Basic Principles of Tumor Immunotherapy and Mechanisms of Tumor Immune Suppression

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Disclosures

There will be discussion about the use of products for non-FDA indications in this presentation.
Topics to be Covered

I. Challenges to using immunotherapy for the treatment of cancer. Cancers are immune suppressive.

II. Approaches to cancer immunotherapy (vaccines, adoptive cell transfer, checkpoint inhibitors, Toll-like receptor agonists, chemotherapy & radiation).
All immune cells (innate & adaptive) can have a role in the immune response to cancers. The interactions between the different cell types can be complex and result in either activation or suppression.

T lymphocytes (adaptive immune cells) are viewed by many researchers as being the most important cancer killer cells, due to their specificity and ability to generate memory.
Can the Immune System Recognize Cancer?

Yes! Cancer cells express proteins that can be recognized by T cells (e.g., mutated proteins, newly expressed proteins, overexpressed normal proteins, oncogene products, post-translationally modified proteins).

If one looks for the presence of tumor antigen-reactive T cells in cancer patients, almost invariably they will be present.

Yet, more than 1.6 million individuals in the US will be diagnosed with a cancer this year, and nearly 600,000 will die.

Why does the immune system do such a poor job at preventing and eliminating cancer?
Why does Cancer Occur in Individuals with ‘Normal’ Immune Systems?

In the late 1950s, scientists (Burnet & Thomas) proposed that the immune system prevented the development of cancer (immune surveillance model). However, this did not explain why cancer occurs in individuals with ‘normal’ immune systems.

To better explain this, and in response to new scientific data, in 2002 Robert Schreiber and colleagues revised the model to explain how the immune system itself shapes how cancer progresses. They referred to this revised model as the “Cancer Immunoediting Model”.

A—Immune Editing: genetic instability of the cancer cells and ‘immune sculpting’ can lead to generation of new variants that are able to escape the immune system.

If Elimination (immune surveillance) is not successful, ultimately ‘the scale’ gets heavily tipped in favor of Escape.

Immunotherapy attempts to “shift the balance” back to the left (elimination).
Using immunotherapy to treat cancer is particularly challenging because unlike foreign pathogens, tumors are ‘self’ tissues (albeit ‘altered self’).

A major hurdle to successful immunotherapy is the immune suppressive environment created by the expanding cancer cells and other recruited cells (all contribute to forming the cancer microenvironment). Researchers are now learning how to inhibit the immune suppression.

Use of immunotherapy in the treatment of cancer is entering a new era. Determining the “right” combinations of different immunotherapies, and how they can be most effectively used with other therapies will be crucial to their success in the clinic.
Cancer-Induced Immune Suppression

It is clear that barriers are in place to prevent the immune system from doing its job and eliminating the cancerous cells.

Biologically, this makes sense since although cancer represents cells whose function has gone awry, the malignant cells are still derived from our own tissues. And, our immune system has many controls in place to prevent it from reacting against our own (or ‘self’) tissues.

If the immune controls fail, the consequence can be development of autoimmune disease, so the immune system is simply doing what it is designed to do – avoid autoreactivity.
How do Cancers Avoid Destruction by T Cells?

- The cancer cells can lose the ability to express proteins (antigens) seen by the T cells and B cells, which now makes them ‘invisibility’ to those cells.

- Cancer cells or other cells recruited by the cancer cells can make substances that actively ‘turn-off’ the cancer-killing immune cells. Examples include: (a) cytokines such as TGF-β, IL-4, IL-6, IL-10, VEGF, GM-CSF; (b) other soluble mediators such as PGE-2, reactive oxygen species (ROS) & gangliosides; (c) enzymes that eliminate amino acids that are important for T cell function, including arginase (ARG) and idoleamine-2,3-dioxygenase (IDO).

- The cancer cells can recruit or help generate other immune cells that actually suppress the cancer-killing cells. Examples: (a) a small subset of T cells (CD4⁺Foxp3⁺) that is very immune suppressive, called regulatory T cells (Tregs); (b) immature myeloid cells named myeloid-derived suppressor cells (or MDSCs); (c) tumor-associated macrophages (TAMs) that localize in cancer tissues.
How do Cancers Avoid Destruction by T Cells?

- Cancer cells and/or other cells in the “cancer microenvironment” can express certain proteins on their surface that directly ‘turn off’ incoming immune cells, including immune checkpoints.
**Approaches to Cancer Immunotherapy**

Rationale for using the immune system to treat cancers instead of chemotherapy or radiation includes increased specificity, less toxicity, and the generation of persistent protection. **A key point** about cancer immunotherapies is that these treatments are likely to work best when the disease has been first reduced by other treatments.

