Microbiome, Inflammation and Cancer

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- Board Member/Founder: IBD Horizons®

IBD_Afzali
Objectives

- Introduction to our microbiome
- Impact of diet and inflammation to the microbiome
- Effect of inflammation on cancer
- Review of inflammatory bowel disease and cancer

We are More Bacteria than Human

- Healthy adult harbors ~100 trillion bacteria in gut alone
- This is 10X the number of human cells we possess
- Humans possess 23,000 genes
- Microbiome contributes ~3,300,000
- Communal gut microbial genome (microbiome) is ~150 times larger than human genome
Microbiome, A Human Organ

- Reasonable to view microbiome as an organ
- Weighs ~1kg although is without distinct structure
- Organized system of cells more akin to immune system than liver
- Dominated by 4 large groups of bacteria or phyla:
  - Actinobacteria
  - Bacteroidetes
  - Firmicutes
  - Proteobacteria

Development of Microbiota

Development of the Microbiota

Single Layer of Intestinal Epithelial Cells Separates Trillions of Bacteria from Lamina Propria
Coevolution of Host and Microbiome

- Evolutionary aligned interests and interplay – neither wishes to harm
- Commensal bacteria provide benefits to host

Expansion of Host Metabolic Capacity by Microbiome

- Bacteria express glycoside hydrolase – converts glycans to useable sugars
  - No enzyme encoded in human genome is capable of digesting glycans, only bacterial enzymes!
- Many carbohydrates are digestible only by bacteria -> SCFA
  - Primary fuel for colonocytes
  - 10-15% of adult energy may be generated by SCFA production, stored as fat
Importance of Host-Microbiome Alignment

- Microbiome may cause disease directly or indirectly, when this delicate balance is disturbed
- Many diseases may result from this dysregulation:
  - Diabetes
  - Obesity
  - Metabolic syndrome
  - Stress/anxiety
  - Cardiovascular disease
  - Rheumatologic diseases
  - Inflammatory bowel disease (IBD)
  - Cancer
Diet, Microbiome and Inflammation are Connected

- Microbiome = complex microbial community that inhabits GI tract, respiratory tract, skin
- Altered microbiota = Dysbiosis
- May be factor in perpetuation of inflammatory diseases

Link Between Diet, TMAO and Microbiome, and CV Risk

- Omnivores produce more TMAO than vegans/vegetarians following ingestion of red meat-derived L-carnitine through microbiota-dependent mechanism
- *Prevotella*-rich microflora had higher plasma levels of TMAO -> greater risk of CV disease

Koeth RA et al. Nat Med 2013
Rheumatic Diseases and Distinct Microbiomes

- Disease States
  - PA, AS, RA
  - Distinct microbiome
  - Different cytokine profile


Role of Microbiome in IBD

- Gut microbiome - implicated in regulating intestinal adaptive immune responses
- Diet plays important role in intestinal immune function:
  - Bacterial metabolites from fiber expand T reg cells in gut, may prevent
  - High fats/sugar promote overgrowth of “inflammatory” bacterial species

Smith PM et al. Science 2013
**Differences in Microbiome associated with IBD**

- Types of bacteria associated with UC/CD different than non-IBD
- Production of pro-inflammatory cytokines
- Distinct in UC vs CD

Forbes JD et al. Inflamm Bowel Dis 2016

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**Inflammation is Critical Component of Tumor Progression**

- Cancers can arise from sites of chronic irritation, inflammation
- Vital component of tumor microenvironment are inflammatory cells
- Inflammation promotes neoplastic processes involved in proliferation, survival, migration
- Tumor cells have co-opted inflammatory signaling molecules and receptors

*Tumors act as wounds that fail to heal*
Microbial Influence in Inflammation and Cancer

Inflammatory bowel disease (IBD) and colorectal cancer

- Gastric intestinal metaplasia
- Barrett's esophagus
- Chronic hepatitis
- Chronic pancreatitis
- Oral leukoplasia
- Atypical adenomatous hyperplasia
- Ductal carcinoma in situ
- Prostatic intraepithelial neoplasia
- Bladder dysplasia
- Cervical dysplasia
- Actinic keratoses

Cancers associated with Inflammatory States

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Gastric intestinal metaplasia</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>Barrett's esophagus</td>
<td>Esophageal cancer</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>Oral leukoplasia</td>
<td>Head/neck cancer</td>
</tr>
<tr>
<td>Atypical adenomatous hyperplasia</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Prostatic intraepithelial neoplasia</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Bladder dysplasia</td>
<td>Bladder cancer</td>
</tr>
<tr>
<td>Cervical dysplasia</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>Actinic keratoses</td>
<td>Skin cancer</td>
</tr>
</tbody>
</table>
Chronic Inflammation Promotes Cancer

- Insulted stromal cells recruit activated inflammatory cells
- Microbial (dysbiosis) triggers inflammatory cells - express factors that stimulate cell growth and progression
- Chronic activation promotes continued inflammation, angiogenesis, and ECM remodeling
- Activated monocyte/macrophages

Mutation → Promotion → Malignant conversion

Epithelial cells → Initiated epithelium → Benign → Carcinoma

Inflammatory Bowel Disease and Colorectal Cancer

Modified from Dan Dixon, Univ South Carolina
21st Century: IBD is a Global Disease

