2-1-2022

Role of microbiome and metabolome in the pathobiology of MS

Ashutosh K. Mangalam

Shailendra Giri
Henry Ford Health, SGIRI1@hfhs.org

Recommended Citation
Mangalam AK, and Giri S. Role of microbiome and metabolome in the pathobiology of MS. Clin Immunol 2022; 108934.

Clinical Immunology 235 (2022) 108934

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Editorial

Role of microbiome and metabolome in the pathobiology of MS

Humans can be considered as holobionts, defined as a host and its closely associated species that interact and function together as a whole. While the term 'holobiont' was first introduced by Lynn Margulis in 1991 [1]; it was Aristotle who first proposed the philosophical concept of "Holism" in the 4th century BCE to suggest that a system's outcome is influenced by the interconnections of its sums and should be studied in its entirety. Humans are colonized with bacteria, viruses, fungi, and other microorganisms, with each playing an essential role in the functioning of the human holobionts. Among all the microbes present on and in the human body, bacteria have been studied in greater detail and it is suggested that an individual's hologenome comprises of more gut bacterial genes than total human genes [2]. Trillions of bacteria (microbiome) living in the human gut have been characterized and studied profoundly in the last decade due to the emergence of NextGen sequencing technologies which allowed better cataloging of the gut microbiome and fueled research to understand its function. Germ-free mice and gnotobiotic mice aided in establishing the importance of human-microbiome interaction in human physiology, especially in the digestion and immune system development that ensures the maintenance of a healthy host state [3,4]. However, alteration in the gut microbiota composition termed as gut dysbiosis can perturb this homeostasis and predispose to various inflammatory and neurological diseases, including multiple sclerosis (MS) [5,6]. Therefore, a better understanding of the bacteria linked with the disease and its outcome will help identify diagnostic markers and microbiome-based therapeutic approaches for human diseases, including MS.

In this special issue, we have compiled articles focused on the role of gut microbiota in MS [7–11]. The first step in deciphering the role of the gut microbiome in MS is to verify that people with MS (pwMS) have altered microbiome. Noto et al. linked published MS microbiome studies to highlight that pwMS do indeed have gut dysbiosis with enrichment and/or depletion of specific bacteria [8]. Despite some variability across these studies, specific common commensals emerged to display similar trends. Commensals such *as Prevotella, Parabacteroides, Adlercreutzia, Faecalibacterium,* and *Lactobacillus* showed reduced relative abundance in pwMS, whereas *Akkermansia, Eggerthella, and Blautia* were enrichment in pwMS. The review also discusses the influence of the gut microbiome on immune cells and potential mechanism that may be involved in regulating the MS pathobiology. MS is an inflammatory disease where autoreactive CD4 T cells of Th1 (IFNγ producing) and Th17 (IL-17 producing) cells have been linked with disease initiation and progression with a concurrent reduction in the frequency or suppressive function of $CD4^{+}CD25^{+}FoxP3^{+}$ regulatory T cells (Tregs). Thus, factors influencing host immunity can play a significant role in disease susceptibility/progression vs. resistance in MS. Gut bacteria can help maintain immune homeostasis by regulating the balance between Tregs and pro-inflammatory Th1/Th17 cells [12]. A shift towards Th1/Th17 responses (reduced Tregs) can leads to inflammation and demyelination in the central nervous system (CNS). Experiments performed in an animal model of MS utilizing specific commensal or Germ-free mice populated with fecal microbiota from pwMS or healthy controls (HC) had shown that *Prevotella histicola* [13] and *Parabacteroides distasonis* could induce CD4 + FoxP3+ Tregs [14], whereas *Akkermansia muciniphila* can induce pro-inflammatory Th1 cells [14]. Thus, gut dysbiosis linked with MS can influence disease through modulation of host pro- or anti-inflammatory, immune response.

