Host-Microbiome Relationships in C. elegans guided by natural diversity and environmental factors

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Abstract

Microbes are widely diverse and prevalent in nature. Microbial diversity within hosts plays an important hurdle in unraveling the role of each component of the microbiome and its relationships in the host physiology. Caenorhabditis elegans is an important micro-organism that has been well-studied as a model for host-microbiome relationships. The gut of C. elegans has a variety of microbial species which makes it a useful host organism to study the microbiome and the gut-brain axis. Understanding the gut microbiome and its role in modulating the host health has implications to researchers across several fields of study and possibly holds the answers to several human diseases. In recent years, research in synthetic biology, microbiology, genome sequencing, and bioengineering techniques have revolutionized microbiome research. Engineering techniques in microfluidics, 3D printing, organ-on-chip, stem cell biology, and laboratory automation have made it easier to design and fabricate high-throughput experimental platforms with validation from simulation software tools like COMSOL. These technologies hold promise to unravel the composition and functions of various microbiome communities on the functioning of various organs and tissues.

Introduction

Model organisms are often chosen for biological studies based on their resemblance to human subjects, the cost of experiments, and the potential for high-throughput studies. C. elegans is a model organism with a fully sequenced genome which offers the flexibility of genetic screening and genome editing using advanced laboratory techniques [1-6]. The C. elegans life cycle is short which allows for high-throughput sequencing and easy culture of the worms on agarose plates, while its transparent body allows to image fluorescent tags and molecules of interest within the C. elegans body [3-8]. These imaging benefits are particularly suitable for characterizing the microbiome of C. elegans and identifying the relationships of specific genes and cells to alterations in the host physiology. Several environmental changes can be produced to understand the effects of toxins on the host-microbiome relationships.

C. elegans and the gut microbiome

The C. elegans has a diverse and well-defined microbiota which helps to understand the genetics of the microbes and host in a controlled manner [3-9]. It is worth noting that the C. elegans cultured in the laboratory may not have the same degree of microbial diversity compared to those in the wild. Still, model organisms provide a unique advantage to explore host and microbial genetics. As with every host, the microbiome and microbial communities in a host organism can be grouped into primary and secondary microbiota [5-11]. Primary microbiota is the microbiota that was inherited in the host early on and is often acquired at birth from parents. The secondary microbiota grows with the host and is affected by the diet and environment. The microbiota is associated with many diseases and health conditions, and as such has garnered considerable interest in the medical communities. The society is interested in addressing the environmental conditions, such as toxins and pollutants, that have a negative influence on the health of the society and in turn creates a disease burden for the society, curbing its productivity and growth potential. The composition of the gut microbiome is influenced by multiple external and internal factors, including family history, genetics, diet, nutrition, environment, age, and lifestyle [10-19]. An imbalance in the gut microbiome has been linked to several health issues, such as inflammatory bowel disease, obesity, diabetes, and even mental health disorders. A number of recent studies are highlighting how the microbiome impacts almost every tissue and organ within our body, be it the skin, stomach, lungs, blood, reproductive organs, and heart [1-9].

Laboratory Tests for Microbiome Analysis

A number of laboratory tests and readouts are available to understand and characterize the microbiome and microbial flora in our body using advanced culturing, imaging and multi-omics tools [20-32]. Characterizing the gut microbiome involves several steps and techniques to analyze and understand the composition, diversity, and function of the microbial communities within the gastrointestinal tract. The most common method is using fecal samples as feces contain a large and diverse representation of the gut microbiome [1-5]. Biopsy samples can also be used through colonoscopy or other medical procedures for local assessment. Microbial culturing is a method which involves the isolation and culture of specific microbial strains in the laboratory, followed by characterization using phenotypic and genotypic methods. Fluorescent probes and electron microscopes can be used to image the microbial cells within the host at varying degrees of clarity. In addition, DNA sequencing can be done by two ways including 16S rRNA Gene Sequencing and metagenomics [4-12]. 16S rRNA Gene Sequencing is a targeted approach that sequences a specific region of the 16S ribosomal RNA gene found in bacteria, allowing identification and classification at the genus or species level. Metagenomic sequencing is a whole-genome approach that sequences all the genetic material in a sample, providing a more comprehensive view of the microbiome, including bacteria, viruses, fungi, and other microorganisms.

