The Biology of Checkpoint Inhibition

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Disclosures

Intellectual Property related to the PD-1 / PD-1 Ligand pathway licensed non-exclusively to:

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Genentech/Roche
Merck
EMD Serono
Boehringer-Ingelheim
Amplimmune/AstraZeneca
Novartis

Consultant: Novartis, BMS, Roche, Lilly
Immunology has offered hope for curing cancer for 100 years

What is different now?

New Strategy
Blockade of pathways used by tumors to inhibit anti-tumor immunity

Checkpoint blockade
T cell activation

- There are positive and negative second signals

Signal 1: Antigen recognition

Signal 2: Co-stimulation
The PD-1 Pathway Inhibits T Cell Activation

- Dephosphorylation
- Reduced TCR signaling
- Reduced cytokine production
- Reduced target cell lysis
- Altered lymphocyte motility
- Metabolic programming

**Diagram:**
- PD-1
- PD-1 ligand
- PD-L1 (B7-H1)
- PD-L2 (B7-DC)
- ITSM
- ITIM
- SHP-2
- Proximal signaling kinases
- CD3
- TCR
- CD8
- MHC
- APC
- CTLA4
- B7-1
PD-1 = Programmed Death-1

• Cloned from a CD3-activated T cell hybridoma undergoing activation-induced cell death (Honjo lab)

• Does not directly activate caspases and cause cell death or apoptosis; not like CD95 (Fas)

• Indirect effect on cell death by reduced cytokines, survival factors
  (less Bcl-xL, more BIM)
Why have negative signals like PD-1?

1. Tune down the immune response after elimination of disease
2. Prevent too strong an immune response damaging tissues
3. Maintain immune tolerance
PD-L2 is a second ligand for PD-1 and inhibits T cell activation

Discovery may shed light on cancer’s shield against the immune system
For years, a question has tantalized cancer researchers: why is the immune system, normally so adept at unmasking and eliminating foreign invaders and abnormal cells, not always spry enough to destroy tumor cells?

A new study by Dana-Farber scientists suggests an answer. In a paper published in the March issue of Nature Immunology, investigators led by Gordon Freeman, Ph.D., of Adult Oncology report that a structure...
PD-L1 on tumors

- Expressed on cell surface of ~30% solid tumors and selected hematologic malignancies
- Inhibits anti-tumor immune responses

Brown = PD-L1  Signoretti, Rodig, Atkins, McDermott; BWH, BIDMC, & DFCI
Where does checkpoint blockade function?

CTLA-4 in the lymph node

PD-1 in the tumor
PD-1 or PD-L1 Blockade Stimulates anti-tumor immune response

CD8+ CTL

Increased cytokines

IFN-γ

antibody drug

PD-1

TCR

PD-L1

MHC

Increased killing

PD-1 is highly expressed on T cells in tumors (TIL)

PD-1 or PD-L1 Blockade can increase T and NK cell function in tumors
Why doesn’t directly stimulating the immune response cure cancer?
Once the tumor gets ahead and expresses PD-L1, Immuno-inhibition is dominant and maintained by a feedback loop.
Agents in Clinical Trials

• Anti-PD-1
  – Nivolumab (BMS)
  – Pembrolizumab (Merck)
  – Pidilizumab (Curetech)
  – MEDI-0680 (Medimmune-AZ)
  – PDR001 (Novartis)
  – REGN2810 (Regeneron)

• Anti-PD-L1
  – Atezolimumab (MPDL3280, Roche-GNE)
  – Durvalumab (MEDI-4736 Medimmune-AZ)
  – Avelumab (MSB0010718C EMD Serono)
  – MDX-1105 (BMS)

Multiple other agents in development
Why the enthusiasm for immunotherapy?

