The Fungal Mycobiome and Human Health

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The Human Microbiome

• The human microbiome is defined as the microbial communities found at several different sites on the human body
• Changes in the microbiome have been associated with different disease states including HIV, cancer and Irritable Bowl Disease
• Up until recently, only the bacterial component of the microbiota have been studied
Change Through Personal Story!!!

• In 1974, my master’s advisor handed me a paper showing that rabbits treated with antibiotics or anti-inflammatory steroids developed the fungal infection candidiasis.

• It made me realize that not only could fungi in the environment negatively impact our health, but fungal species also inhabit the mammalian body, alongside diverse commensal bacteria.

• When one microbial community is knocked out (bacteria), another (fungi) can cause illness.

• If the communities are undisturbed, however, the fungal inhabitants appear to be harmless or perhaps even beneficial.

This realization happened 43 Years Ago!!!
Opined:
- That future human microbiome studies should be expanded beyond bacteria to include fungi, viruses, and other microbes in the same samples.
- Such studies will allow a better understanding of the role of these communities in health and disease

Ghannoum & Mukherjee (2010). Microbe 5(11)
Researching the Mycobiome

• As of November 2015, only 269 of more than 6,000 Web of Science search results for the term “microbiome” even mention “fungus”

• The scientific search engine returns only 55 papers pertaining to the “mycobiome”
Early surveys have revealed several pathogenic species that may increase one’s risk of disease when the healthy microbiome is disrupted.

*Candida* and *Aspergillus* species are among the most common members of the human mycobiome.

When the balance of a microbial community is disrupted, fungal species can flourish and cause disease.
Our first endeavor to unlock the secrets of the fungal community

- Profiling the fungi in the healthy mouth

Oral Cavity in Health

Microbiome
Defining the Healthy Oral Fungal Microbiome (Mycobiome)

**Study Design**

- 20 healthy subjects recruited after obtaining written informed consent (IRB-approved protocol)
- Demographics: 21-60 years of age; 8 F, 12 M; non-smokers; non-diabetic; no antimicrobials for 3 m
- Oral examination
- 15 ml sterile saline rinse for 1 min, expectorate into sterile 50 mL tube, hold on ice till processing
DNA Extraction and PCR Analysis

- DNA extracted from cellular pellet
- Amplified **ITS1** region
  - designed to detect consensus sequences present in a *wide range of fungi*
• Detected 74 culturable and 11 non-culturable genera,
• Total number of species identified were 101.
• The number of species in the oral cavity of each individual ranged between 9 and 23
• 15 genera were present in 20% of the participants (core mycobiome)
• *Candida* species were the most frequent (isolated from 75% of participants), followed by *Cladosporium* (65%), *Aureobasidium*, Saccharomycetales (50% for both), *Aspergillus* (35%), *Fusarium* (30%), and *Cryptococcus* (20%).

• Four of these genera are known to be pathogenic in humans.
**Oral Mycobiome in Healthy Individuals: Conclusion**

- **Surprise:** Humans are colonized with numerous fungal species (85 genera), including the expected (*Candida* spp.), and the unexpected (*Aspergillus, Fusarium, Cryptococcus* spp.).

- **Surprise:** over a 1/3 of the fungi were un-culturable.

- Great individual variation in the fungal flora among 20 healthy individuals was observed.

- These discoveries provide a glimpse of the complexity in the human microbial flora, which now includes numerous fungal species in addition to the bacteria.

- Our findings prepare the way for studies aimed at defining the role of these fungi in health, disease and controlling the bacterial flora (and vice versa).
Mycobiome: “A Tale of Two Diseases”

*A Tale of Two Cities* addresses the fundamentally dual nature of humanity

*With apologies to Mr. Dickens*
THE FIRST CITY:
MYCOBIOME AND HIV INFECTION
Defining the Oral Microbiome in HIV Infection

- Profile the microbes in the healthy mouth
- Changes in the mouth in the setting of HIV disease
- Microbial interactions in HIV setting
Changes in the Oral Microbiome in HIV Setting

