Healthy guts exclude oxygen

4th International Workshop on Microbiome in HIV Pathogenesis, Prevention and Treatment

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Control of microbes by our immune system

Balancing our microbial self

Fighting off bad bugs
What is gut homeostasis?

Gut microbiota of humans

Balancing our microbial self

What is a balanced microbial community?

Immune system
Microbial community structure in the intestine

Gut microbiota of humans

Fiber

Short-chain fatty acids

Gut microbiota of mice

Obligate anaerobes (Bacteroidetes and Firmicutes)
Dysbiosis: shift from obligate to facultative anaerobes

Gut microbiota of humans

Gut microbiota of mice

Obligate anaerobes (*Bacteroidetes* and *Firmicutes*)

Facultative anaerobes (*Proteobacteria*)
Dysbiosis: shift from obligate to facultative anaerobes

**Proteobacteria:** microbial signature of dysbiosis in gut microbiota

Na-Ri Shin*, Tae Woong Whon*, and Jin-Woo Bae

**Obligate anaerobes**
- Bacteroidetes
- Firmicutes

**Facultative anaerobes**
- Proteobacteria

Lupp et al., 2007

Stecher et al., 2007

Barman et al., 2008

Chemically-induced colitis

Salmonella infection

Toxoplasma infection

Antibiotics

Obligate anaerobes (Bacteroidetes and Firmicutes)

Facultative anaerobes (Proteobacteria)

Dysbiosis

**High-fat diet**
- Martinez-Medina et al., 2014
- Carroll et al., 2012
- Arthur et al., 2012

**Irritable bowel syndrome (IBS)**
- Frank et al., 2007
- Krogius-Kurikka et al. 2009
- Mai et al., 2011
- Normann et al., 2013

**Inflammatory bowel disease (IBD)**
- Raetz et al., 2013
- Molloy et al. 2013
- Haag et al. 2012

**Necrotizing enterocolitis (NEC)**
- Mutlu et al., 2014

**HIV enteropathy**
- Bohnhoff et al., 1954
- Saito, 1961

**Salmonella infection**
- Mutlu et al., 2007

**Citrobacter infection**
- Lupp et al., 2007

**Antibiotics**
- Lupp et al., 2007

**Colorectal cancer**
- Krogius-Kurikka et al. 2009
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**Genetically-induced colitis**
- Lupp et al., 2007
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Dysbiosis: shift from obligate to facultative anaerobes

Is there a common driver for gut dysbiosis?

- Obligate anaerobes (Bacteroidetes and Firmicutes)
- Facultative anaerobes (Proteobacteria)

Mai et al., 2011
Normann et al., 2013

Krogius-Kurikka et al., 2009
Carroll et al., 2012

Frank et al., 2007

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Genetically-induced colitis

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Colorectal cancer

Irritable bowel syndrome (IBS)

Genetically-induced colitis

Chemically-induced colitis

Is there a common driver for gut dysbiosis?
Dysbiosis: shift from obligate to facultative anaerobes

Is there a common driver for gut dysbiosis?

- Obligate anaerobes (Bacteroidetes and Firmicutes)
- Facultative anaerobes (Proteobacteria)

**Chemically-induced colitis**

Inflammatory bowel disease (IBD)

Necrotizing enterocolitis (NEC)

Irritable bowel syndrome (IBS)

High-fat diet

Colorectal cancer

Chemically-induced colitis

Genetically-induced colitis

Salmonella infection

Citrobacter infection

Toxoplasma infection

Antibiotics

Mutlu et al., 2014
Antibiotics drive a luminal expansion of *Enterobacteriaceae*

---

**Complex carbohydrates**

- **Clostridia**
- Butyrate
- Mature colonocyte
- **H**₂**O**
- **CO**₂
- **O**₂

---

**Blood vessel**

- **Undifferentiated colonocyte**

---

**Figure**

- **Streptomycin (single dose)**
- **CFU/g colon content**

---

**Bar graph**

- **Mock treatment**
- **Streptomycin treatment**

---

**Colonization resistance**

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**E. coli Nissle 1917**

---

**Mariana Byndloss**
Antibiotics drive a luminal expansion of *Enterobacteriaceae*

**Graph:**
- **Y-axis:** CFU/g colon content
- **X-axis:** Mock treatment, Streptomycin treatment
- **Day 3 after strep**
- **Eubacteria (16S rRNA gene copies/g colon contents):**
  - **Strep:** - 
  - **Strep:** +