Besides T cells, the microbiota can also influence B cell and antibody response of the host. However, it is not clear whether antibodies to gut bacteria are protective, or pathogenic as studies support both arguments. While one study has shown that commensal specific IgA response is necessary for the protection in an animal model of MS [15], another study utilizing human MS samples suggested a role of commensal specific IgA as a disease mediator due to the presence of microbiota specific IgA+ cells in the CNS tissue [16]. In this special issue, Boussamet et al. discuss the role of anti-α1-3Gal antibodies and gut microbiota-specific Gal antigen in the pathobiology of MS [10]. The α-galactosyl carbohydrate epitope (Gal) is expressed in all mammals except old-world monkeys, apes, and humans. Therefore, humans produce a large amount of anti-Gal antibodies as a normal humoral immune response and studies point towards a crucial role of the gut microbiota in the generation of Anti-Gal antibodies. The argument is supported by multiple observations such as low levels of anti-Gal antibody in babies, which increases with age and reaches maximum levels in old age, significantly decreased levels of anti-Gal antibodies after antibiotic intake, and reappearance of anti-Gal antibody post gut flora colonization in mice lacking Gal antigen. Interestingly pwMS show reduced levels of Anti-Gal antibody, and the review by Boussamet et al. discusses the importance of the same in the pathobiology of MS [10]. They suggest that reduction in bacteria expressing Gal antigen may predispose and aid in the progression of MS. Interestingly, increased levels of anti-Gal antibodies have been reported in other inflammatory diseases such as rheumatoid arthritis, Crohn's disease, and Sjogren's syndrome. Thus, further studies are required to better understand the role of the Gal antigen and anti-Gal antibodies directed against commensal bacteria in the pathobiology of MS.

Human evolution is nutrient-centric, and data suggests that we have evolved with the gut microbiome as it allowed us to harvest energy from otherwise indigestible complex starches and sugars. Therefore, it is not surprising that diet has emerged as the strongest factor influencing gut microbiome composition, as highlighted by microbiome changes from fetus to infant to adolescence to adulthood and old age [17]. Diet can

https://doi.org/10.1016/j.clim.2022.108934

Available online 20 January 2022

positively and negatively impact the inflammatory process and diseases such as MS. The review by Sanchez et al. in this special issue discusses in detail the association of different diets such as Swank, calories restriction (CR), ketogenic diet, Mediterranean or Western (high-fat high protein) diet as well as dietary components (vitamins, salt, polyphenols, fiber, short and long-chain fatty acids) with MS [9]. Along the same line, Cantoni et al. discuss their data on how dietary restriction without malnutrition can improve health, including neuroinflammatory disease setting through induction of anti-inflammatory and modulation of neuroendocrine adaptations [7]. Not surprisingly, gut microbiota, especially bacteria belonging to *Lactobacillus* and *Bifidobacterium* genera, are identified to play an important role in the beneficial effect of dietary restriction. These reviews highlight the importance of diet in shaping gut microbiota and suggest diet as a potential therapeutic option to treat MS.

Since emergence of diet as an important modulator of gut microbiota and host immunity, efforts are being made to identify potential dietary components or metabolites with ability to suppress disease. Sell et al. demonstrate that farnesol, a 15-carbon organic isoprenol produced by plants and animals, can suppress disease in an animal model of MS [11]. Farnesol-induced disease protection was associated with reduced trafficking of the inflammatory population to the spinal cord and modulation of gut microbiota characterized by an increase in *Lactobacillus* and *Bifidobacterium*. Noto et al. also discuss gut bacteria's importance in generating metabolites that could modulate host response [8]. Short-chain fatty acids (SCFA) have emerged as essential metabolites produced with the support of gut bacteria, which help in maintaining a healthy state at mucosal surfaces through maintenance of an intact gut barrier [18] and induction of Tregs [19]. Besides SCFA, tryptophan and phytoestrogen metabolism by gut bacteria can also regulate host immunity. Dietary tryptophan had been shown to suppress CNS inflammation and EAE through bacterial metabolism of tryptophan into AHR ligands [20]. We have recently shown that isoflavone (a phytoestrogen) can suppress EAE disease in both chronic as well as relapsing-remitting model of EAE [21]. Additionally, the disease protection was depended on phytoestrogen metabolizing bacteria, specifically those lacking in pwMS such as *Adlercreutzia* and *Parabacteroides*. Interestingly, mice fed a phytoestrogen diet showed microbiome composition like healthy volunteers, whereas mice fed phytoestrogen lacking diet mimicked the microbiome composition of pwMS. These data underline the important role of dietary compounds in modulating CNS diseases by influencing the gut microbiome composition.

