Giorgio Trinchieri

Cancer

as a Disease of the Metaorganism
Humans have co-evolved with microbial partners

- We are a composite of species: bacteria, fungi, viruses, bacteriophages

- Commensal microorganisms
  - inhabit all barrier surfaces of our organism
  - outnumber the human cells by about 3-10 fold
  - their DNA (the microbiome) contains 100 times more genes than our ‘own’ human genome

- The microbiome is an integral part of our genetic landscape and plays a central role in the maintenance and control of host homeostasis
Humans are metaorganisms (symbionts) composed of host and microbial cells with their own genes (metagenome) and shared metabolic processes and products (metabolome).
The human metaorganism

Both microbial and human cells act as sensors for environmental changes communicating reciprocally via signaling pathways that, in part, utilize innate immunity mechanisms.
The human metaorganism

Both microbial and human cells act as sensors for environmental changes communicating reciprocally via signaling pathways that, in part, utilize innate immunity mechanisms.

Environmental factors

Food
Chemicals
Temperature
Radiation
Physical and psychological stress
Pathogens
Pathogens

Metabolism
Cardiovascular, Excretory, Musculoskeletal, and Adipose tissue functions
Neurological, behavioral and cognitive functions
Aging
Hematopoiesis
Circadian rhythm
Inflammation and Immunity
Cancer initiation, progression and response to therapy
Endosymbiosis of α-proteobacteria (SAR11 clade)
Pattern recognition (innate) receptors may have evolved to mediate the bidirectional cross-talk between microbial symbionts and their host.


Endosymbiosis of α-proteobacteria (SAR11 clade)

Pattern recognition receptors

Innate resistance (phagocytic, myeloid) cells

Commensal microbes

Mammalian metaorganisms

Franzenburg et al, PNAS 2012;109:19374
Cancer as a disease of the human metaorganism

TUMOR (cancer genetics)
Intrinsic (oncogene mediated) inflammation

Extrinsic inflammation
Microenvironment
Innate and adaptive immune response

PATTERN RECOGNITION RECEPTORS
(Toll-like receptors, IL-1 receptors, NOD-like receptors, chemotactic receptors, others)

INNATE/IMMUNE CELLS
(myeloid cells, antigen-presenting cells, innate lymphocytes, T and B lymphocytes)
 Colon rectal carcinoma
 Stomach cancer
 Malt lymphoma
 Hepatocellular carcinoma
 Mammary carcinoma
 Thymic lymphoma

Cancer progression and response to immunotherapy and chemotherapy

Tumors

The price of immunity
Romina S Goldszmid & Giorgio Trinchieri
nature immunology
COMMENSAL MICROBIOTA

Inflammation, immunity and cancer

- Chronic inflammation (infections, aseptic)
- Intrinsic/oncogene induced inflammation
- Genomic mutations
- Tumor promotion
- Predisposing conditions (obesity, metabolic syndrome)
- Cancer associated inflammation

Genomic mutations

Response to therapy

Co-morbidities

Primary tumor

- Anti-cancer immune response
- Immuno evasion

- Tumor growth
- Angiogenesis
- Tissue remodeling
- Infiltration and metastasis
- Immune evasion
- Co-morbidities

Response to therapy

- Mets

Anti-cancer immune response

Immuno evasion

Primary tumor

Inflammation, immunity and cancer

Commensal microbiota
Is the response to cancer therapy regulated by the commensal bacteria?

Systemic anti-IL-10R + Intratumor CpG-OGN immunotherapy
Platinum compound (oxaliplatin, cisplatin) chemotherapy

Noriho Iida, Amiran Dzutsev, C. Andrew Stewart, ........ Giorgio Trinchieri, Romina S. Goldszmid
Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment
Science, 2013; 342:967-70
Is the response to cancer therapy regulated by the commensal bacteria?

Systemic anti-IL-10R + Intratumor CpG-OGN immunotherapy
Platinum compound (oxaliplatin, cisplatin) chemotherapy

ANTIBIOTICS
Neomycin
Vancomycin
Imipenem

or Germ-free mice

Sterile subcutaneous transplanted tumor

Noriho Iida, Amiran Dzutsev, C. Andrew Stewart, ........ Giorgio Trinchieri, Romina S. Goldszmid
Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment
Science, 2013; 342:967-70
Antibiotics (ABX) suppress the anti-tumor effect of immune and chemo therapy

MC38 subcutaneous tumor

EL4 subcutaneous tumor
Antibiotics (ABX) suppress TNF-mediated early necrosis of the tumor and decrease inflammatory cytokine production following anti-IL-10R/CpG

MC38 tumor, 72 h after CpG treatment
Antibiotics (ABX) impair oxaliplatin chemotherapy by preventing ROS production from NOX2 (Cybb) expressing myeloid cells

Oxaliplatin induces ROS production in tumors of control but not ABX-treated mice

Oxaliplatin induces NOX2 (Cybb)-mediated ROS production in tumor-associated myeloid cells

EL4 tumors-bearing B6 mice were treated with 10mg/kg oxaliplatin

ROS-induced bioluminescence using the L-012 probe was analyzed 24 hours after oxaliplatin injection

ROS-production analyzed by flow cytofluorimetry in EL-4 tumor-infiltrating myeloid cells ex-vivo 24 hours after oxaliplatin injection
ROS production in oxaliplatin treated tumors is blocked by ABX and it is required for DNA damage after formation of platinum DNA adducts.
Myeloid cell