- Oral rinse samples were collected from 12 uninfected and 12 HIV-infected individuals following informed consent
- **Uninfected controls:** recruited from students/staff at Case
- **HIV infected patients:** recruited from the UH/Case Medical Center, OHARA and AIDS Research (CFAR) Units
- **Information collected:** HAART medication, viral load, CD4 counts, smoking status, age, gender and ethnicity
- **Inclusion criteria:** > 18 yrs, no clinical signs of oral mucosal disease
- **Exclusion criteria:** recent use of antimicrobials/topical or systemic steroids, pregnancy, and insulin-dependent diabetes mellitus
Oral Bacteriome of HIV-infected and uninfected individuals

Relative Abundance (%)

Uninfected

HV-infected
### Bacteriome (n=12)

#### % Abundance

<table>
<thead>
<tr>
<th>Genus</th>
<th>Healthy Uninfected (%)</th>
<th>HIV-infected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus</td>
<td>26.0%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Prevotella</td>
<td>15.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Haemophilus</td>
<td>10.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Rothia</td>
<td>10.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Veillonella</td>
<td>7.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Neisseria</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Fusobacterium</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Porphyromonas</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Granulicatella</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Leptotrichia</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Gemella</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Pasteurella</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Actinomyces</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Aggregatibacter</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Kaistella</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Kaseella</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Hafnia</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Megatropphaera</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Atoleobium</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Neisseria</td>
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<td>5.0%</td>
</tr>
<tr>
<td>Solobacterium</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Campylobacteri/um</td>
<td>5.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Actinobacillus</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Pelobacterium</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
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<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Tannospira</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Filaribacter phalangeri</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Filifactor phalangeri</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Parvimonas phalangeri</td>
<td>5.0%</td>
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<tr>
<td>Paludibacter phalangeri</td>
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<td>5.0%</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>5.0%</td>
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<tr>
<td>Lactobacillus phalangeri</td>
<td>5.0%</td>
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<tr>
<td>Kingella phalangeri</td>
<td>5.0%</td>
<td>5.0%</td>
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<tr>
<td>Hallella phalangeri</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Filifactor phalangeri</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

### Key Observations:

- **HIV-infected:**
  - Number of taxa: 9-14
  - Most common: *Prevotella, Streptococcus* and *Rothia*

- **Uninfected:**
  - Number of taxa: 8-14
  - Most common: *Fusobacterium, Prevotella*, and *Streptococcus*
Core Oral Bacteriome

- 14 genera constituted the core oral bacteriome in both HIV-infected and uninfected, of which 13 (93%) were common to both study groups.
- The core bacteriome of uninfected individuals was similar to earlier study showing 15 taxa in the oral cavity*.
- **Capnocytophaga** – unique to HIV-infected individuals.
- **Aggregatibacter** – unique uninfected individuals.

*Zaura et al. (2009). BMC Microbiol 9: 259*
Oral Mycobiome of HIV-Infected and Uninfected Individuals

Relative Abundance (%)
- **HIV-infected:** Number of taxa: 1-9, most common: *Candida, Epicoccum, and Alternaria*
- **Uninfected:** Number of taxa: 1-9, most common: *Candida, Pichia, and Fusarium*
Core Oral Mycobiome in HIV Setting

- The COM of HIV-infected and uninfected individuals consisted of 5 genera
- Of these, *Candida* and *Penicillium* were common between the two groups, while differing in the remaining genera
- Among the *Candida* species detected, *C. albicans* was the most common (58% in uninfected and 83% in HIV-infected patients), followed by *C. dubliniensis* (17% in both groups)

These results demonstrated a shift in the core mycobiome between HIV-infected and non-infected controls
Correlation Between Oral Bacteriome and Mycobiome in HIV-Infected Patients

- **Uninfected**: 15 bacteria-fungi pairs were significantly correlated
  - Two (Rothia-Cladosporium and Granulicatella-Cryptococcus) negatively correlated; 13 positively correlated

- **HIV-infected**: 12 bacteria-fungi correlations were significant
  - 11 positive and 1 with negative correlation (Campylobacter-Candida)
Systems Biology Approach: HIV

