Belkaid, Y., and Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. Cell 157, 121–141. doi: 10.1016/j.cell.2014.03.011

Bergman, E. N. (1990). Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. Physiol. Rev. 70, 567–590. doi: 10.1152/physrev.1990.70.2.567

Cesar, R., Reigstad, C. S., Backhed, H. K., Reinhardt, C., Ketonen, M., Lunden, G. O., et al. (2012). Gut-derived lipopolysaccharide augments adipose macrophage accumulation but is not essential for impaired glucose or insulin tolerance in mice. Gut 61, 1701–1707. doi: 10.1136/gutjnl-2011-301689

Cani, P. D., and Delzenne, N. M. (2009). Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota. Carr. Opin. Pharmacol. 9, 737–743. doi: 10.1016/j.coph.2009.06.016

Cani, P. D., Possemiers, S., Van de Wiele, T., Guiot, Y., Everard, A., Rottier, O., et al. (2009). Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut 58, 1091–1103. doi: 10.1136/gut.2008.165886

Carvalho, B. M., Guadagnini, D., Tsukumo, D. M. L., Schenka, A. A., Latuf-Filho, P., Vassallo, J., et al. (2012). Modulation of gut microbiota by antibiotics improves insulin signalling in high-fat fed mice. Diabetologia 55, 2823–2834. doi: 10.1007/s00125-012-2648-4

Chang, P. V., Hao, L., Offermanns, S., and Medzhitov, R. (2014). The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc. Natl. Acad. Sci. U.S.A. 111, 2247–2252. doi: 10.1073/pnas.1322291111

Correa-Oliveira, R., Fachi, J. L., Vieira, A., Sato, F. T., and Vinolo, M. A. (2016). Regulation of immune cell function by short-chain fatty acids. Clin. Transl. Immunol. 5:e73. doi: 10.1038/cit.2016.17

Cruz, S. M., and Balkwill, F. R. (2015). Inflammation and cancer: advances and new agents. Nat. Rev. Clin. Oncol. 12, 584–596. doi: 10.1038/nrclinonc.2015.105

Darfeuille-Michaud, A., Boudeau, J., Bulois, P., Neut, C., Glasser, A. L., Barnich, N., et al. (2004). High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn’s disease. Gastroenterology 127, 412–421. doi: 10.1053/j.gastro.2004.04.061

De Filippo, C., Cavalieri, D., Fiorenza, M., Romano, M., Fasano, M., Pellegrini, A., et al. (2010). Impact of diet in shaping gut microbiota revealed by a comparative
study in children from Europe and rural Africa. Proc. Natl. Acad. Sci. U.S.A. 107, 14691–14696. doi: 10.1073/pnas.100563107

Denning, T. L., Wang, Y. C., Patel, S. R., Williams, I. R., and Pulendran, B. (2007). Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. Nat. Immunol. 8, 1086–1094. doi: 10.1038/ni1511

Do, M. H., Lee, E., Oh, M. J., Kim, Y., and Park, H. Y. (2018). High-glucose or -fructose diet cause changes of the gut microbiota and metabolic disorders in mice without body weight change. Nutrients 10:761. doi: 10.3390/nu10060761

Earley, A. M., Graves, C. L., and Shaiu, C. E. (2018). Critical role for a subset of intestinal macrophages in shaping gut microbiota in adult zebrafish. Cell Rep. 25, 424–436. doi: 10.1016/j.celrep.2018.09.025

Fava, F., and Danese, S. (2011). Intestinal microbiota in inflammatory bowel disease: Friend of foe? World J. Gastroenterol. 17, 557–566. doi: 10.3748/wjg.v17.i5.557

Feng, Q., Chen, W. D., and Wang, Y. D. (2018). Gut microbiota: an integral moderator in health and disease. Front. Microbiol. 9:151. doi: 10.3389/fmicb.2018.00151

Forbes, J. D., Chen, C. Y., Knox, N. C., Marrie, R. A., El-Gabalawy, H., de Kievit, T., et al. (2010). Genetic determinants of the gut microbiome in UK twins. Hum. Genet. 127, 171–194. doi: 10.1007/s00439-009-0827-3

Galkina, E., and Ley, K. (2009). Immune and inflammatory mechanisms of atherosclerosis (‘). Annu. Rev. Immunol. 27, 165–197. doi: 10.1146/annurev.immunol.022708.115244

Frank, D. N., St Amand, A. L., Boedeker, E. C., Harpaz, N., Harris, K., Kassis, A., Major, G., and Chou, C. J. (2012). Is the gut microbiota a new regulator of obesity and its metabolic disorders? J. Obes. 2012, 879151. doi: 10.1155/2012/879151

Hauner, H. (2005). Secretory factors from human adipose tissue and their functional role. Proc. Nutr. Soc. 64, 163–169. doi: 10.1079/pnns2005428

Hentges, D. J., Maier, B. R., Burton, G. C., Flynn, M. A., and Tsutakawa, R. K. (1977). Effect of a high-beef diet on the fecal bacterial flora of humans. Cancer Res. 37, 568–571.

