Scientific possibilities in associating microbiome to specific diseases and its bioinformatic and experimental challenges

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Abstract

Microbes play important roles in human health and disease either as individual species or as a consortium. While medical microbiology has traditionally associated a single species with a specific disease, recent knowledge of the diversity of microbes present at different sites of the body has opened our eyes to the dynamic interactions between species, and how community interactions amongst microbes could potentiate disease. More importantly, clinical manifestations of disease symptoms have been hypothesized to arise from cross-interactions between metabolites and signalling molecules secreted by microbes not in direct communication with each other. Such myriad and entangled interactions raise important questions on clinicians and researchers' quest to understand the aetiologies of disease and underpinnings of their progression. Doing so require profiling the microbes present and their community structure, to which mass spectrometry metabolomics could lend a lens. Nevertheless, how do we associate specific diseases to one or two microbiome which may be at different body sites? Do we have the analytical and bioinformatic toolkit to do so? A review paper in *Nature* ("Microbiome-wide association studies link dynamic microbial consortia to disease") seek to illuminate this question. But from the clinical perspective, is associating a microbiome to a specific disease useful, particularly for multifactorial diseases such as metabolic syndrome? To a limited extent, the answer is yes, for it provides an initial direction towards understanding the molecular mechanisms at play in disease manifestations as well as the complex interplay between microbe and host in pathological processes. At a deeper level, however, dynamic changes in microbiome community composition and structure with changing environmental conditions and host physiology meant that tracing the specific steps important to disease processes might be more fruitfully accomplished through the bottom-up approach rather than the top-down methodology inherent in microbiome profiling. Specifically, sets of molecular processes are likely impacted in complex diseases which translate to dysfunctional enzymes, or metabolic pathways and signalling cascades in overdrive. Teasing the complex web of metabolic cum signalling pathways apart in seeking to understand the specific molecular effectors important in disease necessitates a combination of molecular biology and biochemistry techniques coupled with contemporary discovery tools in omics. Such information would provide downstream leads for therapeutic development, which microbiome-wide association studies lend a first pointer. Collectively, associating a microbiome to specific disease states provide a list of candidate microbes that could be aetiological agents of disease, from which further biochemical and molecular biology investigations would uncover the underlying disease mechanisms.

PeerJ Preprints | https://doi.org/10.7287/peerj.preprints.27483v1 | CC BY 4.0 Open Access | rec: 14 Jan 2019, publ: 14 Jan 2019

Keywords: microbiome, metabolic syndrome, microbiome-wide association studies, mass spectrometry, community dynamics, signalling, metabolism, metabolic syndrome,

Subject areas: biochemistry, microbiology, computational biology, molecular biology, genomics,

Disease treatment usually seeks a specific aetiological agent or groups of microbes (or disease factors) in association with a disease. Knowledge of the causative microbe or lifestyle factors enables the tailoring of treatment options, which helps increase the chances of recovery, or at least in the case of chronic diseases, significant improvement in health outcomes. For example, understanding the type of microbe responsible for a specific disease, and whether it is antibiotic resistant facilitates the prescription of appropriate antibiotics for eradicating the disease-causing microorganisms from the body. On the other hand, narrowing down the specific lifestyle factors and dietary preferences helps provide guidance on the specific changes necessary to improve treatment outcomes in, for example, atherosclerosis mediated blockage of coronary artery.

Microbes are present on all surfaces of the human body and forms an intricate but up-to-now poorly understood signalling and metabolic network with human cells. More importantly, many diverse species of bacteria, fungi, viruses and mycoplasmas cohabit human body surfaces with host cells, which is an interesting ecological system important in health and disease. Such collection of microbes at a specific locale is known as a microbiota, and they are differentiated in community structure and dynamics depending on the specific site in and on the human body that microbes reside.

The important concept pertinent to understanding microbiota's function lies in the collective phenotypic presentation of the assemblage of microbes, each playing different roles in the community, such as in metabolism, signalling, and cellular movement. Hence, microbiome function and capabilities are a meshwork of diverse interactions between different microbes which may be symbiont to a nearby species, but a keen nutrient competitor to a more distant microbe. Such entangled web of interactions at the nutrient, signalling and metabolism levels highlight a potential difficulty in understanding, in totality, the meaning and function of metabolic and signalling cross-talks between different species of the same microbiota. Coupled to host cells-microbe interaction, the amount of information and metabolite flows between the microbiota and host portends a significant bioinformatic challenge.

