GUT AND SKIN MICROBIOME IN PATIENTS WITH ATOPIC DERMATITIS BEFORE AND AFTER BALNEOTHERAPY AT THE THERMAL CARE CENTER OF LA ROCHE-POSAY

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INTRODUCTION

Recent findings indicate the gut microbiome has an effect on certain dermatological diseases such as atopic dermatitis (AD). However, parallel analysis of gut and skin microbiome compositions on the same AD patients is lacking. In addition, the intra-individual dynamics and the response of these communities to the improvement of the pathology remain to be studied.

PATIENTS AND METHODS

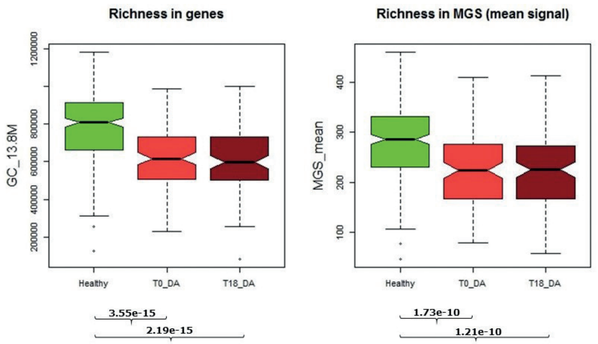
This open label study was conducted between April and September 2016. Skin and gut microbial communities of patients with AD were characterized prior and post a 3-week selenium-rich water balneotherapy treatment at the La Roche-Posay thermal care center (France). Skin bacterial communities were harvested from swabs, taken under axenic conditions from affected and proximal unaffected skin, using a high-throughput sequencing (Illumina) approach that targets a V1-V3 portion of the 16S rRNA bacterial gene as previously described. To analyze the gut microbiota, stool samples were collected, sequenced, and the sequencing reads were mapped on a 9.9M reference genes catalog. Bacterial content was analyzed using clusters of co-abundant genes known as metagenomics species (MGS).

RESULTS

This study included 116 patients diagnosed with moderate to severe AD. After eliminating individuals lacking paired samples from both visits, 83 individuals were analyzed for their gut and skin microbiome profiles. A cohort of 292 healthy individuals from the MetaHit project was used as a control for gut microbiome analyses. These 2 populations do not differ just by the presence or the absence of the atopic dermatitis (e.g. sequencing method/nationality life and diet habits).

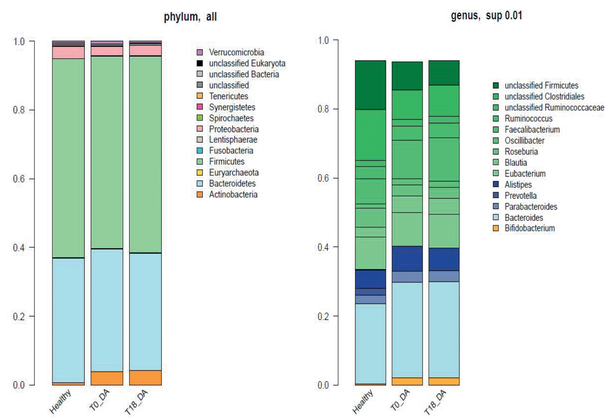
Comparison of the intestinal microbiota of 109 AD patients to 292 healthy people indicated that AD patients have a significant lower richness in genes and in MGS.

Richness data, according to groups



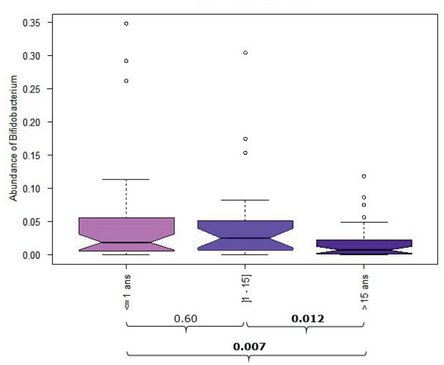
Gut microbiota analysis comparison indicated that Actinobacteria are significantly higher in AD patients (p=1.12e-10). At genus level, AD patients are depleted in Prevotella (p=1.17e-10) and certain Firmicutes genera (Roseburia p=4.17e-3) and enriched in Blautia, Bacteroides and Bifidobacterium genus (p=1.33e-8, 1.36e-7 and 1.13e-6 respectively).

Global intestinal microbiota taxonomic composition in the different groups



AD patients had a significantly higher abundance of Bifidobacterium genus, particularly *B. longum* and *B. adolescentis*. This overabundance was higher for those who contracted AD before the age of 15 years.

Genus Bifidobacterium



This table shows the 31 MGS that appear to be involved in the disease severity or improvement and linked to the status health or AD. Most of the MGS anticorrelated to SCORAD or correlated to SCORAD decrease are specific to healthy people. They might be MGS with beneficial effect on AD. At the opposite MGS correlated to SCORAD or anticorrelated to SCORAD decrease are rather more abundant for AD patients.

