Review paper
UDC 579.61:612.015.2

WITH A LITTLE HELP FROM MY FRIENDS

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Abstract

Based on the anthropocentric view of ourselves, we though that this average human body is alone in its existence in its average lifetime. We also thought that all good or bad living conditions are only due to the genes in our human cells. Recently, there is rapidly increasing evidence about the beneficial relationship our body has with its gut microbiome. The main role of this relationship is to stay healthy and fit. This gut microbiota with 150 times more genes than the genes in the human genome is considered to be the essential organ.

With this tremendous gene potential microbiota affect both health and disease via several mechanisms: (1) they have potential to benefit energy taken from the food, increase the level of nutrient harvest and involve into appetite signaling; (2) they work as a physical barrier that protects from pathogen invasion via competition and antimicrobial substrate production; (3) they are essential in the process of intestinal mucosa production and stimulate normal development of humoral and cellular mucosal immune system. The main characteristic of gut microbiota is their taxonomic and functional diversity, as well as normal variations influenced by age, genetics, environment and diet. But if we state that normal microbiota is a stable balanced group of microorganisms that invade the gut, then what are the limits of resistance of this balance and stability under different amount of stress and perturbation towards dysbiosis? And what are the mechanisms that enable resilience to dietary changes, administration of antibiotics or new species invasion? For example why one person may eat poisoned food and remain healthy while another may become seriously ill? Dysbiosis of gut microbiota is a major ethiopathogenesis of various immune, infectious, metabolic and cancerous disorders, also is a determinator of many physiological states such as: cardiac size, hepatic gene expression, central nervous system function and behavioral patterns.

Understanding the role human microbiome has on variety of serious diseases and conditions may help structuring future personalized medicine based on human microbiome modulation in prevention and treatment. Important efforts from many scientists from the field of microbiology, biology, bioinformatics, statistics, molecular medicine, epidemiology, physics is essential for crucial accomplishment in this complex field of microbiome world.

***Key words**: Microbiota, Diversity, Resilience.*

1. Introduction

If we limit ourselves only on the anthropocentric viewpoint, then we will only see an average human body in its lonely existence in its average lifetime. We assumed that all the good and the bad living conditions are only an outcome of the human genes that are set in the human cells. Suddenly, in the last decade we witness explosions of spectacular researches in the feld of microbiota [1].

2. Human adult gut microbiome

2.1 The role of gut microbiota

Microbiota are defned as a sum of all microorganisms that reside in a host or a specifed part of a host (such as the gastrointestinal tract) [2]. The complete role of the gut microbiota in a human body is one of the hottest topics in current medical research.

There is an increasing evidence of the exclusive beneficial relationship of our body with its microbiome [3, 4, 5, 6, and 7]. The main role of this relationship is to maintain our body healthy and fit. This gut microbiota has 150 times more genes than those in the human genome, thus it is considered to be the essential organ [8, and 9].

With this tremendous gene potential microbiota affects both health and disease through several mechanisms:

(a) The potential to benefit energy taken from the food [10], constantly improving nutrient harvest [11], and the gut-brain appetite signaling [12, 13].

(b) Composing a layer in a form of a physical barrier that protects from pathogen invasion by competition and antimicrobial substrate production [14, 15].

(c) Acting as an essential element in the production of intestinal mucosa and stimulate normal development of humoral and cellular mucosal immune system [16, 17, and 18].

2.2 The stability and diversity of gut microbiota

The main characteristics of gut microbiota are their taxonomic and functional diversity and their stability [19, 20]. The normal microbiota is defined as a stabile balanced group of microorganisms that invade the gut with the potential for normal qualitative and quantitative variations influenced by: human age, genetics, environment, diet, and lifestyle factors [21, 22]. Factors that influence microbiome dynamics in the early life are the most important shapers of a healthy microbiome [23].

The composition of the gut microbiome changes drastically in the infant life to become relatively stable only after the first months of life [24, 25, 26, and 27]. The microbiota is also supposed to be stable and is selected by evolution on a population level [28, 29]. Therefore, the definition of the base of a healthy microbiome should be a sum of a specific microbial gene family combinations, metabolic modules, and regulatory pathways that ensures a perfect host-associated ecology [30, 31].