Incidence Crohn's Disease, 1990-2016

Incidence Ulcerative Colitis, 1990-2016
Chronic Inflammation is a Risk Factor for Cancer

- Patients with UC have a 5 to 7-fold greater risk of getting colon cancer
- UC persisting for 35-40 years increases the risk 20-35%
- Colon cancer associated with IBD has the worst prognosis
- Management with anti-inflammatory agents reduce incidence of cancer
Increased Colorectal Cancer Risk in IBD

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>Crohn's colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Ekbom – Sweden¹,²</td>
<td>5.7 (4.6-7.0)</td>
<td>5.6</td>
</tr>
<tr>
<td>Soderlund – Sweden³</td>
<td>2.7 (2.3-3.2)</td>
<td>2.1 (1.2-3.4)</td>
</tr>
<tr>
<td>Bernstein – Canada ⁴</td>
<td>2.75 (1.9-4.0)</td>
<td>2.64 (1.7-4.1) [All CD]</td>
</tr>
</tbody>
</table>

Large Population-based studies >1000 pts

Overall, 2-3x risk for CRC

Disease Duration:
Risk for CRC in Colitis Increases Over Time

Overall prevalence of CRC in any UC patient is 3.7%
Disease Distribution:
Anatomical Extent of Inflammation Increases Risk for CRC

<table>
<thead>
<tr>
<th>UC</th>
<th>Ekbom (1)</th>
<th>Soderlund (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proctitis</td>
<td>1.7 (0.8-3.2) NS</td>
<td>1.7 (1.2-2.4)</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>2.8 (1.6-4.4)</td>
<td>-</td>
</tr>
<tr>
<td>Pan-colitis</td>
<td>14.8 (11.4-18.9)</td>
<td>5.6 (4.0-4.7)</td>
</tr>
</tbody>
</table>

Meta-Analysis:
• Extensive Colitis – SIR 6.4 (2.4-17.5) (3)
• Extensive Colitis – SIR 4.8 (3.9-5.9) (4)

1. Ekbom NEJM 1990
2. Soderlund GE 2009
3. Lutgens IBD 2013
4. Jess CGH 2012

Family History:
Increases Risk of CRC in IBD Patients

- Large population-based cohort study
- 19,876 UC or CD patients

Results:
- First degree relative with CRC: RR 2.5 (1.4-4.4)
- First degree relative with CRC: <50 yrs: RR 9.2 (3.7-23)

Askling, Gastroenterology 2001
Concomitant Inflammatory Diseases:
Primary Sclerosing Cholangitis Increases Risk for CRC
- 5% of extensive UC patients
- 5% neoplasia risk (p <0.001)

<table>
<thead>
<tr>
<th>Colitis Duration</th>
<th>PSC</th>
<th>No PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>10y</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>20y</td>
<td>31%</td>
<td>5%</td>
</tr>
<tr>
<td>25y</td>
<td>50%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Meta-analyses:
- Neoplasia OR 4.79 (3.58-6.41)
- CRC RR 9.13 (4.52-18.5)

Broome, Hepatology 1995
Soetikno, GIE 2002
Jess, GE 2012

Severity of Inflammation:
More mucosal inflammation increases risk for CRC
- An independent risk factor
- Case-control study (1)
  - Significant effect of histological inflammation score (p<0.001)
  - OR neoplasia 4.69 (95% CI 2.10-10.48; p<0.001) for each score unit increase
- Cohort study (2)
  - Histological inflammation
  - HR neoplasia 3.0 (95% CI 1.4-6.3)
- Macroscopically normal colonoscopy – no inflammation (3)
  - CRC risk over 5 yr period no higher than general population (age & sex matched)

1. Rutter, Gastro 2004
2. Gupta, Gastro 2007
3. Rutter, Gut 2004
Additional Factors: Increased Risk for CRC in IBD

- **Post-inflammatory polyps** = pseudopolyps
  - OR 2.3-2.5 for neoplasia
  - Suggests chronicity of inflammation
- **Young age** at diagnosis of IBD
  - Meta-analysis of pop-based studies:
    - Young age in UC – SIR 8.6 (3.8-19.5)
    - IBD Diagnosis < 30y – SIR 7.2 (2.9-17.8)
  - **Absolute** risk of CRC at young age remains low
  - Probably not independent risk factor, but **composite** risk of:
    - Disease duration ahead; extensive; more severe inflammation
- **Men** with UC had greater risk of CRC SIR 2.6 (2.2-3.0)
  - Women SIR 1.9 (1.5-2.3)

Rutter, Gut 2004
Velayos, Gastro 2006
Jess, CGH 2012
Lutgens, IBD 2013

The Power of the Microbiome

“All diseases begin in the gut.” - Hippocrates
Questions

Free CME/CNE Registration: www.IBDHorizons.org

Save the Date
1st Annual Midwest IBD Meeting

Columbus, OH
8:00 am - 3:30 pm
March 24, 2018

Chair of Symposium: Anita Afzali
Scott D. Lee, Thomas Ullman
Chassan Wahbeh, Feza Remzi
Adam Cheifetz, Brian Feagan

www.IBDHorizons.org