Microbiota and IBD

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Saint-Antoine Hospital

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Microbiota in IBD Pathogenesis

Activation of the gastro-intestinal immune system toward gut microbiota in genetically susceptible hosts and under the influence of environment.
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Activation of the gastro-intestinal immune system toward gut microbiota in genetically susceptible hosts and under the influence of environment.
Outline

• Gut microbiota involvement in IBD

• Example of the role of complex host-microbiota interactions in IBD pathogenesis

• Treatment targeting the gut microbiota
Outline

• Gut microbiota involvement in IBD

• Example of the role of complex host-microbiota interactions in IBD pathogenesis

• Treatment targeting the gut microbiota
Arguments for the involvement of the gut microbiota in IBD pathogenesis
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• Polymorphisms of innate immunity genes involved in bacterial sensing: associated with IBD (GWAS)

• Role of fecal stream in post operative recurrence of CD

• Animal models of colitis depend on gut microbiota

• and.....
Arguments for the involvement of the gut microbiota in IBD pathogenesis

• Polymorphisms of innate immunity genes involved in bacterial sensing: associated with IBD (GWAS)
• Role of fecal stream in post operative recurrence of CD
• Animal models of colitis depend on gut microbiota
• and.....
• There is dysbiosis in IBD patients
Abnormal gut microbiota in IBD

Beta diversity (Bray curtis distance)

Sokol et al. Gut 2017
Abnormal gut microbiota in IBD

Beta diversity (Bray curtis distance)

Alpha diversity

Sokol et al. Gut 2017
Abnormal gut microbiota in IBD

Beta diversity (Bray curtis distance)

Alpha diversity

Sokol et al. Gut 2017
Abnormal gut microbiota in IBD

Faecalibacterium prausnitzii
Abnormal gut microbiota in IBD

Faecalibacterium prausnitzii

Anti-inflammatory effects

Induction of Human Tregs

Epithelial cells

Colitis model

Sokol H et al. PNAS 2008
Sokol et al. IBD 2009
Sarrabayrousse et al. Plos Biol 2014
Godefroy et al. Gastroenterology 2018

Sokol et al. Gut 2017
Outline

• Gut microbiota involvement in IBD

• Example of the role of complex host-microbiota interactions in IBD pathogenesis

• Treatment targeting the gut microbiota
How to interrogate the role of host genetics in modulation of gut microbiota in human?
How to interrogate the role of host genetics in modulation of gut microbiota in human?

Fecal microbiota analysis of patients with 3 types of rare monogenic primary immunodeficiency causing IBD conditions:

• Chronic granulomatous disease
• XIAP deficiency
• TTC7A deficiency

Collaboration with A. Fischer (Imagine UMR 1163)
Specific dysbiosis in 3 types of rare primary immunodeficiency causing IBD-like phenotype

Sokol et al. JACI 2018
Specific dysbiosis in 3 types of rare primary immunodeficiency causing IBD-like phenotype

Sokol et al. JACI 2018
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Specific dysbiosis in 3 types of rare primary immunodeficiency causing IBD-like phenotype

→ Suggest that dysbiosis is not only a nonspecific feature of intestinal inflammation
→ Host genes might also actively modulate the dysbiosis
→ Explore causality in mice model
Genes in IBD

Crohn’s Disease
140 risk loci

Ulcerative colitis
133 risk loci

Identified in GWAS

30

110

23

Khor et al. Nature 2011
Jostins et al. Nature 2012
Genes in IBD

- Crohn’s Disease: 140 risk loci
- Ulcerative colitis: 133 risk loci

Identified in GWAS

- Card9: Important gene in innate immunity to microorganisms

Khor et al. Nature 2011
Jostins et al. Nature 2012
Card9 KO mice are more susceptible to DSS-induced colitis

Susceptibility to colitis transferred by the gut microbiota

Card9 KO mice are more susceptible to DSS-induced colitis

Susceptibility to colitis transferred by gut microbiota

Mecanism related to Tryptophan

*Card*9−/−* mice exhibits impaired tryptophan metabolism*

Key role of Microbiota-derived AhR agonists in intestinal homeostasis

Lamas B et al. *Mucosal Immunology* 2018
Inflammatory bowel disease

Card9: IBD susceptibility gene

Card9^-/- mice

TRYPTOPHAN

Abnormal microbiota function

AhR agonists

↓ IL22

↓ AMP

Susceptibility to inflammation

Epithelial cells integrity

Colitis models

Inflammatory bowel disease

Card9: IBD susceptibility gene

Card9−/− mice

AhR agonist or Bacteria naturally producing AhR agonist

Abnormal microbiota function

Epithelial cells integrity

TRYPTOPHAN

IL22

AMP

Intestinal homeostasis

Inflammatory bowel disease

Card9: IBD susceptibility gene

Human patients with IBD

Abnormal microbiota function

AhR agonists

Susceptibility to inflammation

TRYPTOPHAN

Conclusion 1

- Gut microbiota in IBD pathogenesis: chicken or egg?
Conclusion 1

• Gut microbiota in IBD pathogenesis: chicken or egg?