Data from Steve Hodi & ECCO

Moderate percentage but long-term

Chapman NEJM 2011

High percentage but short-term
Predictive biomarkers help get the right treatment to the right patient
## PD-L1 expression in tumor increases the likelihood of response to PD-1/PD-L1 blockade

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PD-L1 as a predictive marker in the Phase 3 study comparing nivolumab with everolimus in RCC

RJ Motzer et al., NEJM 2015; 373:1803

• Confirm previous studies that higher PD-L1 expression is associated with poorer survival in RCC

• PD-L1 expression was not associated with a PD-1 treatment benefit in RCC
A new era in PD-L1 immunohistochemistry

Now at least 5 good PD-L1 IHC mAbs available

extracellular

5H1   Chen
22C3 Merck - Dako/Quest
28-8  BMS - Dako/Quest

intracellular

SP142 Roche - Spring
E1L3N CST
9A11  Freeman - CST
21% Discordancy between PD-L1 on Primary and Metastasis in ccRCC

- PD-L1 positivity was heterogeneous and almost exclusively detected in high nuclear grade areas ($P < 0.001$).
- Assessment as a predictive biomarker for PD-1 blockade may require analysis of metastatic lesions.
- Pathologists should select high grade tumor areas for PD-L1 IHC analysis to avoid false negatives.

20 positive
33 negative in primary & met
53 cases
PD-L1 on non-clear cell RCC

- 11% PD-L1+ (11 of 101)
  - 6% of chromophobe RCC (2 of 36)
  - 10% of papillary RCC (5 of 50)
  - 30% of Xp11.2 translocation RCC (3 of 10)
  - 20% of collecting duct carcinomas (1 of 5)

- PD-L1+ associated with higher stage \((p=0.01)\) and grade \((p=0.03)\), shorter OS \((p<0.001)\).

What does the immune system see in a tumor to attack?
The immune system can recognize protein coding changes in the tumor cell, called tumor antigens or neoantigens.

**Tumors have 10-200 neoantigens that T cells can attack**

Normal cell  

Tumor cell  

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Fourteenth International Kidney Cancer Symposium  
Miami, Florida, USA—November 6-7, 2015

KidneyCancer.org

www.kidneycancersymposium.com
Mutation frequencies in protein coding regions from 3,083 tumor–normal pairs
Clinical benefit with PD-1 blockade.

- **18% in TN BCa** and her2+ mBC
- **11-20% ORR**
- **18% ORR**
- **24-26% ORR**
- **19-23%**
- **29-40% ORR**

Lawrence, et al. Nature 2013
Groups that respond well to PD-1/PD-L1 therapy

• Highly mutated tumors (MSI, defects in DNA repair)
• Genetically amplified PD-L1 and PD-L2 (Hodgkin)
• With Viral antigens (HPV, Merkel)
• What other groups?
Why do the T cells need PD-1 blockade to attack the tumor?

Anti-tumor immune response is a years long struggle.

T cells have tried, failed, and become dysfunctional or “exhausted”
PD-1 pathway mediates T cell exhaustion in Chronic Viral Infections

Dan Barber
John Wherry
Rafi Ahmed
PD-1 and T cell exhaustion

PD-1 is upregulated in both acute and chronic immune responses but stays high in chronic.

- PD-1\textsuperscript{Hi} cells are “exhausted” and less functional
- PD-1 blockade can revive exhausted T cells
Tumor-Infiltrating T cells (TIL) behave like exhausted T cells
Human Ovarian Tumor Infiltrating T cells (TIL) express high levels of PD-1

% PD-1+

Jaikumar Duraiswamy
George Coukos
T cell exhaustion is more than PD-1
Exhausted Tumor infiltrating lymphocytes express multiple immunoinhibitory receptors:

These are druggable targets for tumor immunotherapy
Co-expression of PD-1 and TIM-3 immune checkpoint molecules in tumor infiltrating CD8 T-cells in ccRCC

Signoretti S and Pignon JC
The Future is Combination Therapy

• PD blockade + other immunoinhibitor blockade:
  *CTLA-4, TIM-3, LAG3, TIGIT, CD244, CD160*

• PD blockade + immunostimulators:
  *anti-OX40, anti-CD137, IL-2, TLR ligands*

• PD blockade + kinase inhibitors:
  *Braf inhibitor, etc*

• PD blockade + others:
  *Angiogenesis blockade, radiation, HDAC inhibitors*

• PD blockade + cancer vaccine, oncolytic virus, or CAR-T
It’s an exciting time to be an oncologist or researcher

- PD-1 works on RCC and a wide range of tumors with
  - moderate percentage of responders
  - good safety profile

- With this success, human creativity has been unleashed and we’re learning to do better
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