Genomic Studies in Microbiome Research

In recent past, there have been significant discoveries in bioinformatics, gene editing, and gene sequencing techniques that has created positive impact on host-microbiome studies [6-15]. A number of high-throughput sequencing methods, such as 16S rRNA sequencing and the shotgun sequencing techniques have evolved recently. Metagenomics on human samples will be important to reveal new information about human-microbiome relationships. In addition, multi-omics studies at various levels can help characterize the phenotypes of microbiome and microbial communities at their gene, protein, and metabolites levels to understand the hierarchical organization within the host body. Recent years have seen a dramatic rise in gut microbiome studies, enabled by the rapidly evolving high-throughput sequencing methods (i.e. 16S rRNA sequencing and shotgun sequencing) [4-17]. Understanding the microbiome could be beneficial in furthering the cause of personalized medicine which will help us understand and modulate several biological mechanisms and pathways, such as the gut-brain axis.

Machine Learning Tools in Microbiome Research

Host–microbe relationships result from a complex, dynamic interaction between various biotic and abiotic factors which is being modelled by machine learning and artificial intelligence techniques [21-32]. The impact of microbiome on the host health and disease resistance is ever-changing and dependent on whether the relationship is mutualistic or pathogenic. The microbial competition also plays a role in defining the host-microbial relationships. By leveraging machine learning, researchers can gain deeper insights into the gut microbiome's role in health and disease, ultimately leading to more personalized and effective interventions. Machine learning plays a significant role in gut microbiome research, offering powerful tools for analyzing complex and high-dimensional data to uncover patterns, make predictions, and generate insights [26-32]. Such algorithms can classify microbial sequences into taxonomic categories using models trained on labeled datasets. Predictive models can predict the relative abundance of microbial taxa based on sequencing data. Unsupervised learning methods like hierarchical clustering and k-means can group similar microbial communities, revealing patterns in diversity. Techniques like Principal Component Analysis and t-SNE (t-Distributed Stochastic Neighbor Embedding) can reduce the genomic data complexity, helping visualize and interpret microbiome composition. Feature selection can help identify key microbial taxa associated with specific host traits, such as health status or dietary habits. Machine learning models can explore correlations between microbiome composition and host variables, such as age, gender, or disease states. They can predict the presence or progression of diseases based on microbiome profiles, and can predict the patient response to interventions like probiotics, antibiotics, or dietary changes.

Future Directions in Microbiome Research

There are several layers of information still unknown to researchers about host-microbiome relationships. The role of microbiome in guiding the host C. elegans behavior, immunity, gut health, and lifespan is becoming apparent as new research studies emerge [6-18]. The microbiome

in *C. elegans* is mostly guided by the host genetics and a number of other factors such as nutrition, immunity, and microbial community interactions. C. elegans provides a good way to culture a specific set of microbes outside the human host. Gram-negative bacteria is the main constituent of the C. elegans gut microbiome. Microbiology can help us identify specific genes in the microbiome, role of specific microbes in colony formation, gene changes under environmental stress, and role of the microbiome in guiding host health and disease resistance.

Studies on *C. elegans* microbiome have revealed some interesting facts about the host–microbiome relationships and mutual interactions, along with the short- and long-term impacts of the microbiome on the host [1-10]. There can be possible directions in the studies conducted on C. elegans and its microbiome. It is possible to identify and characterize the functional traits of the microbiome that produce specific phenotypes and behavioral traits in the host C. elegans. It is also possible to identify and characterize the signaling pathways and immune response of the host in response to different microbial communities and metabolites. It is also possible to understand how the microbial communities and components affect the ageing, reproduction, and lifespan studies of C. elegans and related hosts, along with factors that induce stress and affect the microbial communities. For example, there are several factors that induce stress, including toxins, pathogens, bad diet, and bad interactions between the host and microbes [13-20]. Understanding the stress-inducing factors could lead to new discoveries in mitigating stress factors and improving overall health and well-being.

Conclusion

This article reviewed the importance of studying the host-microbiome relationships using C. elegans as the model organism. C. elegans has a short lifespan and fast reproductive cycle which helps to model the traits being passed over to the progeny. One of the goals in personalized medicine is to engineer gut bacteria with specific traits to help manage and control the states of health and sickness. C. elegans provides the option to genetically modify the gut microbiome and study its influence on host health and disease conditions. In such studies about the C. elegans microbiome, one limitation lies in exploring the target genes without prior knowledge of its function. In most cases, a candidate gene is known and prior knowledge of that gene is needed to explore its effects and genetic variations in the host behavior modulations. One additional challenge lie sin lining the heritable traits of the mother and progeny to identify any evidence of traits being passed to the progeny that are linked to a specific gene. A single gene may limit the impact of the studies being conducted. An alternative is the use of the genome wide analysis that identify new genetic markers of the microbiome that map to identifiable traits of the microbiome. This requires a large number of samples to compensate for the gene-level polymorphism and the diversity of the microbial communities. Another challenge lies in understanding the drug effects on host-microbiome relationships. Drugs may have varying degrees of influence on the microbial

communities and the host. Future studies will help define the targeted studies on host-microbiome relationships that provide value and insights for further studies.

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