Taxonomy of the MGS involved in the microbiota linked to AD

	Cor SC***	Cor Am_score	Status*	Cor richness**	Species	Genus	Family	Order	Phylum
CAG00777	NEG	-		POS	unclassified Olsenella	Olsenella	Atopobiaceae	Coriobacteriales	Actinobacteria
CAG00515	NEG	-		-	Eubacterium eligens	Eubacterium	Eubacteriaceae	Clostridiales	Firmicutes
CAG00112	NEG	-		POS	Blautia sp. CAG:52	Blautia	Lachnospiraceae	Clostridiales	Firmicutes
CAG00463	NEG	-		POS	Faecalibacterium 6 (sp. CAG:82)	Faecalibacterium	Ruminococcaceae	Clostridiales	Firmicutes
CAG00572	NEG	POS		-	unclassified Faecalibacterium	Faecalibacterium	Ruminococcaceae	Clostridiales	Firmicutes
CAG01028	NEG	-	H	-	Ruminococcaceae bacterium LM158	unclassified Ruminococcaceae	Ruminococcaceae	Clostridiales	Firmicutes
CAG01039	NEG	-		POS	unclassified Faecalibacterium	Faecalibacterium	Ruminococcaceae	Clostridiales	Firmicutes
CAG01085	NEG	-	H	POS	unclassified Ruminococcaceae	unclassified Ruminococcaceae	Ruminococcaceae	Clostridiales	Firmicutes
CAG02723	NEG	-	DA	-	unclassified Bacteria	unclassified Bacteria	unclassified Bacteria	unclassified Bacteria	unclassified Bacteria
CAG00448	NEG	-	H	-	Clostridium sp. CAG:122	unclassified Clostridiales	unclassified Clostridiales	Clostridiales	Firmicutes
CAG00452	NEG	-	H	-	Clostridium sp. CAG:167	unclassified Clostridiales	unclassified Clostridiales	Clostridiales	Firmicutes
CAG00882	NEG	-	H	-	Clostridium sp. CAG:288	unclassified Clostridiales	unclassified Clostridiales	Clostridiales	Firmicutes
CAG01177	NEG	-		POS	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	Clostridiales	Firmicutes
CAG01200	NEG	-	H	POS	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	Clostridiales	Firmicutes
CAG50003	NEG	-	H	-	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	Clostridiales	Firmicutes
CAG00268	NEG	-	H	POS	Firmicutes bacterium CAG:24 & uncultured Ruminococcus sp.	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	Firmicutes
CAG00520	NEG	-	H	-	Firmicutes bacterium CAG:56	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	Firmicutes
CAG00831	NEG	-	H	-	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	Firmicutes
CAG00939	NEG	-	H	POS	Firmicutes bacterium CAG:313	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	Firmicutes
CAG00011	POS	-	H	POS	Escherichia coli	Escherichia	Enterobacteriaceae	Enterobacteriales	Proteobacteria
CAG00115	POS	-	DA	-	unclassified Lachnospiraceae	unclassified Lachnospiraceae	Lachnospiraceae	Clostridiales	Firmicutes
CAG00165	POS	-	DA	-	unclassified Lachnoclostridium	Lachnoclostridium	Lachnospiraceae	Clostridiales	Firmicutes
CAG00270	POS	-	DA	-	Oscillibacter sp. KLE 1728 / KLE 1745 / VE202-24	Oscillibacter	Oscillospiraceae	Clostridiales	Firmicutes
CAG00137	POS	-		-	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	Clostridiales	Firmicutes
CAG00054	POS	-	DA	-	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	Firmicutes
CAG00846	POS	-		-	unclassified	unclassified	unclassified	unclassified	Firmicutes
CAG00055	-	POS	H	POS	Roseburia sp. CAG:182	Roseburia	Lachnospiraceae	Clostridiales	Firmicutes
CAG00249	-	NEG	DA	-	Clostridium leptum	Ruminiclostridium	Ruminococcaceae	Clostridiales	Firmicutes
CAG00645	-	POS	H	-	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	Clostridiales	Firmicutes
CAG00720	-	NEG	DA	NEG	Anaerotruncus colihominis	Anaerotruncus	Ruminococcaceae	Clostridiales	Firmicutes
CAG00905	-	POS	DA	-	unclassified Eggerthella	Eggerthella	Eggerthellaceae	Eggerthellales	Actinobacteria

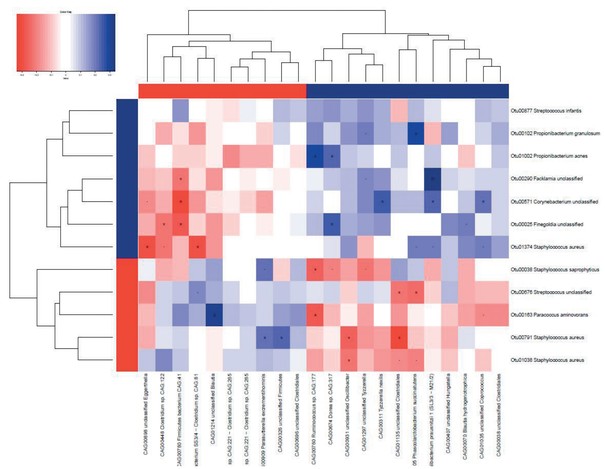
*MGS significantly more abundant for healthy (H) or atopic people (DA)
**MGS known to be correlated with the richness in genes
***Correlation with scorad

CONCLUSION

As previously observed for AD skin microbiota and particularly for affected areas, a poor bacterial biodiversity was also noticed in AD gut microbiota as compared to healthy subjects. In conclusion, there is a contrast in the microbiomes (gut and skin) between healthy and AD people; and we also identified certain MGS that could be markers regarding disease severity.

Interestingly, these MGS belong to Firmicutes and particularly to Clostridiales family. Functional analysis gave no evident biological interpretation. Analyses of gut microbiota did not show any clear effect of the balneotherapy, although the severity of the pathology improved (significant SCORAD decrease). At the level of the skin microbiota, as previously observed, skin bacterial alpha-diversity was significantly lower in affected versus unaffected areas associated with an overrepresentation of Firmicutes and particularly Staphylococci. After balneotherapy, reduced disease severity was associated with a significant increase of alpha-diversity in affected areas.

Correlation between gut and skin microbiota (affected areas) has been also performed (in blue positively correlated to SCORAD and in red negatively correlated to SCORAD).



**pvalue<0.01 - *0.01<pvalue<0.05 - 0.05<pvalue<0.1

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