Radiation and Immunotherapy: How to Ignite Long Term Anti-Cancer Response

Cancer and the Immune System: The Basics

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Current Strategies to Combat Cancers

Mechanics - surgery, 1600BC

Physics - radiotherapy, 1890s

Chemistry - chemotherapy, 1940s

Biology – antibodies, cytokines, 1980s

Immunotherapy!
Immunotherapy (& Immunology) at the Center Stage of Cancer Therapy

• FDA approvals: Provenge, CTLA4 blockade, PD1/PDL1 blockers

• Big Pharma & Biotech Enter Cell-based Immunotherapies (DC, CAR-T, TIL...)

• 2013 Science Breakthrough of the Year; Time Magazine Cover Story- April 4th, 2016

• 2011 Nobel Prize: Ralph Steinman (Dendritic cell function)

• 2015 Lasker Award- James Allison
The challenge: Only a subset of patients respond, in certain cancers. Also, the toxicity is significant in many patients.

Some basic tumor immunology leading to the current immunotherapies;

Immune contexture- a new diagnostic tool?

Role for radiation?

New role for medical physicists?
Timeline of the Development of Immunotherapy

1891
First cancer "vaccine" demonstrated (Coley bacterial toxin)

1909
Cancer occurs spontaneously; immune system recognizes and protects (Elrich)

1960s
Adjuvants (eg, BCG) shown to eradicate some tumors

1960
BCG approved for bladder cancer

Late 1950s
Immunosurveillance theory introduced (Thomas, Burnet)

1970
1986
IFNα approved as cancer immunotherapy

1980
1992
IL-2 approved as cancer immunotherapy

1990
Adoptive immunotherapy for patients with cancer

2000

2010
Ipilimumab approved for metastatic melanoma

BCG = Bacille Calmette-Guérin
IFN = interferon
IL = interleukin
TIL = tumor-infiltrating lymphocyte

Coley WB. Ann Surg 1891;14:199–220
Nature Milestones Cancer 2006; S7-S23.
Mouse with chemical carcinogen-induced tumor

Resect tumor

Isolate CD8+ T cells

Transplant tumor cells into original tumor-bearing mouse

No tumor growth

Transplant tumor cells into syngeneic mouse

Tumor growth

Adaptively transfer T cells into recipient of tumor transplant

Eradication of tumor
Early recognition that the immune status in the host influences anti-tumor cell efficacy of ionizing radiation

"Cryptosporidium parvum" is a protozoan.

Fig. 1 from Helen Stone et al, J Natl Cancer Inst 1979
The immune status of mice is a critical determinant of their susceptibility to tumors induced by chemical carcinogens.

R D Schreiber et al. Science 2011;331:1565-1570
The power of adaptive immunity in the response to chemotherapy

CT26 tumor

Intratumoral chemotherapy

Obeid et al, Nature Medicine, 2007
And, specifically a role for CD8$^+$ T lymphocytes

Obeid et al, Nature Medicine, 2007
T cells control latent tumors

Tumor antigens:

**Tumor-specific: TSA**

Oncogenic mutants of normal cellular genes: ras, bcr-abl, p53
Randomly mutated genes: TSTA’s (tumor-specific transplantation antigens)

Can be identified: biochemical
  cDNA cloning

**Tumor-associated: TAA**

Normal cellular proteins aberrantly expressed

Tyrosinase - melanomas (enzyme melanin biosynthesis)
Cancer/testis antigens: expressed testis and trophoblasts
Oncofetal antigens: developing fetal tissue
  CEA: carcinoembryonic antigen - colo and many cancers,
  AFP: α-fetoptotein - hepatocellular cancer and others
  not specific, can be induced inflammatory conditions

Altered glycolipid and glycoprotein antigens:
  gangliosides - in melanomas
  Mucin-1 - O-linked carbohydrates

Tissue-specific differentiation antigens
Antigen Presenting Cells Initiate a Cascade of Specific T Cell Activities