Gut microbiota

CpG-ODN + anti-IL-10R

TNF

ROS

Oxaliplatin

TBI and adoptive T cell transfer

Total body irradiation (TBI) or cyclophosphamide (CTX) induced transmucosal bacterial translocation

1. Identification of bacterial species

2. Identification of receptors, factors, cell types

3. Cellular and molecular characterization of myeloid cells

Local barrier homeostasis and immunity

Systemic “inflammatory tone” and immune response

Myeloid cells
- Migration
- Differentiation
- Activation
- Epigenetic regulation

Commensal microorganisms

Myelopoiesis
DCpoiesis
Neutrophil homeostasis

Cancer therapy

- CpG-OGN
- TNF, IL-12, ...
- Oxaliplatin
- ROS
- Cyclophosphamide
- L. Zitvogel 2013
- APC functions
- Total body irradiation
- Adoptive T cell transfer
- N. Restifo 2007
- APC functions
Composition of fecal microbiota can be used to segregate mice with high and low intratumoral TNF in response to CpG

Unweighted Unifrac
H$_2$O- drinking mice

16S rDNA analysis using 454 pyrosequencing
Identification of bacterial genera positively and negatively correlating with intratumoral TNF levels after CpG in microbiota perturbation experiments.

Alistipes (Gram-)

Lactobacillus

A. shahii

L. murinum
L. intestinalis
L. fermentum
Oral LPS restores the TNF production impaired by ABX and TLR4 is required for optimal response to i.t. CpG

25 mg/kg BW of LPS was orally administered 3 times/week, 2 weeks prior and 1 week after MCA38 injection
Oxaliplatin tumor treatment requires MyD88 but, unlike CpG, neither TLR4 nor TNF.

Oxaliplatin (10mg/kg) was i.p. injected on day 7 after EL4 s.c. tumor inoculation.
Changes in tumor-infiltrating myeloid cells in ABX treated mice

**Toxoplasma gondii** I.P. infection in ABX treated mice: changes in inflammatory myeloid cells in the infected tissue and decreased resistance to infection
Immunotherapy
Chemotherapy
Resolution of
Infection,
Inflammation
and Immunity

Infection
(acute
inflammation)

Tumor
(chronic
inflammation)

Modified from:
Goldszmid R.S., Dzutsev A., Trinchieri G.
Host immune response to infection and cancer:
unexpected commonalities
Cell Host & Microbe, 15, 295-305, 2014
Toxoplasma gondii peritoneal infection allowed a molecular characterization of inflammatory monocyte differentiation in infected tissues.

Principal component analysis of expression of 125 genes relevant for myeloid cell differentiation and function as determined by Nanostring in sorted cell subsets.


NK cell-derived interferon-γ orchestrates cellular and the differentiation of monocytes into dendritic cells at the site of infection.

Immunity. 2012;36:1047-59
Toxoplasma gondii peritoneal infection allowed a molecular characterization of inflammatory monocyte differentiation in infected tissues.

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**Diagram:****
- **Inflammation (IFN-γ)**
- **Toxoplasma**
- **Monocytes**
- **NK cells**
- **B cells**
- **T cells**
- **Mφ**

**Legend:**
- **Uncontrolled infection**: No IL-12, Impaired Th1
- **After T. gondii infection in the absence of IFN-γ**: Protection

**Text:**

NK cell-derived interferon-γ orchestrates cellular and the differentiation of monocytes into dendritic cells at the site of infection.

Immunity. 2012;36:1047-59

**Graph:**
- Principal component analysis of expression of 125 genes relevant for myeloid cell differentiation and function as determined by Nanostring in sorted cell subsets.
Cellular and molecular characterization of tumor-associated myeloid cells:

Immmgen cell populations identified by the complete NanoString geneset using Gene Set Enrichment Analysis (GSEA) analysis

The CD11c++, MHCII++DC population consists of a mixture of DC types, majority of whom have CD103-CD11b+ phenotype, however there is a visible signature of CD8α+ DCs and pDCs.

Neutrophils (Ly6G +++)
Dendritic cells (CD11c ++; MHCII ++)
Monocyte-derived (Ly6C +; F4/80 +)
Monocyte-like (Ly6C +++)

EL4 tumor (Nanostring, 500 genes)
Gene expression changes in tumor-infiltrating myeloid cells in ABX treated mice

EL-4 tumor, Nanostring, 500 gene expression (PCA analysis)
Commensal Microbiota

Pathogens & Pathobionts

Patter Recognition (Innate) Receptors

Microbial & Host Factors

Innate & Adaptive Immunity Effector Cells

TLRs
IL-1Rs
SCFA-Rs
NODs
NRLPs
AHR
FXR
.....

LPS
Formyl-Met-Leu-Phe
SCFA
DNA, RNA
......
IL-18
IL-1
IL-10
IL-23
IL-22
IL-33
TGF-β
Vitamin A
Serum Amyloid A
IFNs
.....

Macrophages
Neutrophils
Monocytes
Dendritic Cells
......
Th17
Th1
Treg
NK cells
ILC3
.....

Tissue homeostasis,
metabolism, innate and adaptive immunity

Tumor initiation,
growth progression and dissemination,
response to therapy
Medicine’s battlefield strategy: Human body as a battleground

Freely adapted from ideas expressed by Costello et al. Science 336:1255 (2012)
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Our friendly gut bacteria

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