**Legend:**
- **Mock treatment**
- **Streptomycin**
- **"colonization resistance"**

**Image:**
- Complex carbohydrates
- Clostridia
- Butyrate
- Mature colonocyte
- Undifferentiated colonocyte
- Blood vessel
- H₂O
- CO₂
- O₂
- Crypt

**Text:**
- Antibiotics drive a luminal expansion of *Enterobacteriaceae*
- Serendipitous discovery of *E. coli* Nissle 1917
- "colonization resistance"
- 2017 Science 357: 570

**Image:**
- Mariana Byndloss

**Diagram:**
- Interaction between intestinal flora and host physiology
- Notable changes in bacterial diversity following antibiotic treatment
Streptomycin depletes butyrate-producing *Clostridia*

**Butyrate producers:**
- *Ruminococcaceae*
- *Lachnospiraceae*

**Other:**
- *Clostridiaceae*
- *Peptostreptococcaceae*
- *Veillonellaceae*

---

**Eubacteria**

<table>
<thead>
<tr>
<th></th>
<th>Strept: -</th>
<th>Strept: +</th>
</tr>
</thead>
<tbody>
<tr>
<td>16S rRNA gene copies/g colon contents</td>
<td>$10^{13}$</td>
<td>$10^{12}$</td>
</tr>
</tbody>
</table>

**Clostridia**

<table>
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<th></th>
<th>Strept: -</th>
<th>Strept: +</th>
</tr>
</thead>
<tbody>
<tr>
<td>16S rRNA copies/g colon contents</td>
<td>$10^{12}$</td>
<td>$10^{10}$</td>
</tr>
</tbody>
</table>

**Relative abundance of Clostridia families (%)**

Day 3 after strep:
- H2O
- CO2
- O2
- Butyrate
- Complex carbohydrates
- Blood vessel
- Crypt
- Undifferentiated colonocyte
- Mature colonocyte

---

*2017 Science 357: 570*

**Mariana Byndloss**
Streptomycin lowers butyrate levels

- Clostridia (16S rRNA copies/g colon contents)
  - Strep: - +

- Relative abundance of Clostridia families (%)
  - Day 3 after strep

- Butyrate producers:
  - Ruminococcaceae
  - Lachnospiraceae
  - Peptostreptococcaceae
  - Veillonellaceae

- Cecal butyrate (μmol/g)
  - Strep: - +

2017 Science 357: 570

Mariana Byndloss
Streptomycin lowers butyrate levels

Strep: - +
Day 3 after strep

Relative abundance of Clostridia families (%)

Butyrate producers:
- Ruminococcaceae
- Lachnospiraceae
Other:
- Clostridiaceae
- Peptostreptococcaceae
- Veillonellaceae

Butyrate levels

Cecal butyrate (μmol/g)

Strep: - +
Day 3 after strep

(16S rRNA copies/g colon contents)

Strep: - +
Day 3 after strep

H₂O, CO₂, O₂, Butyrate, Complex carbohydrates, Undifferentiated colonocyte, Mature colonocyte, Blood vessel, Antioxidants, Clostridia

Butyrate producers:
- Crypt
- Undifferentiated colonocyte
- Mature colonocyte

H₂O, CO₂, O₂, Butyrate, ATP, ADP, Na⁺, Blood vessel, Antioxidants, Clostridia
Streptomycin lowers butyrate levels

Mock-treated

Hypoxia (< 1% oxygen)

Butyrate

Mock-treated

Lumen

Mucosa

Fabian Rivera-Chavez

2016 CH&M 19:443
Streptomycin increases epithelial oxygenation

- Complex carbohydrates
- Butyrate
- Blood vessel
- Antibiotics
- Clostridia
- H₂O
- Oxygen (O₂) gradient
- Hypoxia (< 1% oxygen)
- Glucose
- Lactate
- ATP
- ADP
- Mock-treated
- Strep-treated

Fabian Rivera-Chavez
2016 CH&M 19:443
Streptomycin increases epithelial oxygenation

Hypoxia
(< 1% oxygen)

