Landscape of Immunotherapy for Urothelial Carcinoma

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Definition of Immunotherapy

• There has been a number of advances in the understanding of the fundamental regulatory mechanisms governing host immune cell activation and function.

• Immunotherapy encompasses targeted manipulations of the host immune response in order to promote effective immune-mediated tumor destruction.
Goals of Immunotherapy

• The primary goal of antitumoral immunotherapy is to generate a systemic antigen-specific T-cell response that is capable of destroying the primary tumor, its potential metastases, and if possible the parent tissues that the tumor arises.

• Before discussing how the immune system may be manipulated to treat GU cancers, we must consider the immune systems role in promotion or elimination of cancer
- The adaptive immune system compromises CD4 (helper) T cells, CD8 (killer) T cells.
- T-cells play an important role in mediating anti-tumor immunity.
The Immune Editing Hypothesis

- Early tumors are recognized by the immune system in a productive, proactive way leading to elimination of tumors.
- Involves a concerted effort between the innate and adaptive immune system.
The Immune Editing Hypothesis

As tumors progress, they acquire genetic and epigenetic alterations that render anti-tumor immune response less effective. Progression can be slowed by an ongoing immune response, however, tumors in this phase can no longer be successfully eliminated.
Ultimately, tumors escape the immune response.

- Mechanisms include:
  - Down regulation of tumor antigens.
  - Induction/expansion of regulatory T cells (Treg) and **aberrant** expression of T cell co-regulatory molecules that actively inhibit the immune response.
Cancer Immunology

• Immunotherapy is an emerging therapeutic option for the treatment of localized and metastatic cancer, from multiple tumor types including melanoma, NSCLC, ovarian, and kidney cancer.

• As the field moves forward, we often forget the predominant role that immunotherapy has played in urothelial cancer.
• 5-year recurrence-free survival rate was 60% in the maintenance arm compared to 41% in the no-maintenance arm \((P < .0001)\)
• 5-year PFS rate was 76% in the maintenance arm compared with 70% in the no-maintenance arm \((P=.04)\)
BCG Initiates an Innate Immune Response

**Innate Immune Response → Adaptive Immune Response**

BCG

- Resting DC
- Activated DC
- TLR’s
- Cytokines
- BCG

Draining Lymph Node

Activated CD4 Helper T Cells (Home to Bladder)

CD4+ T cell
- Tumour antigen
- MHC class II
- Activated DC
- TCR
- CD8+ T cell
- MHC class I

What’s New?

• Negative co-stimulators such as as CTLA-4, PD-1 act to inhibit T-cell function and diminish T-cell survival leading to apoptosis.

• Programmed Death Ligand-1 (PD-L1) and its receptor programmed death-1 (PD-1)

Thompson RH et al., Immunotherapy 2009
How Does PD-L1 Fit In?
Adaptive Immune Resistance

Tumor > Interferon γ > T Cell

PD-L1

Adaptive Up-Regulation Of PD-L1 Turns T Cell OFF
Renal Cell Carcinoma

Thompson RH et al., Cancer Res 2006
What about Urothelial Carcinoma?

Inman et. al., *Cancer* 2007
PD-L1 and Urothelial Cancer

NMIBC therapy?

Inman et. al., Cancer 2007
Expression of PD-L1 by UCC tumors (P < 0.001) and PD-1 by tumor infiltrating lymphocytes (P = 0.012) were significantly associated with increased pathologic stage.

For a subset of patients with organ-confined disease, PD-L1 expression independently predicted all-cause mortality after cystectomy.
CD8+ T Cells and UCC

- Previous TMA of invasive bladder cancer have shown an association between PD-L1 and advanced pathological stage (Boorjian et al., Clin Canc Res 2008; Nakanishi et al., Cancer Immuno Immunother 2007).
- Would tumor infiltrating CD8+ T cells portend a better prognosis?

Figure 3. A) Membranous PD-L1 expression in tumor cells (200x); B) intratumoral CD8+ T cells (400x).
Table 3. Association between demographic, clinicopathologic characteristics, CD8 density, PD-L1 expression and outcome in 50 cystectomy patients with invasive urothelial carcinoma

<table>
<thead>
<tr>
<th>CD8 density</th>
<th>Overall Survival</th>
<th>Disease-Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.12 (0.02-0.68)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for demographic parameters*</td>
<td>0.1 (0.02-0.69)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for pathologic parameters**</td>
<td>0.1 (0.01-0.69)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for neoadjuvant therapy***</td>
<td>0.04 (0.004-0.46)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted for intravesical therapy</td>
<td>0.09 (0.01-0.58)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
MPDL3280A: Circulating Markers in UBC

- Increases in circulating IFNγ, IL-18 and activated CD8+ T cells following treatment with MPDL3280A
- Gene expression data from pretreatment tumors showed that progressors had a proportionally higher myeloid gene signature (e.g., IL8, CCL2)
Figure. Programmed death 1 (PD-1) and its ligands, PD-L1 and PD-L2, deliver inhibitory signals that regulate the balance between T cell activation, tolerance, and immunopathology. Immune responses to foreign and self-antigens require specific and balanced responses to clear pathogens and tumors and yet maintain tolerance. Induction and maintenance of T cell tolerance requires PD-1, and its ligand PD-L1 on nonhematopoietic cells can limit effector T cell responses and protect tissues from immune-mediated tissue damage.
Unanswered Questions!

