Oral Presentations

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Does Human Leukocyte Antigens Heterozygosity Influence the Gut Microbiota?

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Introduction

Within the human major histocompatibility complex (MHC), *human leukocyte antigens (HLA)* genes encode proteins that play a critical role in immune system function. *HLA* genes are some of the most polymorphic genes in the human genome. An individual HLA allele can present T-cells with a restricted repertoire of peptide motifs from self or non-self proteins. Differences between HLA alleles are predominantly due to differences in the peptide binding domain encoded by exons 2 and 3 in HLA class I alleles and exon 2 in HLA class II alleles. This allelic variation and subsequent variation in the peptide binding repertoire can lead to differences in immune response between individuals with different HLA phenotypes (1).

The human body is colonized by thousands of different microbial species that are key to our survival (2). The human microbiota is the ecological community of symbiotic, commensal and pathogenic microorganisms living on the surfaces and in specific niches of organisms (gut, skin, mouth, etc.) (3). The composition of the microbiota differs in various parts of the gastrointestinal tract and is influenced by factors such as pH, host secretion and substrate availability. Host HLA genotype may have a direct impact on the regulation of the host immune system through the recognition of specific molecules of symbiont microorganisms (4). It is not yet known whether HLA molecules control the composition of the microbiome through immune-mediated elimination or by directly influencing bacterial colonization.

In this study, we build on long-standing work in the HLA field and discuss the impact of HLA heterozygosity and homozygosity in shaping and regulating microbiome composition (and vice versa).

Materials and Methods

Thirty-three healthy individuals were included in the study. After nucleic acid isolation from stool samples, the samples were sequenced using the next generation sequencing. The operational taxonomic unit tables were plotted by calculating alpha diversity with R Statistical Computer Language. Statistical analyses were performed using R Statistical Computer Language. Associated pathways were analyzed with the KEGG database.

Results

The mean age was 45.27±12.37 years (27-67). The gender distribution was male/female: 17/16. Most common allels were HLA-A*24:02, HLA-B*35:01, HLA-C*04:01, HLA-DQB1*03:01 HLA-DRB1*13:01. The alpha-diversities of the gut microbiomes of people that are homozygous or heterozygous for five different HLA types (HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1) were compared using a Wilcoxon rank sum test. Diversities were calculated on the genus level. The results of the analyses conducted among the individuals included in our study revealed that individuals with HLA allele heterozygosity had a higher microbiota diversity than individuals with HLA allele homozygosity.

In the microbiota analysis between HLA homozygous and heterozygous individuals, *Corobacteriales Incertae Sedis* (p=0.04), *Streptococcaceae* (p=0.02), undefined *Corlobacterialiales Incertae Sedis* genus (p=0.04), *Streptococcus* (p=0.02) were predominant and statistically significant, whereas in individuals without HLA homozygosity, *Lachnospirales* (p=0.04), *Provetellaceae* (p=0.03), *Lachnospiraceae* (p=0.04), *Provetalla* (p=0.02), undefined *Lachnospiraceae* genus (p=0.04) were predominant and statistically significant. In HLA-A group some of significantly different groups based on p-values are; *Actinobacteria, Negativicutes, Lachnospirales*. In HLA-B group some of significantly different groups based on p-values are; *Streptomyces* spp., *Oscillibacter, Lachnospiraceae* UCG-003.

In HLA-C group some of significantly different groups based on p-values are; *Candidatus Soleaferrea, Bacteroides caccae, Lactobacillus delbrueckii*. In HLA-DBQ1 group some of significantly different groups based on p-values are; *Verrucomicrobiae, Clostridia* UCG-014, *Lachnospirales*. In HLA-DQB1 group some of significantly different groups based on p-values are; *Oscillibacter, Lachnospira*. KEGG pathways are depicted here in three hierarchical levels. Level 1 KEGG pathways are the most broad pathways, which encompass the level 2 and level 3 pathways. The most number of significantly different pathways were seen in HLA-A homozygote vs heterozygote samples.

Discussion

The gut associated microbiome is one of the most studied and related diseases. The role of the HLA complex in some microbiota-related disease development is postulated through the theory of molecular mimicry, among others.

Persons heterozygous at a particular HLA locus may defend against a greater diversity of pathogens compared to homozygous individuals, or the utility of particular alleles may be regulated by pathogen incidence.

Metabolite pathway-mediated up- or down-regulatory interactions of the microbiota with HLA alleles may alter the course of the disease or the immune response.

Keyword: HLA, microbiota, homozygous, heterozygous

References

1. Leen G, Stein JE, Robinson J, Maldonado Torres H, Marsh SGE. The HLA diversity of the Anthony Nolan register. HLA. 2021;97:15-29.
2. Marchesi JR, Adams DH, Fava F, Hermes GD, Hirschfield GM, Hold G, et al. The gut microbiota and host health: a new clinical frontier. Gut. 2016;65:330-9.
3. Lederberg J, McCray AT. 'Ome sweet 'omics - a genealogical treasury of words. Genealogical treasury of words. Scientist. 2001;15:8.
4. Belkaid Y, Harrison OJ. Homeostatic immunity and the microbiota. Immunity. 2017;46:562-76.