Gut microbiota related metabolic pathways in Elite Controllers and HIV-progressors

Abstract #1456

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Background

The gut microbiota is altered in HIV-1 infected patients and this dysbiosis is associated with immune activation and inflammation. However, little is known on the role of gut microbiota alterations and the related metabolic pathways in individuals who naturally can control HIV-1 infection (elite controllers).

Aim

To characterize gut microbiota and its metabolic pathways in elite controllers (EC).

Methods

We analysed gut microbiota in a cohort of patients with HIV infection (n=48) and HIV negative controls matched by age, gender and sexual orientation (n=16). The HIV cohort included 16 EC and 32 patients with untreated progressive HIV infection. Fecal microbiota composition was determined by 16S rRNA sequencing (Illumina, MiSeq). Soluble markers of inflammation (hsCRP, sCD14, hsIL-6, LBP) and metabolites of tryptophan catabolism pathway were analysed in plasma by ELISA or HPLC, respectively. Activation markers on CD4-CD8 T cells (HLA-DR/CD38) were determined by flow cytometry. The functional content of gut microbiota was inferred by PICRUSt analysis.

	EC	Naive	Negative	p-value
Number of individuals	16	32	32	
Age (years, median (IQR))	47 (40.25-54.3)	43.5 (37.3-50.5)	49(44-52.75)	ns
Gender (n, male/female) †	9/7	16/16	8/8	ns
Ethnicity (n)				
Black	9	13	0	
Caucasian	6	17	15	
Latin	1	1	0	
Oriental	0	1	1	
Mode of transmission (n)				
Heterosexually	8	21		
MSM	4	8		
IVDU	1	3		
Blood transfusion	2	0		
Unknown	1	0		
Sexual practice†				
Heterosex	12	24	12	ns
MSM	4	8	4	
Body Mass Index (BMI) (score (IQR))	26.4 (24.1-32.2)	25 (23-30)	24.2 (22.9-25.6)	ns
CD4+ T-cell count (median (IQR)	806 (676-1049)	390 (298-475)	NA	<0.0001
CD8+ T-cell count (median (IQR)*	705 (541-904)	995 (678-1373)	NA	0.02
CD4/CD8+ T-cell ratio (median (IQR)	1.41 (0.74-1.55)	0.38 (0.27-0.51)	NA	<0.0001
CD4+ HLA-DR+ CD38+ T cells % (median (IQR))*	0.44 (0.34-0.75)	7.78 (5.34-14.8)	0.53 (0.39-0.61)	<0.0001
CD8+ HLA-DR+ CD38+ T cells % (median (IQR))*	1.16 (0.77-1.6)	36.9 (23.6-44.9)	0.71 (0.52-1.71)	<0.0001

Table 1) Cohort demographics and characteristics. EC=elite controllers. Naive=viral progressors. Negative=healthy controls.*Kruskal-Wallis test was used for comparison between three groups, and Dunn's Multiple Comparison Test was adapted for "post hoc" testing. Mann-Whitney was applied for comparisons between two groups. †Chi-square test was applied.
NA (not available). ns (non significant) indicates p-value >0.05.

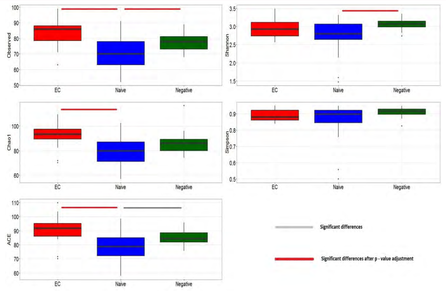


Figure 1) Ecology indicies (number of observed species, Chao1, ACE, Shannon and Simpson) in the studied cohort.
Comparisons were done using a Kruskal-Wallis test including post-hoc pairwaise analyses.

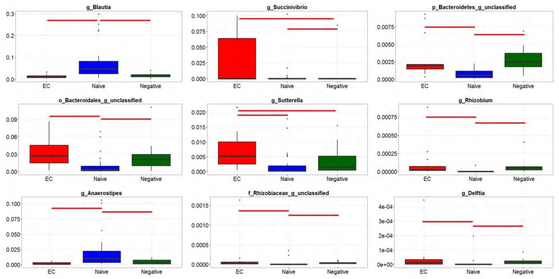


Figure 2) Compositional microbiota differences at the genus level between the HIV infected patients and controls.
Comparisons were done using a Kruskal-Wallis test including post-hoc pairwaise analyses.