The adult gut microbiome is promoted by microbial richness and complexity as a consequence of the gradual development of the gut and is almost similar across adult healthy individuals [32, 33]. At the same time there is a great variability (both qualitative and quantitative), as it has been described at species and strain levels, therefore the gut microbiome is unique in each individual, even if the microbial functions as a whole result are the same [34].

2.3 The resilience potential

Resilience by definition refers to the amount of disturbance a system can absorb while remaining in a functional state. It is the potential of an ecosystem to reorganize and renew in case of failure, also its ability to resist perturbation (as the entry of a pathogen, nutritional variations, host immune response, or medication). With the resilience potential the system returns to a healthy state afterwards [35, 36, and 37].

Recently, there has been new information about the human adult gut microbiome arrangement into a two components: first, the core microbiome, almost stable and hardly influenced by external stimuli, and the second, more dynamic and able to change quickly, responsible for microbial plasticity in different conditions and, as a consequence, susceptible to environmental or lifestyle changes [38].

Understanding mechanisms that ensure resilience would allow define strategies to increase resilience of healthy state and decrease resilience of unhealthy states [39]. As an example, a healthy state with high resilience to pathogen entry enable one person to escape food poising from spoiled food, while others fall ill.

Species richness is an important parameter in pathogen invasion resilience [40]. Beside bacteria, fungi also influence human host physiology and can be modified by different stimuli, including illness [41]. Archaea have been indicated as key elements in gut metabolic functions, and modifications in their composition have also been related to some diseases [42]. Finally, even viruses could be our symbiotic inhabitants and contribute to our health and disease status [43, 44, and 45].

Another essential parameter is functional response diversity that promotes resilience. It is defined as the degree to which species in a community that contribute to the same ecosystem function vary in their sensitivity to ecosystem changes. High functional response diversity may, for instance, allow a relatively rare but functionally similar species to fill a niche when an abundant species is compromised by an environmental disturbance [46]. For instance, following antibiotic administration, a previously rare microbe may increase in abundance to fill an essential niche previously dominated by a microbe with higher antibiotic sensitivity, leading to persistence of the same stable state but with decreased resilience due to a decrease in functional redundancy.

2.4 Dysbiosis

Understanding the limits of gut microbiota resilience cans explain intestinal dysbiosis. Dysbiosis refers to an unbalanced microbiota, which is most of the time supposed to be harmful. Loss of diversity of gut microbiota is a constant finding of dysbiosis. It has been found to be a major ethiopathogenesis of various immune, infectious, metabolic and cancerous disorders, also determines many physiological states such as: cardiac size, hepatic gene expression, central nervous system function and behavioral patterns. Many papers describe loss of diversity in digestive diseases such as Chrohn's disease [47, and 48], irritable bowel syndrome [49, 50], and colorectal cancer [51]; as a risk factor for *Clostridium difficile* colitis relapse [52], and even in obesity [53, 54, and 55]. It is surprisingly been

reported in non-digestive diseases such as autism [56]. Still, whether or not the association is the cause or the consequence has remained unclear. One provocative report recently proposed that gut microbiota may be at the intersection of everything [58]. Finally, a study underline that while some diseases are caused by the presence of potentially pathogenic microorganisms, others are related to the reduction of helpful microorganisms [57].

Quantitative and/or qualitative alterations between microorganisms, not only could play a role in diseases onset, thus increasing our knowledge on diseases pathogenetic mechanisms, but could represent not invasive diagnostic biomarkers or targets for novel therapeutic approaches towards dysbiosis correction [59].

3. Conclusions

- Further research whether disease-related alterations between gut microorganisms are a bystander, outcome or a pathological condition, or only a trigger or a risk factor in a specific disease is a great future challenge.

- While understanding the role human microbiome has on variety of serious diseases and conditions, future personalized medicine based on human microbiome modulation in prevention and treatment may be configured.

- Important efforts from many scientists from the fields of: microbiology, biology, bioinformatics, statistics, molecular medicine, epidemiology, and physics are essential for crucial accomplishment in this complex field of microbiome world.

- Consequently, our perception and understanding of human physiology and pathology must reveal on novel tools for data analysis, integration, correlation and visualization of microbiome functional effects.

4. References

[1] Curcic-Trajkovska B., Jashar Dz. (2016). *Our food and the accompanying person(s)*. Journal of Hygienic Engineering and Design, Vol.14, pp. 13-18.