Hurni, D. A., Ross, I. L., Himes, S. R., Sasamoto, R. T., Wells, C. A., and Ravasi, T. (2002). The mononuclear phagocyte system revisited. J. Leukoc. Biol. 72, 621–627.

Janeway, C. A. Jr., and Medzhitov, R. (2002). Innate immune recognition. Annu. Rev. Immunol. 20, 197–216. doi: 10.1146/annurev.immunol.20.030801.084359

Kaiser, P., Diard, M., Stecher, B., and Hardt, W. D. (2012). The streptococcal mouse model for Salmonella diarrhea: functional analysis of the microbiota, the pathogen’s virulence factors, and the host’s mucosal immune response. Immunol. Rev. 245, 56–83. doi: 10.1111/j.1600-065X.2011.01070.x

Kamada, N., Hisamatsu, T., Okamoto, S., Chinen, H., Kobayashi, T., Sato, T., et al. (2008). Unique CD14 intestinal macrophages contribute to the pathogenesis of Crohn disease via IL-23/IFN-gamma axis. J. Clin. Invest. 118, 2269–2280. doi: 10.1172/jci46160

Karim, M., Cao, Y., Greten, F. R., and Li, Z. W. (2002). NF-kappaB in cancer: from innocent bystander to major culprit. Nat. Rev. Cancer 2, 301–310. doi: 10.1038/nrc780

Kinoshita, M., Suzuki, Y., and Saito, Y. (2002). Butyrate reduces colonic paracellular permeability by enhancing PPARgamma activation. Biochem. Biophys. Res. Commun. 293, 827–831. doi: 10.1016/s0006-291x(02)00294-2

Klampfer, L., Huang, J., Sasazuuki, T., Shirasawa, S., and Augenlicht, L. (2003). Inhibition of interferon gamma signaling by the short chain fatty acid butyrate. Mol. Cell Biol. 28, 159, 1855–862.

Kles, K. A., and Chang, E. B. (2006). Short-chain fatty acids impact on intestinal adaptation, inflammation, carcinoma, and failure. Gastroenterology 130(2 Suppl. 1), S100–S105. doi: 10.1053/j.gastro.2005.11.048

Knip, M., and Siljander, H. (2016). The role of the intestinal microbiota in type 1 diabetes mellitus. Nat. Rev. Endocrinol. 12, 154–167. doi: 10.1038/nrendo.2015.218

Korpela, K., Salonen, A., Virta, L. J., Kekkonen, R. A., Forslund, K., Bork, P., et al. (2016). Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. Nat. Commun. 7:10410. doi: 10.1038/ncomms10410

Lapapette, Q., Glasser, A. L., Huet, A., Xavier, R. J., and Darfeuille-Michaud, A. (2010). Crohn’s disease-associated adherent-invasive E. coli are selectively favoured by impaired autophagy to replicate intracellularly. Cell Microbiol. 12, 99–113. doi: 10.1111/j.1462-5882.2009.01381.x

Le Poul, E., Loison, C., Struyf, S., Springael, J. Y., Lannoy, V., Decobecq, M. E., et al. (2003). Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. J. Biol. Chem. 278, 25481–25489. doi: 10.1074/jbc.M30143200

Lecomte, V., Kaakoush, N. O., Maloney, C. A., Raiupria, M., Huinao, K. D., et al. (2015). Changes in gut microbiota in rats fed a high fat diet correlate with obesity-associated metabolic parameters. PLoS One 10:e0126931.

