The Microbiome in Cancer Immunotherapy

Sandip Patel, MD
Assistant Professor
UCSD Center for Microbiome Innovation
Co-Leader, Experimental Therapeutics (Phase 1)
Deputy Director, San Diego Center for Precision Immunotherapy
Assistant Director, Clinical Trials Office
Experimental Therapeutics, Thoracic Oncology, Cancer Immunotherapy Programs, Center for Personalized Cancer Therapy

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Common Types of Immunotherapy

- **Vaccines**
  - Peptide/Protein/Tumor cell lysates
  - Viral
  - Dendritic Cell
  - Oncolytics
- **Small molecule agonists and inhibitors**
  - IDO
  - TGF-beta
- **Cytokines**
  - IL-2
- **Immune checkpoint blockade**
  - CTLA-4
  - PD-1, PD-L1
- **Cellular therapy**
  - CARs, TCRs

Immune System Function and Immune Response

Basic Concepts in Tumor Immunology: Immunoediting


Immunologic Synapses Within Tumor Microenvironment

Clinical Biomarkers
CheckMate 057: OS in NSCLC-nonsquamous

Nivolumab (n = 292)
Docetaxel (n = 290)
mOS, mo 12.2 9.4
HR = 0.73 (96% CI: 0.59, 0.89); P = .0015

1-yr OS rate = 51%
1-yr OS rate = 39%

Nivolumab
Docetaxel

At Risk, n
Nivolumab 292 232 194 169 146 123 62 32 9 0
Docetaxel 290 244 194 150 111 88 34 10 5 0


PD-L1 IHC

H&E
PD-L1(SP142)
PD-L1(SP263)

Tumor cell

Immune cell

Figure 1: Staining with PD-L1 monoclonal antibodies in tumor and immune cells. Histology of urothelial carcinoma (upper panels) and metastatic lung adenocarcinoma (lower panels). Tissues were stained with hematoxylin-eosin and PD-L1 monoclonal antibodies (SP142 and SP263, respectively).

Nakasaki, Jacobs, Fadare, Patel, Hansel (pending)
Biomarker Enrichment - OS in NSCLC with Pembrolizumab

- PD-L1 expression on tumor membrane
- 50% cutoff point

Garon et al. NEJM 2015

PFS by TMB Subgroup & PD-L1 Expression

CheckMate-026 TMB Analysis: Nivolumab in First-line NSCLC

The Intersection of the Gut and the Immune System

Immune Checkpoint Inhibitor Colitis

- Ipilimumab-induced ileocolitis with deep ulcerations in the colon

**Microbiota in Inflammatory Bowel Disease**

Major differences in microbiome profile between HC (healthy control) and:
- Ulcerative colitis (UC)
- Collagenous colitis (CC)
- Colonic Crohn’s Dz (CCD)
- Ileal Crohn’s Dz-not resected (ICD-nr)
- Ileal Crohn’s Dz-resected (ICD-r)

Halfvarson, Knight, Jansson. Nat Micro 2017

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**Microbiome Modulates Response to Immunotherapy**

- Where a mouse was ordered seemed to determine response to anti-PD-L1 (JAX vs TAC).
- This difference was driven by gut microbiota.
- The commensal microbial composition can influence spontaneous antitumor immunity, as well as a response to immunotherapy with αPD-L1 mAb.
  - Combination treatment with both JAX fecal transfer and αPD-L1 mAb improved tumor control (Fig. D)
  - αPD-L1 alone was significantly more efficacious in JAX mice compared with TAC mice (Fig. G).

Which bacterial species?