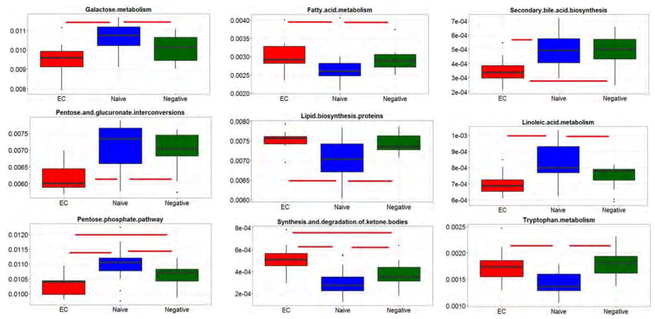


Figure 3) Functional analysis at KEGG level III. Comparisons were done using a Kruskal-Wallis test including post-hoc pairwaise analyses.

	EC	Naive	Negative	p-value*
Soluble marker: median(IQR)				
LBP (ng/ml)	3727 (2206-15123)	6805 (5984-8031)	2862 (1956-3705)	0.0004
sCD14 (pg/ml)	$1.7x10^6$ (1.53-1.95 $x10^6$)	$1.47x10^6$ (1.46-1.71$x10^6$)	$1.5x10^6$ (1.44-1.65$x10^6$)	0.087
IL-6 (pg/ml)	1.73 (1.18-3.20)	NA	0.84 (0.67-1.78)	0.035
hs-CRP (pg/ml)	1.37 $x10^6$ (757063-2.7 $x10^6$)	NA	635419 (378718-941463)	0.005
Tryptophan catabolism:				
Tryptophan (umol/L)	53.1 (51.4-60.5)	46.2 (40.5-50.8)	66.1 (60.3-73.1)	<0.0001
Kynurenine (umol/L)	1.4 (1.3-1.6)	1.65 (1.3-2)	1.7 (1.4-1.9)	0.36
Anthralinic acid (nmol/L)	12.2 (10.1-16.2)	21.6 (16.3-28.8)	15.3 (11.6-20.6)	0.0007
Kynurenic acid (nmol/L)	40.5 (36.2-50.6)	30.3 (17.6-48.9)	54.2 (48.9-70.2)	0.0015
3-Hydroxykunrenin (nmol/L)	45.9 (33.8-59.6)	35.1 (29.5-48.7)	41.9 (33.1-53.1)	0.42
Xanthurenic acid (nmol/L)	11.8 (8.4-19.5)	9.2 (3.4-14.5)	19.9 (15-27.8)	0.0013
3-Hydroxyantralinic acid (nmol/L)	27.2 (22.5-35.5)	31.6 (20-47.7)	31.5 (23.4-41.1)	0.57
Quinilonic acid (nmol/L)	349 (262.3-448.5)	474.4 (352.2-669.2)	359 (304-425)	0.039
K/T ratio	24.8 (21.2-30.8)	34.8 (31.2-46.9)	24.6 (20.8-28.9)	0.0001

Table 2) Soluble markers of inflammation and metabolites of tryptophan catabolism in plasma. Kruskal-Wallis test was used for comparison between three groups, and Dunn's Multiple Comparison Test was adapted for "post hoc" testing. Mann-Whitney was applied for comparisons between two groups.

Results

- Several alpha diversity measures (Observed species, Chao1 and ACE) were significantly higher in EC compared to patients with progressive infection and uninfected controls. The microbiota of patients with progressive infection had the lowest richness.
- EC had higher mean abundance of *Succinivibrio, Sutterella*. In contrast, *Blautia* and *Anaerostipes* were significantly enriched in patients with progressive infection.
- Soluble markers of inflammation were not increased in EC as compared to matched healthy controls besides CRP and IL-6. Higher levels of cellular immune activation were observed in patients with progressive infection, and their kynurenine/tryptophan ratio (indicating IDO-1 enzymatic activity) was significantly increased.
- In EC, abundance of bacterial genes encoding carbohydrate metabolism pathways were reduced, instead lipid and fatty acid metabolism metagenome was increased.

Conclusions

- Elite controllers show a significantly higher gut microbiota richness compared to untreated HIV infected patients, and their microbiota have a distinct metabolic profile.
- Our data implicate that re-shaping of the microbiota may be an adjuvant therapy even in patients with progressive HIV-1 infection.

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