2016 CH&M 19:443
Oxygen drives an expansion of *Escherichia coli*

**cydA**  **cydB**  Cytochrome *bd* oxidase  
(microaerobic conditions)

**E. coli**  Nissle 1917  **cydAB** mutant

---

2017 Science 357: 570
Oxygen drives an expansion of *Escherichia coli*

**Diagram:**
- Complex carbohydrates
- Antibiotics
- Butyrate
- Blood vessel
- O$_2$ gradient
- Crypt
- E. coli
- Clostridia

**Chemical Reactions:**
- H$_2$O + Butyrate → O$_2$
- H$_2$O + CydA → CydB
- Cytochrome bd oxidase (microaerobic conditions)

**Graph:**
- CI in colon contents (E. coli wt vs. cydAB)
- Strep: - +

**Legend:**
- 0.1%
- 1%
- 10%

**Reference:**
2017 Science 357: 570
Oxygen drives an expansion of *Escherichia coli*

**Cytochrome bd oxidase**

- **cydA**
- **cydB**

*Cytochrome bd oxidase (microaerobic conditions)*

**CI in colon contents**

- **E. coli Nissle 1917**
- **cydAB mutant**

**Graph:**
- **X-axis:** 0, 2, 4, 6, 8, 10, 12
- **Y-axis:** 0, 2, 4, 6, 8, 10, 12

- **Legend:**
  - **Strep:** - + +
  - **Tributyrin:** - - +

**Image:**
- **Complex carbohydrates**
- **Antibiotics**
- **Clostridia**
- **Tributyrin**
- **C2H2O2**
- **Blood vessel**
- **Undifferentiated colonocyte**
- **Mature colonocyte**
- **Crypt**
- **Butyrate**
- **H2O**
- **CO2**
- **O2**

**Text References:**
- 2017 Science 357: 570
Oxygen drives an expansion of *Escherichia coli*

**cydA**  **cydB**  
Cytochrome *bd* oxidase  
(microaerobic conditions)

**E. coli**  
Nissle 1917  
cydAB mutant

**Cl in colon contents**  
(E. coli wt vs. cydAB)

| Strep: | - | + | + | + |
| Tributyrin: | - | - | + | - |
| C17: | - | - | - | + |
Is there a common driver for gut dysbiosis?

- Necrotizing enterocolitis (NEC)
- Irritable bowel syndrome (IBS)
- Inflammatory bowel disease (IBD)
- Chemically-induced colitis
- Genetically-induced colitis
- High-fat diet
- Colorectal cancer
- Salmonella infection
- Toxoplasma infection
- HIV enteropathy
- Antibiotics
- Citrobacter Infection
- O₂

Mariana Byndloss
Is there a common driver for gut dysbiosis?

- Necrotizing enterocolitis (NEC)
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- Irritable bowel syndrome (IBS)
- Inflammatory bowel disease (IBD)

Depletion of Butyrate-Producing *Clostridia* from the Gut Microbiota Drives an Aerobic Luminal Expansion of *Salmonella*
Is there a common driver for gut dysbiosis?

Dysbiosis

- Necrotizing enterocolitis (NEC)
- HIV enteropathy
- Toxoplasma infection
- Antibiotics
- Citrobacter infection
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- Chemically-induced colitis
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- Irritable bowel syndrome (IBS)
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- Colorectal cancer

Virulence factors enhance Citrobacter rodentium expansion through aerobic respiration

Depletion of Butyrate-Producing Clostridia from the Gut Microbiota Drives an Aerobic Luminal Expansion of Salmonella
Oxygen as a driver of gut dysbiosis: What can we learn about homeostasis?

Microbial Respiration and Formate Oxidation as Metabolic Signatures of Inflammation-Associated Dysbiosis

Chemically-induced colitis

Genetically-induced colitis

Necrotizing enterocolitis (NEC)

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Antibiotics

Citrobacter Infection

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Depletion of Butyrate-Producing Clostridia from the Gut Microbiota Drives an Aerobic Luminal Expansion of Salmonella

Virulence factors enhance Citrobacter rodentium expansion through aerobic respiration

Sebastian E Winter
UT Southwestern Medical Center

Christopher Lopez

Mariana Byndloss

Fabian Rivera-Chavez

Elizabeth R. Hughes, 1, 6 Maria G. Winter, 1, 6 Breck A. Duerkop, 3 Luisella Spiga, 1 Tatiana Furtado de Carvalho, 1 Wenhan Zhu, 1 Caroline C. Gillis, 1 Lisa Bühler, 1 Madeline P. Smoot, 1 Cassie L. Behrendt, 1 Sara Chen, 1 Renato L. Santos, 2 Lora V. Hooper, 3, 6 and Sebastian E. Winter 1, 6