Restifo et al., Nat. Reviews in Immunology, 2012
Adaptive Tumor Immunity:

1. T cell recognition of tumor Ags
2. High frequency of tumor-specific T cells
3. T cell trafficking to lymph nodes & tumors
Advantages of T Cell-Based Cancer Immunotherapy

1. Exquisite specificity for target; limit collateral damage.
2. Target non-resectable tumors.
3. T cells can target tumors at sites throughout the body.
4. Long-lasting protection.
The Cancer-Immunity Cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Chen and Mellman Immunity 39; 2013
Immunological Surveillance
Ehrlich, Burnet & Thomas

Paul Ehrlich (1909) First to conceive of the concept of Cancer Immunosurveillance. Predicted that cancer would occur at “incredible frequency” if host defenses did not prevent the outgrowth of continuously arising cancer cells.

Lewis Thomas (1957) “primary function of cellular immunity....is to protect from neoplastic disease”

Macfarland Burnet (1957) “It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provide an effective immunological reaction with regression of this tumor and no clinical hint of its existence”
Tumor Elimination - Equilibrium - Escape

Transformed cells (Tumor antigens) can be eliminated or reach an equilibrium or escape stage. Elimination is facilitated by Elimination (Cancer Immunosurveillance) mechanisms such as CD8+ T cells, NK cells, perforin, and TRAIL. In equilibrium, genetic instability and immune selection can lead to escape. Factors like p53, Rb, Ras, carcinogens, radiation, chronic inflammation, and inherited viruses can influence transformation.
Mechanisms of Tumor Escape from Immune Responses

- Loss of MHC or TAP
- Loss of co-stimulatory molecules
- Antigenic variation
- Secretion of immunosuppressive factors
  - e.g. TGF-b, IL-10
- T cells don’t penetrate solid tumors
- Exhaustion of T cells
- T regulatory cells suppress anti-tumor responses
HIFU, RFA, Hyperthermia?

Chen and Mellman Immunity 39; 2013
Adoptive T cell Therapies Help to Overcome Some Barriers to Effective T Cell Control of Tumors.
CAR T cell transfer immunotherapy

1st, 2nd, and 3rd generation CARs

Cytotoxicity

Proliferation / Cytokine Production

Survival

Casucci et al, J Cancer, 2011
Park, Disc Med, 2010
PD-L1/PD-1 binding inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
Survival with nivolumab significantly better survival vs. docetaxel in patients with previously treated squamous-cell NSCLC

P < 0.001

Brahmer et al, NEJM 2015
Different immune cell infiltrates are associated with good or poor prognosis

Tumor-infiltrating lymphocytes - Correlation with survival in ovarian cancer patients

Zhang et al. NEJM 348:203, 2003
<table>
<thead>
<tr>
<th>Immune contexture</th>
<th>Parameters: positive association with survival</th>
</tr>
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<tbody>
<tr>
<td>Type</td>
<td>CTLs (CD3+CD8+)</td>
</tr>
<tr>
<td></td>
<td>Memory T cells (CD45RO+)</td>
</tr>
<tr>
<td>Location</td>
<td>Core of the tumour</td>
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<tr>
<td></td>
<td>Invasive margin</td>
</tr>
<tr>
<td>Density</td>
<td>Number of cells per mm²</td>
</tr>
<tr>
<td></td>
<td>1 10 100 1,000 10,000</td>
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<tr>
<td>CD3⁺CT</td>
<td></td>
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<tr>
<td>CD3⁺IM</td>
<td></td>
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<tr>
<td>CD8⁺CT</td>
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<tr>
<td>CD8⁺IM</td>
<td></td>
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<tr>
<td>CD45RO⁺CT</td>
<td></td>
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<tr>
<td>CD45RO⁺IM</td>
<td></td>
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<tr>
<td>Functional orientation</td>
<td>T(_h)1 cell-associated factors (IFNγ, IL-12, T-bet and IRF1)</td>
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<tr>
<td></td>
<td>Cytotoxic factors (granzymes, perforin and granulysin)</td>
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<tr>
<td></td>
<td>Chemokines (CX3CL1, CXCL9, CXCL10, CCL5 and CCL2)</td>
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<tr>
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<td>(T_{h17}) cells, (T_{reg}) cells and (T_{h2}) cells have a variable effect on survival, depending on tumour type</td>
</tr>
<tr>
<td>TLS</td>
<td>Presence and quality</td>
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</tbody>
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Cancer classification using the “Immunoscore”: a worldwide task force

