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Changes in the Intestinal Microbiome and Alcoholic and Nonalcoholic Liver Diseases: Causes or Effects?



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The prevalence of fatty liver diseases is increasing rapidly worldwide; after treatment of hepatitis C virus infection becomes more widespread, fatty liver diseases are likely to become the most prevalent liver disorders. Although fatty liver diseases are associated with alcohol, obesity, and the metabolic syndrome, their mechanisms of pathogenesis are not clear. The development and progression of fatty liver, alcoholic, and nonalcoholic liver disease (NAFLD) all appear to be influenced by the composition of the microbiota. The intestinal microbiota have been shown to affect precirrhotic and cirrhotic stages of liver diseases, which could lead to new strategies for their diagnosis, treatment, and study. We review differences and similarities in the cirrhotic and precirrhotic stages of NAFLD and alcoholic liver disease. Differences have been observed in these stages of alcohol-associated disease in patients who continue to drink compared with those who stop, with respect to the composition and function of the intestinal microbiota and intestinal integrity. NAFLD and the intestinal microbiota also differ between patients with and without diabetes. We also discuss the potential of microbial therapy for patients with NAFLD and ALD.

Keywords: Dysbiosis; Diabetes; Metagenomics; Translocation; Intestinal Permeability.

The microbiota maintains a symbiotic relationship within the intestine and contributes to various functions such as digestion, vitamin synthesis, and resistance to colonization of the intestine by pathogens.[1] The microbiota is hugely diverse. An estimated 10–100 trillion microorganisms are present in each gram of stool, with approximately 500–1000 highly prevalent species[2]; these strongly are linked to an individual's gut metabolome. The microbiota provide its host with an extensive set of otherwise inaccessible metabolic capabilities and approximately 150-fold more genes than human cells.[3] There are several methods to define and interpret the composition of the gut microbiota (Table 1). Ultimately, bacteria are presented as phylum, order, family, genus, or species, in relative abundance values. Before comparing different studies, the uniformity of the depth of coverage of each subject in the study (ie, number of reads per sample) should be taken into consideration.

The gut microbiota elicits innate and adaptive immune mechanisms that cooperate to protect the host and maintain intestinal homeostasis. Activation of innate host defense depends on specific pattern-recognition receptors, including the family of Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-containing protein-like receptors. Of the 11 TLRs that have been identified in human beings, TLRs 2, 4, and 9 are involved in interactions between the gut microbiota host immune response, recognizing and becoming activated by gram-positive and gram-negative bacteria.[4]

The liver regulates systemic metabolism and the distribution of substances through the human gut, and also regulates numerous hormone and immune responses.[5] Communication between the liver and the intestine is facilitated by bile acids, which mediate absorption of dietary fats and vitamins and act as ligands for receptors that include nuclear-receptor farnesoid X receptor (FXR) and G-protein–coupled bile acid receptor 1 (or TGR5), which regulate the enterohepatic circulation.[1] A decrease in total fecal bile acids directly affects overgrowth of intestinal bacteria. FXR-deficient mice are protected from genetic- and diet-induced obesity but not hepatic steatosis.[6] The intestinal microbiota therefore might contribute to liver disease by modifying intestinal bile acids and regulating FXR signaling. Studies of expression patterns of bacterial genes and profiles of bile acids might help to determine how modulation of FXR could contribute to liver disease.

Abbreviations used in this paper: **ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDR, cirrhosis dysbiosis ratio; DHA, docosahexaenoic acid; FXR, farnesoid X receptor; GLP, glucagon-like peptide; IL, interleukin; NAFLD, nonalcoholic liver disease; NASH, nonalcoholic steatohepatitis; TLR, Toll-like receptor; TNF, tumor necrosis factor.**

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Table 1. Strategies for Analyzing the Microbiota

Name	Input	Output	Primary Features	Analysis
Quantitative Insights into Microbial Ecology[80]	16S RNA raw sequence data (FASTA sequences)	i) Clustered OTU file ii) Taxonomy file iii) BIOM file iv) Newick formatted tree file	Tool for performing microbial community analysis	Sequence alignments, clustering, α diversity analysis, network analysis, β diversity analysis, PCO, UNIFRAC, heat map
Mothur[81]	16S RNA raw sequence data (FASTA)	i) Clustered OTU file ii) Taxonomy file iii) BIOM file iv) Newick formatted tree file	Tool for performing microbial community analysis	Sequence alignments, clustering, α diversity analysis, network analysis, β diversity analysis, PCO, UNIFRAC, heat map
Metastats[82]	Feature abundance matrix (tabular format)	*P* value, Q value, and variance	Detection of differentially abundant features (taxa, pathways, subsystems, and so forth) between clinical metagenomic data sets	Nonparametric *t* test with false-discovery rates
Ribosomal Database Project[83]	16S RNA raw sequence data (FASTA)	Abundance table, Bayesian probabilities (taxa information, probabilities)	Assignment of relative abundance to sequences	Bayesian probability of genera abundance
LEfSE [84]	Feature abundance matrix (tabular format)	Linear discriminant scores, histogram, cladograms	Detection of differential features	Kruskal–Wallis test Wilcoxon test Linear discriminant analysis
Correlation analysis[85]	Feature abundance matrix (tabular format)	Correlation network (matrix format)		Spearman correlation
PICRUSt[86]	16S RNA raw sequence data (FASTA)	KEGG pathway scores, COG scores	Prediction of KEGG pathways	Gene content prediction
HUMAnN[87]	Raw sequence data (FASTA)	KEGG pathway scores	Prediction of KEGG pathways	Gene content prediction
MetaPhlAn[88]	Raw sequence data (FASTA), CDC calls (the list of gene or hypothetical gene start and end nucleotide positions), taxonomic classification of the genomes		Profiling microbial communities	Estimation of the relative abundance of microbial cells, identify microbes populating a microbial community
MetAMOS[89]	Raw sequence data	i) FASTA sequence of the contigs, scaffolds, or variant motifs belonging to specified taxonomic levels ii) Collection of all unclassified or potentially novel contigs contained in the assembly iii) HTML report with detailed assembly statistics and summary charts	Metagenomic de novo assembly	Classification methods, de novo assembly

BIOM, biological observation matrix; CDC, Centers for Disease Control; COG, Clusters of Orthologs Groups; OTU, operational taxonomy units; PCO, principal component analysis; UNIFRAC, unique fraction metric.