HIV enteropathy

Fabian Rivera-Chavez

Lillian F. Zhang, 1 Franziska Faber, 1 Christopher A. Lopez, 1 Mariana X. Byndloss, 1 Erin E. Olsen, 1 Gege Xu, 1 Eric M. Velazquez, 1 Carlito B. Lobrella, 1 Sebastian E. Winter, 1 and Andreas J. Bäumler 1, 6

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HIV enteropathy

Virulence factors enhance Citrobacter rodentium expansion through aerobic respiration

Sebastian E. Winter, 1 Andrea J. Bäumler 1, 6
Peroxisome proliferator-activated receptor gamma (PPAR-γ)

PPAR-γ is mainly expressed in adipose tissue, macrophages and epithelial cells in the colon (colonocytes)

M1 macrophage

IFN-γ

Nos2

D-glucose → pyruvate

Anaerobic glycolysis (Warburg effect)

M2 macrophage

IL-4

STAT6

β-oxidation

PPAR-γ

Nos2

CO₂

Fatty acids

O₂

CO₂

CO₂

D-glucose лactate

iNOS

β-oxidation
Butyrate depletion and inflammation cooperate to increase epithelial oxygenation

Complex carbohydrates → Clostridia → Butyrate → β-oxidation → PPAR-γ → CO₂ → O₂

WT (Pparg^{fl/fl}Villin^{−/−} mice) → WT

Pparg (Pparg^{fl/fl}Villin^{cre/−} mice) → WT

Mock

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Butyrate depletion and inflammation cooperate to increase epithelial oxygenation

**Complex carbohydrates**

- Clostridia
  - Butyrate

**Anaerobic glycolysis**

- Glucose
  - Lactate

**Oxygen**

**E. coli**

1:1

1% DSS: 

- WT
- Pparg

Cl colon contents

(E. coli wt vs. cydAB)

**2017 Science 357: 570**
How does antibiotic treatment generate an inflammatory signal?

**Induction of Colonic Regulatory T Cells by Indigenous Clostridium Species**

Nicholas Appel1,2, Clarissa Campbell1,2, Xingyu Pan1,2, Stanislav Dikic1,2, Jord van der Ven1,2, Paul de Roo1,2, Hu Liu1,2, Justin R. Cress1, Klaus Pfeffer1, Paul J. Coffie3,4 & Alexander Y. Rudensky1,2

Metabolites produced by commensal bacteria promote peripheral regulatory T cell generation

Yukihiko Furasawa1,2,3, Yuki Ohara1,2,4, Shintarō Fujita1,2,3, Takahiro A. Endo1,2, Gaku Naito1,2, Daisuke Takahashi1,2, Yumiko Nakayama1,2, Chikako Ueta1,2, Keiho Kato1,2, Hironori Kato1,2, Masami Takahashi1,2, Noriko N. Honda1,2, Shinmoku Murakami1,2, Fumi Miyazaki1,2, Shengo Hino1,2, Koji Matsuki1,2, Satoshi Ono1,2, Yumiko Fujihara1,2, Trevor Lockert1,2, Julie M. Clarke2, David L. Topp1,2, Masaru Tomita1,2, Shohel Horoi1,2, Osamu Gohara1,2, Tatsuya Morita1,2, Haruhiko Koseki1,2, Ann Kilchhitz1,2, Keiya Honda1,2, Koji Hase3,4 & Hiroshi Ohno3,4

The Microbial Metabolites, Short-Chain Fatty Acids, Regulate Colonic Treg Cell Homeostasis

Patrick M. Smith,1 Michael R. Howitt,2 Nikolai Panikov,3 Monia Michaud,4 Carey Ann Gallini,2 Mohammad Bohlooly-Y,5 Jonathan N. Glickman,6,7 Wendy S. Garrett1,2,4

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How does antibiotic treatment generate an inflammatory signal?