- Currently histopathological stage scoring is based on TNM
- Patients of same stage can have very different outcomes
- Little value in predicting response to therapy
- Long-term outcome may involve immune response
- “Immunoscore” = immunological biomarker

Immune-Mediated Inhibition of Metastases after Treatment with Local Radiation and CTLA-4 Blockade in a Mouse Model of Breast Cancer

Sandra Demaria, Noriko Kawashima, Anne Marie Yang, Mary Louise Devitt, James S. Babb, James P. Allison, and Silvia C. Formenti

Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial

Irradiation and anti–PD-L1 treatment synergistically promote antitumor immunity in mice

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²Department of Pathology, University of Chicago, Chicago, Illinois, USA.

Am J Clin Oncol. 2015 Feb;38(1):90-7. doi:
10.1097/COC.0b013e3182868ec8.
Immune-priming of the Tumor Microenvironment by Radiotherapy: Rationale for Combination With Immunotherapy to Improve Anticancer Efficacy.
Shahabi V¹, Postow MA, Tuck D, Wolchok JD.

Anti-PD-1 Blockade and Stereotactic Radiation Produce Long-Term Survival in Mice With Intracranial Gliomas
Zeng et al, 2013
A growing awareness of problems in reproducibility of pre-clinical research, including cancer research

*NATURE | PERSPECTIVES OPEN*

• A call for transparent reporting to optimize the predictive value of preclinical research: Story C. Landis et al., *Nature* 490, 2012

“We recognize that achieving a meaningful improvement in the quality of reporting will require a concerted effort by investigators, reviewers, funding agencies and journal editors. Requiring better reporting of animal studies will raise awareness of the importance of rigorous study design to accelerate scientific progress.”

BACKGROUND: Clinical testing of new therapeutic interventions requires comprehensive, high-quality preclinical data. Concerns regarding quality of preclinical data have been raised in recent reports. This report examines the data on the interaction of 10 drugs with radiation and provides recommendations for improving the quality, reproducibility, and utility of future studies.

CONCLUSIONS: There is a need for improved experimental design, execution, and reporting of preclinical testing of agents that are candidates for clinical use in combination with radiation.

Improved design, execution, common measures of enhancement, and consistent interpretation of preclinical studies of drug-radiation interactions will provide rational guidance for prioritizing drugs for clinical radiotherapy trials and for the design of such trials.
The Importance of Dosimetry Standardization in Radiobiology
Marc Desrosiers, Larry DeWerd, James Deye, Patricia Lindsay, Mark K. Murphy, Michael Mitch, Francesca Macchiarini, Strahinja Stojadinovic, and Helen Stone. Journal of Research of the National Institute of Standards and Technology, 2013

1) Radiation equipment and methods are increasing in variety and complexity.
2) Radiation biologists rarely receive training in radiation dosimetry.
3) Radiation biologists usually use irradiation equipment dedicated to research that is not shared with and calibrated by their clinical colleagues.
4) Radiobiologists now rarely work with radiation physicists as part of their joint routine duties, and there are fewer radiation physicists who are trained in the unique characteristics of the equipment used and problems involved in performing dosimetry in support of radiation biology.

As with the collaboration between the biologist and statistician, which aids in determining the required sample size of the experiments, the biologist-physicist collaboration can aid in determining the accuracy and precision required by a given experimental design and the methods needed to achieve these.