- Profile the fungal community and coined the term “Mycobiome” (101 fungal species detected)
- Changes in the mouth in the setting of HIV disease
- Microbial/metabolite interactions in HIV setting

Defined Microbial Interactions in the HIV Setting

- Is there an association between *Candida* colonization and members of the core microbiome?
- *Pichia* and *Cladosporium* were detected in uninfected individuals only
- *Penicillium* was present in both HIV-infected and uninfected individuals, at the same level (25%)
- Presence of *Pichia* coincided with absence of *Candida*, and *vice versa*
- No association with *Candida* colonization was found for *Cladosporium* or *Penicillium*
- These results suggested that *Pichia* is antagonistic to *Candida*
Does *Pichia* Exhibit Antagonistic Interaction with *Candida*?

- **Hypothesis:** *Pichia* inhibits *Candida* growth.

- To test this hypothesis, we evaluated the effect of *Pichia* on *Candida*.

- Effect on growth, germination, and biofilm formation.

- Biofilms were grown in the presence or absence of spent media obtained from cultures of *Pichia* or *Penicillium* (control).

- Biofilms were quantified by XTT assay.

- Effect on biofilm architecture was monitored by confocal laser scanning microscopy (CLSM).
Effect of *Pichia* Spent Medium on Pathogenic Fungi

- PSM inhibited growth of *Candida*, *Aspergillus* and *Fusarium*

![Growth curves for Candida, Aspergillus, and Fusarium with untreated and PSM-treated conditions.](image-url)
Pichia Causes Stunted Filamentation

- PSM induced formation of stunted filaments in Candida
Activity of *Pichia* Against Fungal Biofilms

- **Exposure to *Pichia* Cells**
  - *P* ≤ 0.002 compared to controls

- **Exposure to Spent Medium**
  - Spent medium from *Pichia* (PSM) inhibited biofilms
  - Spent medium from *Penicillium* had not effect on *Candida* biofilms

- **Effect of *Pichia* cells on *Candida* biofilm formation**
  - *Candida* and *Pichia* were co-incubated [(C:P) = 3:1, 1:1, or 1:3] and biofilm formation was monitored
  - *Pichia* cells inhibited *Candida* biofilms

- **Effect of spent media from *Pichia* or *Penicillium* on *Candida* biofilms**
  - Spent medium from *Pichia* (PSM) inhibited biofilms
  - Spent medium from *Penicillium* had not effect on *Candida* biofilms
Activity of PSM Against Fungal Biofilms: Confocal Analysis

- Effect of spent medium from *Pichia* biofilms was determined by confocal microscopy.
- *Pichia* spent medium inhibited biofilm formation.
- Thickness of biofilms formed in presence of *Pichia* spent medium was significantly reduced compared to untreated control.
- *Penicillium* spent medium had no effect on the architecture or thickness of biofilms.
Efficacy of PSM in a Murine Model of Oral Candidiasis

- Wild-type C57BL/6 mice were immunosuppressed, fed tetracycline in drinking water to prevent bacterial growth
- Mice were anesthetized, scratches made on the dorsum of the tongue, and challenged with *C. albicans* GDH (10⁸ blastospores)
- Mice were divided into 3 groups (n = 4):
  - Treated with *Pichia* supernatant, 100 µl in the oral cavity twice a day
  - Treated with topical nystatin as comparator (widely used clinically to treat oral candidiasis)
  - Untreated and vehicle-treated control
- Treatment began on day 4 post inoculation, mice were sacrificed on day 7
- Infection score of tongues was assessed on a scale of 0 (no lesions) to 3 (wide-spread fungal plaques and mucosal erosive)
- Tongues were harvested for determination of fungal burden and histopathology
PSM is Efficacious Against Oral Candidiasis in a Murine Model

- Infection score of PSM-treated mice was significantly reduced compared to untreated mice ($P = .011$)
- Tongue fungal CFU was significantly reduced in PSM-treated mice vs. untreated controls ($P = .04$)
- Extensive tissue invasion by fungal hyphae and disruption of the epithelium in untreated controls and nystatin-treated mice, while PSM-treated tongues had only superficial hyphal invasion

- Mycobioime studies identified a new way to combat oral candidiasis
PSM Activity is Mediated by Protein(s)