Both!
Conclusion 1

Genetics → Vicious circle → Environment

STOP STOP

Environment → Vicious circle → Genetics
Outline

• Gut microbiota involvement in IBD

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Conclusion 1

Genetics → Vicious circle → Environment

STOP

STOP
Conclusion 1

- Probiotics
- Antibiotics
- Fecal microbiota transplantation
Fecal transplantation

Healthy microbiota

Disease-associated microbiota
Randomised controlled trials

3 published studies in ulcerative colitis

All performed in active patients and with the aim to induce remission
Randomised controlled trials

3 published studies in ulcerative colitis

- Enema (1/w for 6w)
  - Remission at week 7: FMT 9/38, Control 2/37, p = 0.03

- Duodenal infusion (w0 & w3)
  - Remission at week 12: FMT 11/41, Control 3/40, p = 0.02

- Colonoscopy & enema (1+ 5/w for 8w, multidonor)
  - Remission at week 8: FMT 12/38, Control 3/35

- Colonoscopy & 2 enema (over 7 days, multidonor)

- 3 of 4 trials positive, High heterogeneity
- Small n
- Effect size similar to early phase conventional molecules
- No maintenance data

No Randomized controlled trial in CD
No Randomized controlled trial in CD

IMPACT-Crohn Study

Original concept and design:
→ Target both immune system and microbiota
IMPACT-Crohn Study

Pilot study, 9 patients /group
IMPACT-Crohn Study

Pilot study, 9 patients /group
IMPACT-Crohn Study

Time (week)

Flare-free survival (%)

FMT
Sham
8
9
7
4
5
3
Number at risk

Steroid-free clinical remission (%)

FMT
Sham
p = 0.13

Week 10

0
20
40
60
80
100

Week 10
IMPACT-Crohn Study

CDEIS

1 patient not evaluable in each group (bowel cleansing problem)

Paired Wilcoxon test
IMPACT-Crohn Study

**CDEIS**

<table>
<thead>
<tr>
<th>Group</th>
<th>CRP (mg/l)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM T</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Sham transplantation</td>
<td>0.8</td>
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</table>

1 patient not evaluable in each group (bowel cleansing problem)

**CRP**

<table>
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<th>Group</th>
<th>CRP (mg/l)</th>
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</thead>
<tbody>
<tr>
<td>FM T</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Sham transplantation</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

5 patients

1 patient not evaluable (no sample available)
IMPACT-Crohn Study

Alpha diversity

Anova with corrections for multiple comparisons
For donor, delta was calculated with mean of FMT group at D0
For SHAM group, the mean of the Sorensen with each donor is indicated.

IMPACT-Crohn Study

Microbiota similarity between donor and recipient at 6 weeks
IMPACT-Crohn Study

Microbiota similarity between donor and recipient at 6 weeks

No colonization by donor microbiota = FMT failure

2 types of microbiota profile following FMT

For SHAM group, the mean of the Sorensen with each donor is indicated
IMPACT-Crohn Study

Microbiota similarity between donor and recipient at 6 weeks

→ 2 types of microbiota profile following FMT

For SHAM group, the mean of the Sorensen with each donor is indicated
IMPACT-Crohn Study

Microbiota similarity between donor in the follow up

For SHAM group, the mean of the Sorensen with each donor is indicated.
Donor PC1 (42.6%) donor

FMT failure W-2

W0 W10 W14 W18 W24
FMT failure

Donor

PC1 (42.6%)

PC2 (22.2%)

PC3 (15.0%)

W-2

W 0

donor

(1_17)

W 0

W-2
(1_17)

PC2 (22.2%)

W 0

PC3 (15.0%)

W-2

W 10

PC1 (42.6%)

W 2

W 6

FMT failure

W 0

W 2

W 10

W 14

W 18

W 24

Donor
Colonization by donor microbiota is associated with maintenance of remission in CD.
Conclusion
Therapeutic tool

FMT
Conclusion
Therapeutic tool

FMT

Consortium
Conclusion
Therapeutic tool

Faecalibacterium prausnitzii

FMT
Next generation Probiotics

Consortium
Single strain
Conclusion
Therapeutic tool

Faecalibacterium prausnitzii

FMT  →  Consortium  →  Single strain  →  Next generation Probiotics  →  Postbiotics

Nextbiotix
Saint Antoine Hospital

L Beaugerie  Nion-Larmurier
H Sokol  A Bourrier
P Seksik  C Landman
J Kirchgesner  C Martineau
P Marteau  C Delattre

Sokol’s lab
M Lavie-Richard
ML Michel
N Rolhion
G Da Costa
S Touch
A Magniez
A Lavelle
J Planchais
M Straub
J Glodt
L Dupraz
A Agus
C Oeuvey
C Michaudel
M Modoux
C Danne
P Langella

Collaborators
S Taleb  UMR 942 Inserm
A Fischer  Imagine UMR 1163
P Emond  U930 Inserm
JM Launay  U970 Inserm
D Skurnik  U1151 Inserm
HP Pham  ILTOO Pharma
RJ Xavier  Broad/Harvard
D Klatzmann

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