- Bifidobacterium (BIF) seemed to be the sensitizing bacterial strain
- Transfer of BIF into deficient mice led to improved anti-tumor responses with anti-PD-L1

Melanoma patients with more gut microbiome diversity response better to anti-PD-1


V. Gopalakrishnan et al. Science 2017;science.aan4236
Different Bacteria Portend Response or Resistance to Anti-PD-1 in Melanoma

V. Gopalakrishnan et al. Science 2017;science.aan4236

Gut bacteria influence response to anti-PD-1

Bertrand Routy et al. Science 2017;science.aan3706
Fusobacterium nucleatum RNA present in colon primary tumors and metastasis

Fusobacterium persist in patient-derived xenografts
Treatment of Fusobacterium colonized PDX with metronidazole reduces tumor growth in mice

Susan Bullman et al. Science 2017;science.aal5240

What about other immune checkpoints? Anti-CTLA-4

In mice, anti-CTLA-4 seems to work best with Bacteroides fragilis.

T cell (CD4) responses to B. fragilis specifically were associated with reductions in tumor size.

Vétizou et al. Science 2015;350:1079-1084
What about bone marrow transplant?

- After auto-SCT there was an increase of Proteobacteria and a reduction of Bacteroidetes
- After allo-SCT there was an increase of Bacteroidetes and a reduction of Firmicutes
- Patients who developed graft versus host disease (GvHD) harbored more Firmicutes and Proteobacteria and less Bacteroidetes

Chiusolo et al. Blood 2015;126:1953
How Different Bacterial–induced Mechanisms can Lead to Cancer

https://doi.org/10.1371/journal.ppat.1006480
http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006480

Bacteria can stimulate inflammation, and vice versa

Schwabe Science 2012
Specific bacterial mechanisms of oncogenesis

<table>
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<tr>
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<th>Bacterial mechanism</th>
<th>Hallmark affected</th>
<th>Mouse models</th>
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<td><em>Escherichia coli</em></td>
<td>colicin</td>
<td>genome instability and mutations</td>
<td>in vivo collagen assays</td>
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<td><em>Toll-like 2</em></td>
<td>unknown mechanism</td>
<td>tumor-promoting inflammation</td>
<td>AOM/DSS xenograft model</td>
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<tr>
<td><em>Bacteroides thetaiotaomicron</em> and <em>Bacteroides fragilis</em></td>
<td>unknown mechanism</td>
<td>induces avoiding immune destruction</td>
<td>MCA266 sarcoma, Ret melanoma, and MC38 CRC xenograft</td>
<td>[16]</td>
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Microbiome and Metabolome are Connected

[Link to the study by Winter SE, Lopez CA, & Baumler AJ (2013) Microbiome and Metabolome are Connected, EMBO reports, Vol 14, p. 319-327 (2013)]


http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006480
Metabolic receptors (aryl hydrocarbon) promote Tregs

Antibiotics compromise the efficacy of PD-1 blockade in cancer patients?

• Antibiotic effect or patient population effect?
• Judicious use of antibiotics is important regardless

Bertrand Routy et al. Science 2017;science.aan3706
Microbiome protection from immune-related colitis

- Patients with melanoma receiving ipilimumab had less immune-related colitis if they had higher bacteroides spp
- Increase in Thiamine and Riboflavin protective from colitis
  - Levels decreased in Crohn’s

Dubin et al. Nat Comm 2017

Translational Research Directions

- Stool microbiota are important in oncogenesis
  - Whether direct modulation of bacteria (probiotics/antibiotics) OR
  - Understanding and modifying their downstream immune effects is more important is unknown

- At a population level, most patients with these microbiota signatures do not develop cancer
  - Understanding host factors key

- Bacteria modify tumor-promoting inflammation, and the tumor microenvironment modifies bacteria
  - What is the inciting event?
  - What is the most important to modify?

- Many bacterial species in these studies are on both responder and nonresponder lists – need larger, prospectively defined datasets
  - Increased clarity with shotgun sequencing in prospective cohorts
Clinical Questions

- Should we be giving probiotics to cancer patients receiving immunotherapy?
  - Not yet
    - Bifidobacterium?
    - Non-toxic bacteroides?

- Should we be giving antibiotics to cancer patients receiving immunotherapy?
  - Judiciously
    - For antibiotics resistance and for microbiome interaction with immunotherapy

- Can microbiome influence cancer development
  - Personalized probiotics as prevention
  - May be a key public health intervention going forward