- Role of metabolites in PSM activity
  - Extracted metabolites from PSM
  - No effect on *Candida* biofilm formation

- Role of proteins in PSM activity
  - Biofilms were exposed to *Pichia farinosa* supernatant (PSM) treated with proteinase K (PK; 100, 200 or 500 µg)
  - Compared to untreated PSM
  - Biofilm formation evaluated by confocal microscopy, biomass determination and colony forming units (CFUs)
Effect of PSM Proteins on *Candida* Biofilms: Confocal Microscopy

(A) Control

(B) +PSM

(C) +PSM+PK (100 µg)

(D) +PSM+PK (200 µg)

(E) +PSM+PK (500 µg)

(F) Biofilm Thickness (µm)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Biofilm Thickness (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>100 ± 5</td>
</tr>
<tr>
<td>PSM</td>
<td>70 ± 3</td>
</tr>
<tr>
<td>PK (100 µg)</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>PK (200 µg)</td>
<td>50 ± 1</td>
</tr>
<tr>
<td>PK (500 µg)</td>
<td>40 ± 0.5</td>
</tr>
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</table>

*Significant difference compared to Control.
Recent Focus
In Collaboration with Michael Lederman and Nick Fundeburg
Diversity Index

Mycobiome

(A) P = 0.350
P = 0.091

Index

Bacteriome

(B) P = 0.033
P = 0.702

Shannon

HC IF IS
Abundance of 8 bacterial species differed significantly among the 3 groups.

*Collinsella stercoris*, which was significantly decreased in HC compared to IF and IS ($P = .350$ and .008, respectively)
Regression analysis: BMIs of IF patients were associated with abundance of the *Collinsella* ($R^2 = 0.53$)

*Collinsella* has been reported to be a risk factor for heart attack and linked to alteration in serum lipids.
THE SECOND CITY: MYCOBIOME AND CROHN’S DISEASE
Bacteriome and Mycobiome Interactions Underscore Microbial Dysbiosis in Familial Crohn’s Disease


ScienceDaily: September 20, 2016 Press Release
A fungus has been identified as a key factor in the development of Crohn’s disease:

An international team of researchers has identified for the first time Fungus as key factor in Crohn’s disease

### Subjects Demographics

<table>
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<th>Variable</th>
<th>CD</th>
<th>NCR</th>
<th>NCU</th>
<th>Total</th>
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<td>Families</td>
<td>9</td>
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<td>4</td>
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<td>Individuals</td>
<td>20</td>
<td>28</td>
<td>21</td>
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<tr>
<td>Female</td>
<td>12</td>
<td>13</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>15</td>
<td>8</td>
<td>31</td>
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<tr>
<td>Age (mean, yrs)</td>
<td>44.5</td>
<td>48.4</td>
<td>41.3</td>
<td>45.1</td>
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</table>

CD – Crohn’s disease patients  
NCR – Non-Crohn’s, Related individuals  
NCU – Non-Crohn’s, Unrelated individuals

### Clinical Details of CD Patients

<table>
<thead>
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<th>Age Category</th>
<th>CD</th>
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</thead>
<tbody>
<tr>
<td>A1 (&lt;=16 yr)</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>A2 (17-40 yr)</td>
<td>8</td>
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<td></td>
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<tr>
<td>A3 (&gt;= 40 yr)</td>
<td>12</td>
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<table>
<thead>
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<tr>
<td>L1 (Terminal Ileum)</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2 (Colon)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L3 (Ileum-Colon)</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>L4 (Upper GI Tract)</td>
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<table>
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<tr>
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<tr>
<td>B2 (Stenotic)</td>
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<td>B3 (Penetrating)</td>
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<tr>
<td>Remission</td>
<td>8</td>
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Fungal-Fungal Genera Correlations

Number of genera = 28

Associations among fungal genera in:
Red circles: negative associations, while blue circles positive associations.
Significant* Correlations of *C. tropicalis* with Bacterial Species in CD Patients