Lee, S. H., Starkey, P. M., and Gordon, S. (1985). Quantitative analysis of total macrophage content in adult mouse tissues. Immunochemical studies with monoclonal antibody F4/80. J. Exp. Med. 161, 475–489. doi: 10.1084/jem.161.3.475

Ley, R. E., Backhed, F., Turnbaugh, P., Lozupone, C. A., Knight, R. D., and Gordon, J. I. (2005). Obesity alters gut microbial ecology. Proc. Natl. Acad. Sci. U.S.A. 102, 11070–11075. doi: 10.1073/pnas.0504978102

Li, J., Hsu, C. H., and Mountz, J. D. (2012). Managing macrophages in rheumatoid arthritis by reform or removal. Curr. Rheumatol. Rep. 14, 445–454. doi: 10.1007/s11926-012-0272-4

Liu, X., Zou, Q., Zeng, B., Fang, Y., and Wei, H. (2013). Analysis of fecal Lactobacillus community structure in patients with early rheumatoid arthritis. Curr. Microbiol. 67, 170–176. doi: 10.1007/s00282-013-0338-1

Lu, Y., Fan, C., Li, P., Lu, Y., Chang, X., and Qi, K. (2016). Short chain fatty acids prevent high-fat-diet-induced obesity in mice by regulating G protein-coupled receptors and gut microbiota. Sci. Rep. 6:37589. doi: 10.1038/srep37589

Luche, E., Cousin, B., Girardou, L., Serino, M., Waget, A., Barreau, C., et al. (2013). Metabolic endotoxemia directly increases the proliferation of adipocyte...
Ulevitch, R. J., and Tobias, P. S. (1995). Receptor-dependent mechanisms of cell stimulation by bacterial endotoxin. *Annu. Rev. Immunol.* 13, 437–457. doi: 10.1146/annurev.iy.13.040195.002253

Vrieze, A., Out, C., Fuentes, S., Jonker, L., Reuling, I., Kootte, R. S., et al. (2014). Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin sensitivity. *J. Hepatol.* 60, 824–831. doi: 10.1016/j.jhep.2013.11.034

Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L., Ferrante, A. W. Jr., et al. (2003). Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Invest.* 112, 1796–1808. doi: 10.1172/jci19246

Wellen, K. E., and Hotamisligil, G. S. (2005). Inflammation, stress, and diabetes. *J. Clin. Invest.* 115, 1111–1119. doi: 10.1172/jci25102

Wu, G. D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y. Y., Keilbaugh, S. A., et al. (2011). Linking long-term dietary patterns with gut microbial enterotypes. *Science* 334, 105–108. doi: 10.1126/science.1208344

Xie, W., Li, M., Xu, N., Lv, Q., Huang, N., He, J., et al. (2013). MiR-181a regulates inflammation responses in monocytes and macrophages. *PLoS One* 8:e58639. doi: 10.1371/journal.pone.0058639

Yang, H. E., Li, Y., Nishimura, A., Jheng, H. F., Yuliana, A., Kitano-Ohue, R., et al. (2017). Synthesized enone fatty acids resembling metabolites from gut microbiota suppress macrophage-mediated inflammation in adipocytes. *Mol. Nutr. Food Res.* 61:1700064. doi: 10.1002/mnfr.201700064

Yona, S., Kim, K. W., Wolf, Y., Mädner, A., Varol, D., Breker, M., et al. (2013). Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. *Immunity* 38, 79–91. doi: 10.1016/j.immuni.2012.12.001

Zeng, M. Y., Inohara, N., and Nunez, G. (2017). Mechanisms of inflammation-driven bacterial dysbiosis in the gut. *Mucosal Immunol.* 10, 18–26. doi: 10.1038/mi.2016.75

Zhang, X., Shen, D., Fang, Z., Jie, Z., Qiu, X., Zhang, C., et al. (2013). Human gut microbiota changes reveal the progression of glucose intolerance. *PLoS One* 8:e71108. doi: 10.1371/journal.pone.0071108

Zhang, Y. J., Li, S., Gan, R. Y., Zhou, T., Xu, D. P., and Li, H. B. (2015). Impacts of gut bacteria on human health and diseases. *Int. J. Mol. Sci.* 16, 7493–7519. doi: 10.3390/ijms16047493

Zhu, L., Baker, S. S., Gill, C., Liu, W., Alkhouri, R., Baker, R. D., et al. (2013). Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. *Hepatology* 57, 601–609. doi: 10.1002/hep.26093

Zhu, Y., Li, X., Chen, J., Chen, T., Shi, Z., Lei, M., et al. (2016). The pentacyclic triterpene Lupeol switches M1 macrophages to M2 and ameliorates experimental inflammatory bowel disease. *Int. Immunopharmacol.* 30, 74–84. doi: 10.1016/j.intimp.2015.11.031

Zuo, T., and Ng, S. C. (2018). The gut microbiota in the pathogenesis and therapeutics of inflammatory bowel disease. *Front. Microbiol.* 9:2247. doi: 10.3389/fmicb.2018.02247

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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