[2] Bäckhed S., Bäckhed F., Bäckhed F. (2013). *The gut microbiota-masters of host development and physiology*. Nature Reviews Microbiology, 11, (4), pp. 227-238.

[3] Helander H. F., Fandriks L. (2014). *Surface area of the digestive tract - revisited*. Scand. J. Gastroenterol., 49, (6), pp. 681-619.

[4] Shanahan F. (2002). *The host-microbe interface within the gut*. Best Pract. Res. Clin. Gastroenterol., 16, (6), pp. 915-931.

[5] Guarner F., Malagelada J. (2003). *Gut flora in health and disease*. Lancet, 361, pp. 512-519.

[6] Hollister E. B., Gao C., Versalovic J. (2014). *Compositional and functional features of the gastrointestinal microbiome and their effect on human health.* Gastroenterology, 146, (6), pp. 1449-1458.

[7] Savage D.C. (1997). *Microbial ecology of the gastrointestinal tract.* Annu. Rev. Microbiol., 31, (1), pp. 107-33.

[8] O'Hara A. M., Shanahan F. (2006). *The gut flora as a forgotten organ*. EMBO Report, 7, (7), pp. 688-693.

[9] Ursel L. K., Haiser H. J., Van Treuren W., Garg N., Reddivari L., Vanamala J. (2104). *Intestinal metabolome: an intersection between microbiota and host.* Gastroenterology, 146, (6), pp. 1470-1476.

[10] Turnbaugh P. J., Ley R. E., Mahowald M. A., Magrini V., Mardis E. R., Gordon J. I. (2006). *An obesity-associated gut microbiome with increased capacity for energy harvest.* Nature, 444, (7122), pp. 1027-1031.

[11] Roberfroid M. B., Bornet F., Bouley C., Cummings J. H. (1995). *Colonic microflora: nutrition and health.* Nutr. Rev., 53, (5), pp. 127-130.

[12] Cani P. D., Dewever C., Delzenne N. M. (2004*). Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats.* Br. J. Nutr., 92, (3), pp. 521-526.

[13] Perry R. J., Peng L., Barry N. A., Cline G. W., Zhang D., Cardone R. L. (2106). *Acetate mediates a microbiome-brain-β-cellaxis to promote metabolic syndrome*. Nature, 534, (7606), pp. 213-217.

[14] Cash H. L., Witham C. V., Behrendt C. I., Hooper I. V. (2006). *Symbiotic bacteria direct expression of an intestinal bactericidial lecithin*. Science, 313, (5790), pp. 1126-1130.

[15] Hooper L. V., Staoenbeck T. S., Hong C. V., Gordon J. I. (2003). *Angiogenins: a new class of microbicidal proteins involved in innate immunity.* Nat. Immunol., 4, (3), pp. 269-273.

[16] Nguyen Q. N., Himes J. E., Martinez D. R., Permar S. R. (2016). *The Impact of the Gut Microbiota on Humoral Immunity to Pathogens and Vaccination in Early Infancy.* DOI: 10.1371/journal.ppat.1005997.

[17] Gensollen T., Iyer S. S., Kasper D. L., Blumberg R. S. (2016). *How colonization by microbiota in early life shapes the immune system.* Science, 352, (6285), pp. 539-544.

[18] Wesemann D. R. (2015). *Microbes and B cell development.* Adv. Immunol.,125, pp. 155-178.

[19] Huttenhower C., Gevers D., Knight R., Abubucker S., Badger J. H., Chinwalla A. T. (2012*). Structure, function and diversity of the healthy human microbiome.* Nature, 486, 207-214.

[20] Faith J. J., Guruge J. L., Charbonneau M., Subramanian S., Seedorf H., Goodman A. L. (2013). *The long-term stability of the human gut microbiota.* DOI: 10.1126/science.1237439.

[21] Carmody R. N., Gerber G. K., Luevano Jr J. M., Gatti D. M., Somes L., Svenson K. L., Turnbaugh P. J. (2015). *Diet dominates host genotype in shaping the murine gut microbiota.* Cell Host Microbe,17, pp. 72-84.

[22] David L. A., Maurice C. F., Carmody R. N., Gootenberg D. B., Button J. E., Wolfe B. E. (2014). *Diet rapidly and reproducibly alters the human gut microbiome.* Nature, 505, pp. 559- 663.

