Cancer Immunoeediting: From Immunosurveillance to Personalized Cancer Immunotherapy

Milestones in Cancer Immunotherapy
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Disclosure Information

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*I will not be discussing off-label- or investigational-use of any drug in my presentation*
The Beginnings

Paul Ehrlich (1909): First to formally propose a host protective role of immunity against cancer.

Predicted that cancer would occur at “incredible frequency” if host defenses did not prevent the outgrowth of continuously arising cancer cells.
Proposed the term “Cancer Immunosurveillance” to describe natural immune resistance against cancer. Predicted that T lymphocytes were the major effector cells in this process.
Jumping On the Cancer Immunosurveillance Bandwagon (c. 1965)
The Premature Demise of the Cancer Immunosurveillance Hypothesis (c.1973)

Osias Stutman used these observations to argue against Cancer Immunosurveillance:

- **Nude CBA/H mice did not show higher rates of spontaneous tumors compared to wild type mice.**

- **Nude CBA/H mice did not develop more chemically-induced tumors compared to wild type mice nor did they show shortened latency periods for tumor generation.**
Jumping Off the Cancer Immunosurveillance Bandwagon (c. 1973)
Cancer Immunosurveillance: “Twenty” Years of Solitude
Lloyd J. Old
Why Reinvestigate the Cancer Imunosurveillance Hypothesis?

- Demonstration that IFN-γ plays a critical role in preventing outgrowth of certain tumor types
- Realization that Nude CBA/H mice used by Stutman were not ideal models of immunodeficiency
- Generation of better mouse models of immunodeficiency
- Generation of mAbs capable of blocking innate or adaptive immunity in WT mice
- Defining the chemical nature of tumor specific antigens
Experimental Support for Cancer Immunosurveillance

Shankaran et al. Nature 2001
Evidence That Editing of Tumor Cell Immunogenicity Promotes Tumor Outgrowth

129/SvEv Tumors  RAG2⁻/- Tumors

Tumors from RAG2⁻/- mice are “unedited” (display high immunogenicity) and thus are good models of nascent tumors.

Tumors from WT mice are “edited” (display reduced immunogenicity) and thus are models of clinically apparent, mature tumors.

Shankaran et al, Nature 2001
The 3 Es of Cancer Immunoediting

Transformed cells

Elimination

Normal tissue

Intrinsic tumor suppression (senescence, repair, and/or apoptosis)

Carcinogens
Radiation
Viral infections
Chronic inflammation
Inherited genetic mutations

Equilibrium

Tumor dormancy and editing

Extrinsic tumor suppression

Escape

Tumor growth promotion

Cancer Immunoediting

Schreiber, Old and Smyth, Science 2011
What are the targets of cancer immunoediting and by what mechanism does editing occur?
Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting

Nature 482:400-404 (2012)

- Used exome and transcriptome sequencing and epitope prediction to show that a R913L point mutation in Spectrin-β2 formed a highly antigenic tumor specific mutant antigen (TSMA) responsible for spontaneous rejection of the d42m1 unedited MCA sarcoma.

- d42m1 tumor cell variants that escape in vivo elimination lack mutant Spectrin-β2 expression.

- Cancer immunoediting occurs via T cell mediated immunoselection.
Moving from Natural Resistance to Cancer to Therapeutically Induced Cancer Control

Can edited tumors be controlled by checkpoint blockade immunotherapy?

If so what are the antigenic targets of T cells that are reinvigorated by this therapy?

Can we improve upon checkpoint blockade therapy?
Edited tumors are susceptible to cancer immunotherapy

Whole exome sequencing/RNA-Seq + epitope prediction can identify tumor specific mutant antigens (TSMA) in edited tumors

TSMA are favored targets for T cells activated by checkpoint blockade

Personalized cancer vaccines targeting TSMA are specific and safe and can be as effective as checkpoint blockade therapy
Edited T3 MCA Sarcoma Cells Are Rejected in Mice Following Checkpoint Blockade Immunotherapy

Gubin et al. Nature 2014
Current Method for Predicting and Validating Mutational Class I Epitopes

Epitope Prediction:
Use multiple (3) algorithms, median binding affinity to MHC I

Apply Filters
- Processing
- Neo-epitopes
- Hypothetical proteins

Synthesize Peptides

Gubin et al. Nature 2014
Rapid Identification and Validation of Dominant Tumor Specific Mutant Antigens in T3 MCA Sarcomas

Filtered Epitopes

Affinity value

Tetramer Staining CD8+ TIL

Functional Analysis CD8+ TIL

Mutant H-2Kb epitopes

mAlg8(A506T) ITYTWTRL

mLama4(G1254V) VGFNFRTL

mAlg8(A506T) mLama4(G1254V)

% IFNγ/TNFα

Mutant H-2Kb epitopes

mAlg8(A506T) mLama4(G1254V)
Comparable Efficacies Between Checkpoint Blockade and Personalized Cancer Vaccines

Tumor-Specific Antigen Vaccine

- mLama4 +mAlg8
- Poly I:C
- HPV control

Checkpoint Blockade Therapy

- αPD-1+ αCTLA-4
- αPD-1
- αCTLA-4

Percent mouse survival

Days post-transplant

SLP Vaccine on d+3, +9, +15, +21

Checkpoint mAbs on d+3, +6, +9

Gubin et al. Nature 2014
Tumor Specific Mutant Neoantigen Vaccine Extends the Anti-PD-1 Therapeutic Window for T3

αPD-1 Tx

mLama4/mAlg8 TSMA Vaccine

Days post-transplant

Days of Tx start

% Response

Mean diameter (mm)

% Response

Combo Therapy Started on d6

Cntrl vac+IgG

TSMA vac+IgG

Cntrl vac+αPD1

TSMA vac+αPD1

Tumor Specific Mutant Neoantigen Vaccine Extends the Anti-PD-1 Therapeutic Window for T3
Eight Week Time Frame from Biopsy to Personalized Cancer Vaccine

1. **Exome sequence + RNA-Seq tumor vs normal**
   - 2 weeks

2. **Data analysis**
   - Select candidate epitopes
   - 2 days

3. **Short peptide synthesis**
   - 2 weeks

4. **Tetramer Generation**
   - 2 days

5. **Long peptide vaccine synthesis**
   - 3 weeks

6. **Analyze PBL for neoantigen specific T cells**
   - 4 days

7. **Initiate vaccine treatment**
The immune system protects against cancer development and shapes cancer immunogenicity via Cancer Immunoediting.

Highly antigenic, tumor specific antigens are favored targets of cancer immunoediting (some are mutant neoantigens).

After cancer immunoediting, cancers display reduced (but not absent) immunogenicities but often can be controlled by immunotherapy.

Mutant neoantigens remaining in tumors after editing are favored targets of T cells reinvigorated by checkpoint blockade therapy.

Personalized cancer immunotherapies (vaccines/ACT) targeting tumor specific mutant neoantigens are now possible and are currently being explored in the clinic.
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