The collection of articles in this special issue highlights the crucial role that gut microbiota plays in the pathobiology of MS. Efforts are underway to harness the enormous potential of the gut microbiota as potential therapeutic agents to treat MS. Multipronged approaches, including fecal microbiota transplant, probiotic-based therapies, or dietary interventions, are being actively investigated. As diet is emerging a strong influencer of gut microbiota composition, dietary intervention offers an exciting opportunity to modulate the gut microbiota non-invasively to treat diseases. There are at least ten clinical trials currently registered on federal clinical trial website (www.clinicaltrials.gov) to determine the role of diet on modulating MS and data from these studies is being eagerly awaited to determine the potential of diet and gut microbiome-based therapeutic intervention.

References

[1] M.A. O'Malley, From endosymbiosis to holobionts: evaluating a conceptual legacy, J. Theor. Biol. 434 (2017) 34–41.

[2] J.A. Gilbert, M.J. Blaser, J.G. Caporaso, J.K. Jansson, S.V. Lynch, R. Knight, Current understanding of the human microbiome, Nat. Med. 24 (2018) 392–400.

[3] Y. Bhattarai, P.C. Kashyap, Germ-free mice model for studying host-microbial interactions, Methods Mol. Biol. 1438 (2016) 123–135.

[4] M. Rothe, M. Blaut, Evolution of the gut microbiota and the influence of diet, Benef. Microbes 4 (2013) 31–37.

[5] S.N. Freedman, S.K. Shahi, A.K. Mangalam, The "gut feeling": breaking down the role of gut microbiome in multiple sclerosis, Neurotherapeutics 15 (2018) 109–125.

[6] S.K. Shahi, S.N. Freedman, A.K. Mangalam, Gut microbiome in multiple sclerosis: the players involved and the roles they play, Gut Microbes 8 (2017) 607–615.

[7] C. Cantoni, Y. Dorsett, L. Fontana, Y. Zhou, L. Piccio, Effects of dietary restriction on gut microbiota and CNS autoimmunity, Clin. Immunol. 108575 (2020).

[8] D. Noto, S. Miyake, Gut dysbiosis and multiple sclerosis, Clin. Immunol. 108380 (2020).

[9] J.M.S. Sanchez, A.B. DePaula-Silva, J.E. Libbey, R.S. Fujinami, Role of diet in regulating the gut microbiota and multiple sclerosis, Clin. Immunol. 108379 (2020).

[10] L. Boussamet, E. Montassier, J.P. Soulillou, L. Berthelot, Anti alpha1-3Gal antibodies and gal content in gut microbiota in immune disorders and multiple sclerosis, Clin. Immunol. 108693 (2021).

[11] L.B. Sell, C.C. Ramelow, H.M. Kohl, K. Hoffman, J.K. Bains, W.J. Doyle, K. D. Strawn, T. Hevrin, T.O. Kirby, K.M. Gibson, J.B. Roullet, J. Ochoa-Reparaz, Farnesol induces protection against murine CNS inflammatory demyelination and modifies gut microbiome, Clin. Immunol. 108766 (2021).

[12] J.L. Round, S.K. Mazmanian, The gut microbiota shapes intestinal immune responses during health and disease, Nat. Rev. Immunol. 9 (2009) 313–323.

[13] A. Mangalam, S.K. Shahi, D. Luckey, M. Karau, E. Marietta, N. Luo, R.S. Choung, J. Ju, R. Sompallae, K. Gibson-Corley, R. Patel, M. Rodriguez, C. David, V. Taneja, J. Murray, Human gut-derived commensal Bacteria suppress CNS inflammatory and demyelinating disease, Cell Rep. 20 (2017) 1269–1277.

[14] E. Cekanaviciute, B.B. Yoo, T.F. Runia, J.W. Debelius, S. Singh, C.A. Nelson, R. Kanner, Y. Bencosme, Y.K. Lee, S.L. Hauser, E. Crabtree-Hartman, I.K. Sand, M. Gacias, Y. Zhu, P. Casaccia, B.A.C. Cree, R. Knight, S.K. Mazmanian, S. E. Baranzini, Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 10713–10718.