[23] Koenig J. E., Spor A., Scalfone N., Fricker A. D., Stombaugh J., Knight R. (2011). *Succession of microbial consortia in the developing infant gut microbiome.* Proc. Natl. Acad. Sci., USA., 108, (Suppl.1), pp. 4578-4585.

[24] Yatsunenko T., Rey F. E., Manary M. J., Trehan I., Dominguez-Bello M. G., Contreras M. (2012). *Human gut microbiome viewed across age and geography.* Nature, 486, pp. 222-227.

[25] Backhed F., Roswall J., Peng Y., Feng Q., Jia H., Kovatcheva-Datchary P. (2015). *Dynamics and stabilization of the human gut microbiome during the first year of life.* Cell Host Microbe, 17, (6), pp. 852.

[26] Mackie R. I., Sghir A., Gaskins H. R. (1999). *Developmental microbial ecology of the neonatal gastrointestinal tract.* Am. J. Clin. Nutr., 69, (5), pp. 1035-1045.

[27] Dominguez-Bello M. G., Costello E. K., Contreras M., Magris M., Hidalgo G., Fierer N., Knight R. (2010). *Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns.* Proc. Natl. Acad. Sci., USA, 107, pp. 11971-11975.

[28] Ochman H., Worobey M., Kuo C. H., Ndjango J. B. N., Peeters M., Hahn B. H. (2010). *Evolutionary relationships of wild hominids recapitulated by gut microbial communities*.
DOI: 10.4161/gmic.26039.

[29] Jalanka-Tuovinen J., Salonen A., Nikkilä J., Immonen O., Kekkonen R., Lahti L. (2011). *Intestinal microbiota in healthy adults: temporal analysis reveals individual and common core and relation to intestinal symptoms.*
DOI: 10.1371/journal.pone.0023035.

[30] Xu Z., Malmer D., Langille M. G., Way S. F., Knight R. (2014). *Which is more important for classifying microbial communities: who's there or what they can do?* ISME J., 8, pp. 2357-2359.

[31] Martiny J. B., Jones S. E., Lennon J. T., Martiny A. C. (2015). *Microbiomes in light of traits: a phylogenetic perspective.*
DOI: 10.1126/science.aac9323.

[32] Lee S. M., Donaldson G. P., Mikulski Z., Boyajian S., Ley K., Mazmanian S. K. (2013). *Bacterial colonization factors control specificity and stability of the gut microbiota.* Nature, 501, (7467), 426-429.

[33] Allison S. D., Martiny J. B. H. (2008). *Resistance, resilience, and redundancy in microbial communities.* Proc. Natl. Acad. Sci. USA, 105, 105, pp. 11512-11519.

[34] Lynch S. V., Pedersen O. (2016). *The Human Intestinal Microbiome in Health and Disease.* N. Engl. J. Med., 375, pp. 2369-2379.

[35] Mosca A., Leclerc M., Hugot J. P. (2016). *Gut Microbiota Diversity and Human Diseases: Should We Reintroduce Key Predators in Our Ecosystem?*
DOI: 10.3389/fmicb.2016.00455.

[36] Martinez I., Muller C. E., Walter J. (2013). *Long-term temporal analysis of the human fecal microbiota revealed a stable core of dominant bacterial species.*
DOI: 10.1371/journal.pone.0069621.

[37] Gibson M. K., Pesesky M. W., Dantas G. (2014). *The Yin and Yang of Bacterial Resilience in the Human Gut Microbiota.* J Mol Biol., 426, (23), pp. 3866-3876.

[38] Kundu P., Blacher E., Elinav E., Pettersson S. (2017). *Our gut microbiome: The evolving inner self.* Cell, 171, (7), pp. 1481-1493.

[39] Lozupone C. A., Stombaugh J. I., Gordon J. I., Jansson J. K., Knight R. (2012). *Diversity, stability and resilience of the human gut microbiota.* Nature, 489, (7415), pp. 220-230.

[40] Levine J. M., D'antonio C. M. (1999). *Elton revisited: a review of evidence linking diversity and invasibility.* Oikos, 87, pp. 15-26.

[41] Iliev I. D., Leonardi I. (2017). *Fungal dysbiosis: Immunity and interactions at mucosal barriers.* Nat. Rev. Immunol., 17, (10), pp. 635-646.