With growing understanding of microbiota's role in potentiating different stages of disease progression as well as other states of health, there is increasing research seeking to find microbial potentiators of disease within the microbiota closest in distance to the disease site. But what is the relevant question one should ask in associating a microbe or groups of microbes to a specific disease? Enter the concept of microbiome-wide association studies. In a review paper published

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in *Nature*, Rob Knight and coauthors ("Microbiome-wide association studies link dynamic microbial consortia to disease", *Nature*, Vol. 535, pp. 94-103, Link)[1] reviews recent research concerning the possibilities of linking different microbiota to specific diseases at the individual and population level. Specifically, the concept revolves around the association of metabolites pertinent to specific diseases to the microbes responsible for their secretion.

But, due to the presence of a large diversity of microbes in each microbiota, and the possibility of cross interaction between microbiota at different locales for engendering a specific disease, significant difficulty exists in pinpointing a causative link between a microbe to a specific disease, especially in multi-factorial diseases. Specifically, while it is technically possible to understand the aetiological agent of a disease (such as infectious disease) with respect to Koch's Principles, it remains difficult to identify the specific factors that may be responsible for potentiating each stage of a complex disease such as diabetes. In complex diseases such as metabolic syndrome, multiple metabolites secreted by microbes as well as the inflammation they caused, together with environmental factors associated with changeable lifestyle add to the plethora of links and connections requiring understanding, which makes the firm association of a specific set of factors to a syndrome difficult.

Looking at the broader scale of the problem, attempts at linking a specific microbiome to a disease is a mathematically under-determinate question, due to the myriad interactions between microbes that together result in genesis of disease. In essence, specific disease symptoms only arises due to the presence of a specific set of microbes that secrete metabolites or signalling molecule important to disease. More importantly, bioinformatic challenge aside, the larger question revolves around the utility of understanding, in broad terms, how one microbiome affects disease progression, where the focus should be on uncovering the specific molecular mechanisms resulting in disease.

From the disease treatment perspective, micro-scale understanding of the specific pathways and enzymes responsible for different pathologies at the clinical level give rise to leads suitable for the development of pharmaceutical agents that act, at the molecular level, in ameliorating clinical symptoms. Thus, what is the clinical value of understanding the association between microbiome and disease? Are we limited by the technology necessary to tease apart the complex web of microbes, signalling molecules and metabolites, that in aggregate, lead to observed phenotypic presentation of disease? Or, do we lack the bioinformatic capacity and capability to dissect entangled web of interactions of microbial species each performing different roles in the microbiome as they energize an environment suitable for their growth, but which may be detrimental for the host? Specifically, since a single metabolite could be secreted by multiple microbes, it would be hard to associate a metabolite to a specific microbe using omics discovery methods and bioinformatic approaches.

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Collectively, understanding the microbiome responsible for specific diseases point us one step closer to determining the aetiological agent and processes underpinning disease manifestation and progression. While modern discovery science approaches centred on genome sequencing and mass spectrometry metabolomics opens up wide swathe of data space amenable for bioinformatic analysis, they nevertheless face daunting challenges in identifying critical links between specific microbes, metabolites, signalling factors or processes underlying diseases, particularly those of the multifactorial nature, such as the emerging global health threat of metabolic syndrome. Thus, what is the future trajectory of research seeking a correlation between microbiome and disease, in what is known as microbiome-wide association studies? The answer is the approach may not yield knowledge precise enough to answer basic clinical questions such as how changes in microbiome composition affect the severity of disease. But, profiling the microbiome composition at specific body sites do offer a glimpse into the dynamics of how microbes interact and shape human physiological processes, whose mysteries remain elusive as we probe deeper into host-microbe interactions.

References

1. Gilbert, J. A. *et al.* Microbiome-wide association studies link dynamic microbial consortia to disease. *Nature* **535,** 94–103 (2016).

Conflicts of interest

The author declares no conflicts of interest.

Funding

No funding was used in this work.

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