**Antibiotic Treatment**

- **Clostridia**
  - SCFAs
  - Butyrate
  - Anaerobic glycolysis
  - PPAR-γ

**Complex carbohydrates**

**β-oxidation**

**CO₂**

**O₂**

**ADP**

**ATP**

**Tregs**

**Inflammation**

**Treg**

**CD4⁺ FOXP3⁺ cells**

**CD3⁺-enriched CD4⁺ FOXP3⁺ cells**

**Cecal concentration (μmol/g)**

- Acetate
- Propionate

**Graphs:**

- Bar graphs showing CD3⁺-enriched CD4⁺ FOXP3⁺ cells (% of total CD3⁺-enriched colonic cells) and cecal concentration (μmol/g) with statistical significance indicated by asterisks.

2017 Science 357: 570
How does antibiotic treatment generate an inflammatory signal?

Streptomycin treatment results in reduced SCFAs (butyrate, acetate, propionate) and lactate production, and increased glucose uptake and anaerobic glycolysis.

**CD3+ enriched CD4+ FOXP3+ cells (%) of total CD3+ enriched colonic cells**

- **Wild type** vs. **Pparg deficient**

**Cecal concentration (μmol/g)**

- Acetate
- Propionate

**Colonic contents (wild type vs. aerobic respiration deficient)**

- **Isotype control** vs. **anti-CD25**
Respiration drives post-antibiotic expansion of *Enterobacteriaceae*

- **Streptomycin**
  - Clostridia
  - Enterobacteriaceae
  - SCFAs
  - Butyrate
  - Anaerobic glycolysis

- **iNOS**
  - ROS
  - NO
  - NO$_3^-$
  - Nitrate
  - Nar Knar GHJI
  - Nar Unar ZYWV
  - Nap FDAGHBC
  - Colonocyte Nos2 mRNA
  - Colonization resistance

- **Nitrite**
  - Colon contents
    - (wild types vs. aerobic respiration deficient)

- **Nos2**
  - 1000-fold
  - 10-fold

- **Respiration drives post-antibiotic expansion of Enterobacteriaceae**

- **Colonization resistance**
  - (wild types vs. aerobic respiration deficient)**

- **Day 3 after strep**
  - WT
  - Pparg

- **Strep**
  - -
  - +
Respiration drives post-antibiotic expansion of *Enterobacteriaceae*

SCFAs → Butyrate → Clostridia

NO₃⁻ → O₂ → Enterobacteriaceae

Anaerobic glycolysis

**Respiration** drives post-antibiotic expansion of *Enterobacteriaceae*

**iNOS**

**Cl in feces**

(E. coli wt vs. cydAB, napA, narG, narZ)

**Cl colon contents**

(wild types vs. aerobic respiration deficient)

**WT** vs. **Pparg + anti-CD25**

**1000-fold**

**10-fold**

**NOS2**

**E. coli cydAB, napA, narG, narZ**
What is gut homeostasis?

Balancing our microbial self

Immune system
PPAR-γ signalling and $T_{\text{regs}}$ cooperate to maintain gut homeostasis

Balancing our microbial self

Anaerobic glycolysis

$\beta$-oxidation

$\text{NaS}2$

CO$_2$

ATP

ADP

O$_2$

SCFAs

Butyrate

$T_{\text{regs}}$

Inflammation

Immune system

PPAR-γ

Virtuous PPAR-γ cycle

Obligate anaerobes

Anaerobiosis

Obligate anaerobes

Butyrate

Hypoxia
Can we remediate dysbiosis by reinstating epithelial control to limit the flow of oxygen into the gut lumen?
DSS induces colitis by triggering ER stress

The Unfolded Protein Response and Chemical Chaperones Reduce Protein Misfolding and Colitis in Mice

STEWART SIYAN CAO,1,2 ELLEN M. ZIMMERMANN,3 BRANDY-MENGCHIEH CHUANG,1 BENBO SONG,4 ANOSIKE NWOKOYE,2 J. ERBY WILKINSON,5 KATHRYN A. EATON,6,7 and RANDAL J. KAUFMAN1,2

Tauroursodeoxycholic acid inhibits experimental colitis by preventing early intestinal epithelial cell death

Debby Laukens1,5, Lindsey Devisscher1,5, Lien Van den Bossche1, Pieter Hindryckx1, Roosmarin E Vandenbroucke2,4, Yves-Paul Vandewynckel1, Claude Covelle4, Brigitta M Brinkman4, Claude Libert2,4, Peter Vandensaele1,5 and Martine De Vos1

