BASIC MECHANISM OF TUMOR IMMUNE SUPPRESSION

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GOALS

• Understand that immune suppression is one of the hallmarks of all cancers.
• Be familiar with common cellular and molecular mechanisms of immune suppression.
• Recognize that the pervasive nature of cancer immune suppression creates ample opportunities for immunotherapy.
IMMUNE SYSTEM DOES CARE ABOUT CANCER
ANSWERS FROM THE HALF-CENTURY QUEST

- Tumor antigen
- Tumor-specific T cell
- Tumor-specific antibody
- Immune tolerance

I Mellman et al. Nature 480, 480-489 (2011)
NEW ONCOLOGY PARADIGM IN 2015:
TREATING THE IMMUNE SYSTEM, NOT THE CANCER

Chimeric Antigen Receptor

WHAT EVERYONE IS TALKING ABOUT

Checkpoint blockade against PD-1 pathway is broadly effective against advanced cancers:

- Melanoma
- Lung cancer
- Bladder cancer
- Renal cell carcinoma
- Head and neck cancer
- Triple negative breast cancer
- Lymphoma etc.
CAUTION AGAINST CHECKPOINT BLOCKERS

- Clinical experience remains limited
- > 50% patients do not benefit
- No effective biomarkers to separate R from NR
- Unclear of optimal clinical use
It Takes An Army
PRINCIPLES OF ANTI-TUMOR IMMUNITY

**Immunity**
- Mature dendritic cells
- Co-stimulatory molecules (CD28, ICOS, 4BB etc.)
- Effector T cells
- Effector antibodies
- IFN-γ etc.

**Tolerance**
- Immature dendritic cells
- Immune checkpoints (CTLA4, PD-1 etc.)
- Regulatory T and B cells
- Myeloid suppressor Cells (MDSCs, Mφ)
- TGF-β etc.

**Antigen presentation**

**Anti-tumor**

**Pro-tumor**
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TUMOR IMMUNE SUPPRESSION

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SUPPRESSION ≠ EVASION

Evasion
- Loss of antigens
- Loss of antigen-presentation machineries (e.g., MHC, TAP)
- Immune shield

Suppression
- Immature dendritic cells
- Immune checkpoints (CTLA4, PD-1 etc.)
- Regulatory T and B cells
- Myeloid suppressor Cells (MDSCs, Mφ)
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Suppression
- Loss of antigen-presentation machineries (e.g., MHC, TAP)
- Immune shield
IMMATURE (TOLEROGENIC) DC

Low MHC
Low antigen presentation
Low co-stimulatory molecules
High co-inhibitory molecules
High IDO (Indoleamine 2,3-dioxygenase)
TGFβ


Prostate, breast, renal, liver, lung cancer, HNSCC, myeloma, leukemia, neuroblastoma, melanoma, glioma, etc
TUMOR-DCs PROMOTE OVARIAN CANCER

4-HNE:
unsaturated aldehyde 4-hydroxy-trans-2-nonenal

IMMUNE CHECKPOINTS

Receptor + Receptor -

CD28  OX40  GITR  CD137  CD27  CTLA-4  PD-1  TIM-3  BTLA  VISTA  LAG-3

Agonistic antibodies  T cell stimulation  Blocking antibodies

Tolerance  Exhaustion  Deletion

Nature 480, 480–489 (22 December 2011)
REGULATORY T CELLS

- **1970/1980** “Suppressor” T cells proposed but discredited
- **1990s** CD4+CD25+ “Regulatory T cells” by Shimon Sakaguchi

- **Early 2000s** Discovery of Treg master transcription factor *Foxp3* (Brunkow et al. Nat Gen 2001; Bennett et al, Nat Gen 2001; Wildin et al., Nat Gen 2001; Chatila et al., JCI 2000)
REGULATORY T CELLS

2010

Selective Depletion of Foxp3+ Regulatory T Cells Improves Effective Therapeutic Vaccination against Established Melanoma

Katjana Klages1, Christian T. Mayer2, Katharina Lahi3, Christoph Loddenkemper4,5, Michele W.L. Teng6, Shin Foong Ngio6, Mark J. Smyth6, Alf Hamann7, Jochen Huehn1, and Tim Sparwasser2
REGULATORY B CELLS

December 3, 2009; Blood: 114 (24)
REGULATORY B CELLS

Breg suppression of anti-tumor response

- TGF-β
- PD-L1
- CD25
- CD86
- MHC-II

Indirect

Indirect

↑ Treg expansion

↓ Suppress T cell proliferation & function

↓ Suppress Th1 IFN-γ production

↓ Suppress CD8+ CTL activity

↓ Suppress CD8 & NK cell infiltration

↑↑ Tumor Growth

Treg

Tumor

Breg

B cell

December 3, 2009; Blood: 114 (24)
MYELOID-DERIVED SUPPRESSOR CELL (MDSC)

Nature Reviews Immunology 12, 253-268 (April 2012)
TUMOR-ASSOCIATED MACROPHAGES (TAM)
TARGETING MYELOID CELLS FOR TREATMENT OF CANCER

TARGETING MYELOID CELLS FOR TREATMENT OF CANCER

Carlos Alberto Gomez-Roca, MD
Phase I study of RG7155, a novel anti-CSF1R antibody, in patients with advanced/metastatic solid tumors. 2015 ASCO
TGF-β: A MASTER IMMUNE REGULATOR

Yang et al. (2010) Trends in Immunology
TAKE HOME MESSAGE

- Immature dendritic cells
- Immune checkpoints (CTLA4, PD-1 etc.)
- Regulatory T and B cells
- Myeloid suppressor Cells (MDSCs, Mφ)
- TGF-β etc.

Cancer immune suppression

- Validation of tumor surveillance
- Opportunity for immunotherapy