Published in final edited form as:

J Cell Physiol. 2017 November ; 232(11): 2929–2930. doi:10.1002/jcp.25719.

Dysbiosis and disease: many unknown ends, is it time to formulate guidelines for dysbiosis research?

Sudhakar Veeranki^{1,2} and Suresh C. Tyagi¹

¹Department of physiology, University of Louisville, Louisville, KY, USA, 40243

Abstract

Dysbiosis has been implicated in modulation of disease and treatment outcome. It also has been linked to the reproducibility concerns. However, research community needs guidelines on animal models and dysbiosis research to tackle the complexities associated with it. There is a necessity for multi-disciplinary collaborative approach in setting up certain guidelines to hasten the dysbiosis research in a hassle-free manner.

In a recent commentary, it was brought into light that a common antibiotic in animals' water was used to treat the symptoms associated with the multiple sclerosis (Servick, 2016). Though the findings were accidental in nature, they have uncovered a very significant confounding factor in the form of dysbiosis (Nehra et al., 2016), which could compromise the reproducibility in the scientific data or leads to different interpretation. In another example, Doxycycline has been reported to ameliorate myocardial infarction, but the changes in the microbial populations and their metabolites have not been highlighted, which might have contributed to the functional outcome as well (Camp et al., 2004). In light of the new evidence (Servick, 2016), it is mandatory to consider dysbiosis as a modulatory factor in understanding of drug effects and disease pathophysiology. At the same time, one needs to exercise caution while implicating the dysbiosis as a cause. The reason being high cost and many unknown loosely knit ends in the dysbiosis research. For example, high fat feeding leads to changes in the gut microbiota, especially the ones that produce H₂S (Lecomte et al., 2015). However, the contribution of such changes to the GI and plasma H₂S pools is yet to be uncovered. Furthermore, comparisons between conventional and germ free mice revealed that even though, the plasma free H₂S levels were reduced in the germ free mice, the free H₂S levels and CSE enzyme (one of the key endogenous H₂S producer) activity levels vary across different tissues (Shen et al., 2013). The causes for such variation is currently unknown. In another example, It was reported that the microbial metabolomics might differ without significant changes in the microbial diversity between the vegan and omnivorous individuals (Wu et al., 2016), implying the significance of evaluation of microbial metabolomics in parallel with microbial quality and quantity. Even more perplexing thing about the dysbiosis is it can start from the modulations in the early life experiences and could potentially contribute to the onset of metabolic disease (Nehra et al., 2016) later in the

²Correspondence should be addressed to Sudhakar Veeranki, Department of physiology, University of Louisville, Louisville, KY, USA, 40243. s0veer02@louisville.edu.

The authors do not have any conflict of interest.

life. These scenarios prompted us to come with a set of tasks to be done to effectively direct the future research in the dysbiosis and to provide microbially uniform animals for research with a multi-disciplinary collaborative effort from industry and academia to save research dollars. The Fig. 1, shows the factors that could potentially modulate microbiota content in apparently normal individuals. The following needs to be considered in setting up the guidelines for the effective evaluation of the dysbiosis in the disease onset or treatment outcome. The list is by no means exhaustive and should be updated periodically.

1. The changes in the immune system and its influence on the microbiota and bioactive microbially derived metabolites (BMDM) need to be clarified. Genetics of an individual, age, sex and metabolic disease such as diabetes alter immune system and possibly the microbiota. It is currently unknown whether such changes in the immune system accelerate the rate of dysbiosis.
2. What are the changes in the BMDMs (quantitative and qualitative) after dysbiosis in different scenarios and diseases? What are their effective levels to have a significant functional alteration? What are the systemic and organ specific influences?
3. Is gut microbiota profiling enough to know the extent of dysbiosis and qualitative and quantitative changes in the BMDMs?
4. What needs to be done to create a uniform gut microbiota among the research animals irrespective of their source/strain/housing conditions to avoid confounding influence of microbiota changes and results can be reproduced in different labs.
5. Diabetes and obesity are bound to alter food ingestion pattern, digestion efficiency, water intake, energy metabolism and gut peristalsis. How these changes influence microbiota and BMDMs?
6. Assessment of the intactness of the GI tissue, which limits the availability of the BMDMs and possibly regulates microbiota composition need to be done simultaneously.
7. Modulatory effects from the dormant microbiomes in the blood and other tissues of individuals, which do not exhibit overt inflammatory symptoms, need to be clarified. For example, metabolic disorders.
8. Last but not least, how to create an animal model as close as possible to harbor human microbiota to have clinical relevance. What are the differences in the BMDMs between the research animals and humans?

Acknowledgments

The manuscript is supported by funding from the NIH grants: [HL108621](#), [HL074185](#) and [DK104653](#).

Bibliography

- Camp TM, Tyagi SC, Aru GM, Hayden MR, Mehta JL, Tyagi SC. Doxycycline ameliorates ischemic and border-zone remodeling and endothelial dysfunction after myocardial infarction in rats. *J Heart Lung Transplant*. 2004; 23(6):729–736. [PubMed: 15366434]
- Lecomte V, Kaakoush NO, Maloney CA, Raipuria M, Huinao KD, Mitchell HM, Morris MJ. Changes in gut microbiota in rats fed a high fat diet correlate with obesity-associated metabolic parameters. *PloS one*. 2015; 10(5):e0126931. [PubMed: 25992554]
- Nehra V, Allen JM, Mailing LJ, Kashyap PC, Woods JA. Gut Microbiota: Modulation of Host Physiology in Obesity. *Physiology (Bethesda)*. 2016; 31(5):327–335. [PubMed: 27511459]
- Servick K. Of mice and microbes. *Science*. 2016; 353(6301):741–743. [PubMed: 27540148]
- Shen X, Carlstrom M, Borniquel S, Jadert C, Kevil CG, Lundberg JO. Microbial regulation of host hydrogen sulfide bioavailability and metabolism. *Free radical biology & medicine*. 2013; 60:195–200. [PubMed: 23466556]
- Wu GD, Compher C, Chen EZ, Smith SA, Shah RD, Bittinger K, Chehoud C, Albenberg LG, Nessel L, Gilroy E, Star J, Weljie AM, Flint HJ, Metz DC, Bennett MJ, Li H, Bushman FD, Lewis JD. Comparative metabolomics in vegans and omnivores reveal constraints on diet-dependent gut microbiota metabolite production. *Gut*. 2016; 65(1):63–72. [PubMed: 25431456]

Fig. 1.

Factors affecting the balance between eubiosis and dysbiosis. Vertical (exogenous factors) and horizontal (host factors).