[15] O.L. Rojas, A.K. Probstel, E.A. Porfilio, A.A. Wang, M. Charabati, T. Sun, D.S. W. Lee, G. Galicia, V. Ramaglia, L.A. Ward, L.Y.T. Leung, G. Najafi, K. Khaleghi, B. Garcillan, A. Li, R. Besla, I. Naouar, E.Y. Cao, P. Chiaranunt, K. Burrows, H. G. Robinson, J.R. Allanach, J. Yam, H. Luck, D.J. Campbell, D. Allman, D. G. Brooks, M. Tomura, R. Baumann, S.S. Zamvil, A. Bar-Or, M.S. Horwitz, D. A. Winer, A. Mortha, F. Mackay, A. Prat, L.C. Osborne, C. Robbins, S.E. Baranzini, J.L. Gommerman, Recirculating intestinal IgA-producing cells regulate Neuroinflammation via IL-10, Cell 177 (2019) 492–493.

[16] A.K. Probstel, X. Zhou, R. Baumann, S. Wischnewski, M. Kutza, O.L. Rojas, K. Sellrie, A. Bischof, K. Kim, A. Ramesh, R. Dandekar, A.L. Greenfield, R. D. Schubert, J.E. Bisanz, S. Vistnes, K. Khaleghi, J. Landefeld, G. Kirkish, F. Liesche-Starnecker, V. Ramaglia, S. Singh, E.B. Tran, P. Barba, K. Zorn, J. Oechtering, K. Forsberg, L.R. Shiow, R.G. Henry, J. Graves, B.A.C. Cree, S. L. Hauser, J. Kuhle, J.M. Gelfand, P.M. Andersen, J. Schlegel, P.J. Turnbaugh, P. H. Seeberger, J.L. Gommerman, M.R. Wilson, L. Schirmer, S.E. Baranzini, Gut microbiota-specific IgA(+) B cells traffic to the CNS in active multiple sclerosis, Sci. Immunol. 5 (2020).

[17] P. Kundu, E. Blacher, E. Elinav, S. Pettersson, Our gut microbiome: the evolving inner self, Cell 171 (2017) 1481–1493.

[18] K.E. Bach Knudsen, H.N. Laerke, M.S. Hedemann, T.S. Nielsen, A.K. Ingerslev, D. S. Gundelund Nielsen, P.K. Theil, S. Purup, S. Hald, A.G. Schioldan, M.L. Marco, S. Gregersen, K. Hermansen, Impact of diet-modulated butyrate production on intestinal barrier function and inflammation, Nutrients 10 (2018).

[19] H. Zeng, H. Chi, Metabolic control of regulatory T cell development and function, Trends Immunol. 36 (2015) 3–12.

[20] V. Rothhammer, I.D. Mascanfroni, L. Bunse, M.C. Takenaka, J.E. Kenison, L. Mayo, C.C. Chao, B. Patel, R. Yan, M. Blain, J.I. Alvarez, H. Kebir, N. Anandasabapathy, G. Izquierdo, S. Jung, N. Obholzer, N. Pochet, C.B. Clish, M. Prinz, A. Prat, J. Antel, F.J. Quintana, Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor, Nat. Med. 22 (2016) 586–597.

[21] S.N. Jensen, N.M. Cady, S.K. Shahi, S.R. Peterson, A. Gupta, K.N. Gibson-Corley, A. K. Mangalam, Isoflavone diet ameliorates experimental autoimmune encephalomyelitis through modulation of gut bacteria depleted in patients with multiple sclerosis, Sci. Adv. 7 (2021).

Ashutosh K. Mangalam, Ph.D.[a,b,c,*], Shailendra Giri, Ph.D.[d]

[a] *Department of Pathology, University of Iowa, Iowa City, IA 52242, USA*

[b] *Graduate Program in Immunology, University of Iowa, Iowa City, IA 52242, USA*

[c] *Graduate Program in Molecular Medicine, University of Iowa, Iowa City, IA 52242, USA*

[d] *Department of Neurology, Henry Ford Hospital, Detroit, MI 48202, USA*

[*] Corresponding author at: Department of Pathology, University of Iowa Carver College of Medicine, 25 S. Grand Avenue, 1080A ML, Iowa City, IA 52242, USA.

E-mail addresses: ashutosh-mangalam@uiowa.edu (A.K. Mangalam), Sgiri1@hfhs.org (S. Giri).