<table>
<thead>
<tr>
<th>Bacterial Taxon</th>
<th>Pearson Correlation</th>
<th>P-value</th>
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<tbody>
<tr>
<td><em>Alkalimonas amylolytica</em></td>
<td>.701</td>
<td>.001</td>
</tr>
<tr>
<td><em>Aquamonas haywardensis</em></td>
<td>.743</td>
<td>.000</td>
</tr>
<tr>
<td><em>Enterobacter hormaechei</em></td>
<td>.808</td>
<td>.000</td>
</tr>
<tr>
<td><em>Enterobacter ludwigii</em></td>
<td>.725</td>
<td>.000</td>
</tr>
<tr>
<td><em>Enterobacter pyrinus</em></td>
<td>.687</td>
<td>.001</td>
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<tr>
<td><em>Erwinia chrysanthemi</em></td>
<td>.577</td>
<td>.008</td>
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<td>.733</td>
<td>.000</td>
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<tr>
<td><em>Erwinia soli</em></td>
<td>.491</td>
<td>.028</td>
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<tr>
<td><em>Erwinia toletana</em></td>
<td>.757</td>
<td>.000</td>
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<td><em>Escherichia coli</em></td>
<td>.569</td>
<td>.009</td>
</tr>
<tr>
<td><em>Pantoea agglomerans</em></td>
<td>.697</td>
<td>.001</td>
</tr>
<tr>
<td><em>Profftia tarda</em></td>
<td>.575</td>
<td>.008</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>.651</td>
<td>.002</td>
</tr>
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</table>

- 13 Different bacterial species significantly correlated with *C. tropicalis*
- *S. marcescens* and *E. coli* were significantly increased in CD patients
- Since microbes in the gut exist in biofilms, we hypothesized that CT, EC and SM cooperate in CD to influence host immune response
Biofilm Thickness

Side-view

i. CT+EC+SM; ii. CT+SM; iii. CT+EC
iv. CT; v. SM alone; vi. EC alone

Organism

CT - C. tropicalis, EC - E. coli, SM - S. marcescens
CT + EC + SM
(A) CT + EC

(B) CT + SM

(C) CT + EC + SM

(D) CT + EC + SM
Cooperative Evolution of Fungi and Bacteria: A Strategy that is beneficial to both

- Microbial communities, in their yearning to survive within the host, developed cooperative evolutionary strategies that culminate in the creation of robust biofilms
- **Fungi:** Gaining virulence factors (filamentation, increased SAP secretion) thereby enhancing their ability to invade the host.
- **Bacteria:** Develop antibacterial tolerance afforded by living under the protective Fungal matrix umbrella.
- Microbe-induced production of mucolytic enzymes (lead to barrier dysfunction, Resulting in tissue damage and lesion formation).
  - *Ruminococcus gnavus and C. albicans:* produce mucolytic enzymes that can Degrade the protective mucin layer of the gut epithelium, contributing to lesion formation

- **The Host:** this interkingdom cooperation impacts the host immune system:
  - Under the influence of enteric pathogens and immunomodulatory components of fungal biofilms, levels of proinflammatory cytokines increase, causing oxidative damage and apoptotic cell death.
Interkingdom cooperation between fungi and bacteria. Chronic wounds are complex systems of multispecies fungal and bacterial biofilms. These biofilms provide a protected milieu for microbes living in close proximity. Fungal cells form the biofilm core while bacteria associate around the periphery of the cells. The fungal hyphae and microbial-secreted enzymes/metabolites facilitate invasion of the skin epidermis/dermis leading to host tissue damage and inflammatory response manifested by an increase in proinflammatory cytokine production (panel A). Panel B shows disruption of the biofilm matrix by zymolase thereby unmasking the microbes. Consequently, treatment with antifungal agents (e.g., echinocandins) and antibiotics leads to microbial cell death (gray/black color) and a decrease in the production of proinflammatory cytokines. IFN-γ, gamma interferon; TNF-α, tumor necrosis factor alpha; IL-6, -17, and -23, interleukins 6, 17, and 23, respectively.
Cooperative Evolutionary Strategy between the Bacteriome and Mycobiome

Ghannoum, M.
Collaborators

- Center for Medical Mycology (Case, UH): Center for Medical Mycology:
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