– What are the target antigen(s) when BCG results in cure?
– Besides PD-1 /PD-L1, what are the other mechanisms of escape in UCC?
– Does chemotherapy promote or prohibit an anti-UCC immune response?
– Do the epigenetic changes in UCC render it more or less immunologically sensitive?
– Would combination therapies including chemotherapy, immunotherapy and even radiation therapy results in more durable responses? And what is appropriate timing/sequence of therapy?
Goal

• To develop a physiologically relevant, genetically engineered mouse model (GEMM) of UC, and use this model to optimize combinatorial immunotherapy / chemotherapy and immunotherapy / radiation therapy regimens for the treatment of UC.
Why use GEMM?

• An induced model is preferable, as such models allow the development of natural immune tolerance to tumors which is a characteristic of human tumors evolving and escaping immune recognition.

• Adenovirus expressing Cre recombinase (Ad-Cre) into the bladders of $p53^{flox/flox};Pten^{flox/flox}$ mice develop invasive tumors with associated CIS and LN spread within 60-90 days (Puzio-Kuter AM et al., Genes and Development 2009)
GEMM and Combined Therapy

1) Does PD-1 blockade add to cytotoxic chemotherapy in UC development,
2) does PD-1 blockade combined with RT improve survival and progression of UC.

Combined Immunotherapy and Chemotherapy Cohort -

- p53 or Pten single mutants (control; 10 mice per group)
- \( p53^{flox/flox};Pten^{flox/flox} \)
- \( p53^{flox/flox};Pten^{flox/flox} \) treated with chemotherapy (cisplatin 10mg/kg i.p. x 4 doses over 2 weeks; 17)
- \( p53^{flox/flox};Pten^{flox/flox} \) treated with anti-PD-1 abx (10mg/kg i.p. x 6 doses over 2 weeks; 32)
- \( p53^{flox/flox};Pten^{flox/flox} \) treated with cisplatin for weeks followed by 2 week treatment with anti-PD-1
- \( p53^{flox/flox};Pten^{flox/flox} \) treated with PD-1 for weeks followed by 2 week treatment with cisplatin
- \( p53^{flox/flox};Pten^{flox/flox} \) treated with simultaneously with cisplatin and anti-PD-1.

Combined Immunotherapy and Radiation Therapy (RT) Cohort -

- p53 or Pten single mutants (control; 10 mice per group)
- \( p53^{flox/flox};Pten^{flox/flox} \)
- \( p53^{flox/flox};Pten^{flox/flox} \) treated with anti-PD-1 abx (10mg/kg i.p. x 6 doses over 2 weeks; 32)
- \( p53^{flox/flox};Pten^{flox/flox} \) treated with radiation therapy to bladder (12 Gy x 1 as described; 32)
- \( p53^{flox/flox};Pten^{flox/flox} \) treated with simultaneously with anti-PD-1 and RT.
Summary

• Cancer immunotherapy is a rapidly advancing field of both clinical and pre-clinical study, and progress in this area has been especially strong in genitourinary cancers.

• The future of immunotherapy will most likely involve combination approaches, including surgery, immune checkpoint blockade, radiation therapy, conventional chemotherapy.
Adaptive Immune Response

- Undifferentiated CD4 Helper T Cell
- IL-12
  - T\textsubscript{H}1
    - IL-2, TNF-\textalpha, IFN-\gamma
  - T\textsubscript{H}2
    - IL-4
- IL-4
  - T\textsubscript{H}2
  - IL-10, IL-13
- TGF-\beta
  - T\textsubscript{reg}
    - TGF-\beta, IL-10

BCG Response

BCG Failure
CD8+ T Cells Express PD-1
In the Tumor Microenvironment

Outline

• Immune Editing Hypothesis.
• Immunotherapy in Urologic Oncology.
• Intravesical immunotherapy – BCG.
• PD-1 (Marker of Antigen Encounter) and PD-L1 (Marker of Pre-existing Immune Activation) and urothelial cancer.
• Unmet Needs and Future Directions for research and therapy.