DSS-induced colitis

5-aminosalicylic acid (5-ASA)
Excessive intestinal epithelial repair response

DSS induces colonic crypt hyperplasia

The Unfolded Protein Response and Chemical Chaperones Reduce Protein Misfolding and Colitis in Mice

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5-aminosalicylic acid
(5-ASA)
Blood vessel
Undifferentiated colonocyte

DSS increases epithelial oxygenation

Excessive intestinal epithelial repair response

Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-γ

Christel Rousseaux, Bruno Lefebvre, Laurent Dubuquoy, Philippe Lefebvre, Olivier Romano, Johan Auerx, Daniel Metzger, Walter Wyll, Béatrice Desvergne, Gian Carlo Naccari, Philippe Boulieu, Amaury Forcé, Philippe Bulol, Antoine Cortot, Jean François Colombel, and Pierre Desreumaux

5-aminosalicylic acid (5-ASA)
ER stress

5-ASA restores epithelial hypoxia

Mock
2.5% DSS
2.5% DSS + 5-ASA

Control
5-ASA

E. coli in colon contents
CFU/g

5-aminosalicylic acid (5-ASA)
5-ASA restores epithelial hypoxia

E. coli

\[ \text{cydAB} \]
\[ \text{napA} \]
\[ \text{narG} \]
\[ \text{narZ} \]

Excessive intestinal epithelial repair response

Colonic crypt hyperplasia

Undifferentiated colonocyte

ER stress

DSS

\( \text{E. coli} \)

\( \text{NR cydAB} \)

\( \text{NO}_3^- \cdot \text{O}_2 \)

\( \text{O}_2 \)

\( \text{O}_2 \) gradient

Blood vessel

\( 10\% \)

\( 1\% \)

\( 0.1\% \)

\( 10^7 \)

\( 10^6 \)

\( 10^5 \)

\( 10^4 \)

\( 10^3 \)

\( 10^2 \)

\( \text{CFU/g} \)

Control

5-ASA

Mock

2.5% DSS

5-aminosalicylic acid (5-ASA)

E. coli in colon contents

5-ASA restores epithelial hypoxia
5-ASA restores epithelial hypoxia

Excessive intestinal epithelial repair response

Blood vessel

Colonic crypt hyperplasia

Undifferentiated colonocyte

O$_2$ gradient

E. coli

cydAB

napA

narG

narZ

DSS-induced colitis

CI in feces

(wt vs. cydAB napA narG narZ)

WT

Mock DSS

Control  5-ASA

E. coli in colon contents (CFU/g)

Mock  2.5% DSS

5-aminosalicylic acid (5-ASA)

Control  5-ASA

O$_2$ gradient

10%  1%  0.1%  0.01%  0.001%
Can we remediate dysbiosis by reinstating epithelial control to limit the flow of oxygen into the gut lumen?
Can we remediate dysbiosis by reinstating epithelial control to limit the flow of oxygen into the gut lumen?

Gut dysbiosis: a microbial signature of epithelial dysfunction

5-aminosalicylic acid (5-ASA)

PPAR-γ

Anaerobic glycolysis

β-oxidation

O₂

CO₂

ATP

ADP

iNOS

O₂

SCFAs

Butyrate

Proteobacteria

Gut homeostasis

Gut dysbiosis

Gut dysbiosis: a microbial signature of epithelial dysfunction

Obligate anaerobes

SCFAs

Butyrate

Tregs

Inflammation

Anaerobic glycolysis

β-oxidation

PPAR-γ

O₂

CO₂

ATP

ADP

iNOS

O₂

5-aminosalicylic acid (5-ASA)

Proteobacteria

SCFAs

Butyrate

Tregs

Glucose

Lactate

Inflammation

Inflammation

Anaerobic glycolysis

O₂

O₂

O₂

O₂

O₂
Can we remediate dysbiosis by reinstating epithelial control to limit the flow of oxygen into the gut lumen?

miR-180a and miR-212 Disrupt the Intestinal Epithelial Barrier through Modulation of PPARγ and Occludin Expression in Chronic Simian Immunodeficiency Virus–Infected Rhesus Macaques

Vinay Kumar, Joshua Mansfield, Rong Fan, Andrew MacLean, Jian Li and Mahesh Mohan

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