[42] Koskinen K., Pausan M. R., Perras A. K., Beck M., Bang C., Mora M., Schilhabel A., Schmitz R., Moissl-Eichinger C. (2017). *First insights into the diverse human archaeome: Specific detection of archaea in the gastrointestinal tract, lung, and nose and on skin.*
DOI: 10.1128/mBio.00824-17.

[43] Virgin H. W. (2014). *The virome in mammalian physiology and disease.* Cell, 157, (1),pp. 142-150.

[44] Cadwell K. (2015). *Expanding the role of the virome: Commensalism in the gut.* J. Virol., 89, pp. 1951-1953.

[45] Cadwell K. (2015). *The virome in host health and disease.* Immunity, 42, (5), pp. 805-813.

[46] Elmqvist T., Folke C., Nyström M., Peterson G., Bengtsson J., Walker B. (2003*). Response diversity, ecosystem change, and resilience.* Front. Ecol. Environ.,1, pp. 488-494.

[47] Sha S., Xu B., Wang X., Zhang Y., Wang H., Kong X. (2013). *The biodiversity and composition of the dominant fecal microbiota in patients with inflammatory bowel disease.* Diagn. Microbiol. Infect. Dis., 75, (3), pp. 245-251.

[48] Matsuoka K., Kanai T. (2015). *The gut microbiota and inflammatory bowel disease.* Semin. Immunopathol., 37, (1), pp. 47-55.

[49] Carroll I. M., Ringel-Kulka T., Siddle J. P., Ringel Y. (2012). *Alterations in composition and diversity of the intestinal microbiota in patients with diarrheapredominant irritable bowel syndrome.* Neurogastroenterol. Motil., 24, (6), pp. 521-530.

[50] Durbán A., Abellán J. J., Jiménez-Hernández N., Salgado P., Ponce M., Ponce J. (2012). *Structural alterations of faecal and mucosa-associated bacterial communities in irritable bowel syndrome: microbial diversity in irritable bowel syndrome.* Environ. Microbiol. Rep., 4, (2), pp. 242-247.

[51] Ahn J., Sinha R., Pei Z., Dominianni C., Wu J., Shi J. (2013). *Human gut microbiome and risk for colorectal cancer.* J. Natl. Cancer Inst., 105, (24), pp. 1907-1911.

[52] Chang J. Y., Antonopoulos D. A., Kalra A., Tonelli A., Khalife W. T., Schmidt T. M. (2008). *Decreased diversity of the fecal Microbiome in recurrent Clostridium difficile-associated diarrhea.* J. Infect. Dis., 197, (3), pp. 435-438.

[53] Cotillard A., Kennedy S. P., Kong L. C., Prifti E., Pons N., Le Chatelier E. (2013). *Dietary intervention impact on gut microbial gene richness.* Nature, 500, (7464), pp. 585-588.

[54] Tagliabue A., Elli M. (2013). *The role of gut microbiota in human obesity: recent findings and future perspectives.* Nutr. Metab. Cardiovasc. Dis., 23, (3), pp. 160-168.

[55] Turnbaugh P. J., Hamady M., Yatsunenko T., Cantarel B. L., Duncan A., Ley R. E. (2009). *A core gut microbiome in obese and lean twins.* Nature, 457, (7228), pp. 480-484.

[56] Kang D. W., Park J. G., Ilhan Z. E., Wallstrom G., LaBaer J., Adams J. B. (2013). *Reduced incidence of prevotella and other fermenters in intestinal microflora of autistic children.* PLoS ONE, 8(7): e68322. DOI: 10.1371/journal.pone.0068322.

[57] Cani P. D. (2017). *Gut microbiota-At the intersection of everything?* Nat. Rev. Gastroenterol. Hepatol., 14, pp. 321-322.

[58] Duvallet C., Gibbons S. M., Gurry T., Irizarry R. A., Alm E. J. (2017). *Meta-analysis of gut microbiome studies identifies disease-specific and shared responses.* Nat. Commun., 8, (1), pp. 1784.

[59] D'Argenio V. (2018). *Human Microbiome Acquisition and Bioinformatic Challenges in Metagenomic Studies.* Int. J. Mol. Sci., 19, (2), pp. 383.