**Types of immunotherapy** *(more detail on following slides):*

1. Chemotherapy and radiation (conventional treatments that can help activate the immune system)

2. Vaccines and adjuvants

3. Cellular

4. Antibodies

*Clinical advances in these areas spurred Science Magazine to proclaim Cancer Immunotherapy its ‘Breakthrough for 2013’!*
**Immune Activating Properties of Chemotherapy and Radiation**

Radiation and certain chemotherapeutic drugs can help activate T cell immunity in at least three ways: (a) By inducing ‘immunogenic death’ of cancer cells, which helps increase the numbers of cancer antigen-reactive T cells; (b) By reducing the overall disease burden; this reduces immune suppression and reduces the numbers of tumor cells that must be eliminated (#s game); (c) As a consequence of reduced immune suppression, the ‘good’ immune cells, including cancer-killing T cells and NK cells, can work more effectively.

Interestingly, localized irradiation can have systemic (or distant) effects. This phenomenon is referred to as an “abscopal” effect. This effect has been reported clinically, but specific mechanisms involved are not well understood. Likely influenced by dosing & fractionation of the radiation.

Cyclophosphamide is an example of a chemotherapeutic agent known to have immune activating properties. It can reduce immune suppression, but the dose and timing of administration can also be important, in order to avoid direct targeting of the cancer-killing immune cells.
Importantly, use of radiation and chemotherapy in ways that have relatively low toxicities may help set the stage for other therapies that more specifically activate cells of the immune system, including T cells. A common theme with cancer immunotherapy is the need to combine approaches.
Cancer Vaccines

Vaccines can come in many forms (source of cancer antigens): proteins, protein fragments (peptides), antigen-presenting immune cells exposed to the proteins/peptides, intact cancer cells, gene vectors that express proteins/peptides.

There are several challenges to using vaccines as cancer therapies:

a. Unlike vaccines used to prevent infectious diseases, almost all cancer vaccines have been used for treatment. Likely to work best in a setting of ‘minimal’ disease.

b. Most cancer antigens do not elicit strong responses, unlike foreign proteins from infectious agents.

c. We still understand relatively little about ideal dosing and timing of administration.

d. Scientists know that inclusion of adjuvants in cancer vaccines are important. Adjuvants help generate T cell reactivity and B cell-produced antibodies by activating innate immune cells through Toll-like receptors (TLR) expressed by these cells. Problem: few adjuvants have been approved for clinical use. In early phase clinical trials, TLR agonists (eg., bacterial or viral products) or immune-activating cytokines have been used, but it is unclear which of these is the best.
Cancer Vaccine Examples

There are many experimental vaccines that have or are being tested in both experimental animal models and early phase clinical trials. The only FDA approved vaccines are the following:

**Human papilloma virus (HPV) vaccine** (preventive vaccine for cervical cancer).

**Hepatitis B virus (HBV) vaccine** (can protect against liver cancer driven by the virus).

**Sipuleucel-T vaccine** (treatment of advanced prostate cancer). Dendritic cells (a type of antigen-presenting cell) are isolated from the cancer patient and exposed to *prostatic acid phosphatase* (a prostate cancer antigen) and injected back in to the patient (3 treatments, 2 weeks apart). Now being tested in patients with less advanced disease.

One of the more interesting experimental approaches is the development of personalized cancer vaccines based on the mutations present in a patient’s own tumor.
Adoptive T Cell Immunotherapy (ACT)

The idea is to: (a) isolate T cells with cancer reactivity (one source is the tumor; TILs), or (b) isolate non-specific T cells from the blood and impart cancer reactivity by genetically engineering the cells to express specific antigen receptors (outside of the body).

The T cells can then be expanded to large numbers in culture, and returned to the patient.

The 2 ACT approaches noted above are depicted in the following slides.
**ACT Approach 1:**  
*Immunotherapy with Tumor-Infiltarating T Cells*

- **Isolate tumor-infiltrating T cells**
- **Culture with beads or artificial antigen-presenting cells +/- cytokines (IL-2, IL-7, IL-15, IL-21)**
- **Expand T cells to relatively large numbers**
- **Transfer back to patient +/- preconditioning (chemotherapy) to provide “space” for the incoming cells**

**Future:** These T cells could be genetically engineered to be resistant to immune suppression.
**ACT Approach 2:**
Immunotherapy with Genetically Engineered T Cells

1. Isolate T cells from **peripheral blood**
2. Culture with beads or artificial antigen-presenting cells +/- cytokines (IL-2, IL-7, IL-15, IL-21)
3. Expand to relatively large numbers
4. Transfer back to patient +/- preconditioning (chemotherapy) to provide “space” for the incoming cells

**Engineer the T cells to express a chimeric antigen receptor (CAR) (or a cancer antigen-specific T cell receptor)**

From: Lee et al., Clin. Cancer Res, 2012
Cancer Immunotherapy using Antibodies

It is unclear just how important B cells, and the antibodies they make, are in controlling cancer. However, there is no doubt that antibodies can be potent anti-cancer drugs.

Monoclonal antibody technology was developed in the 1970s (Kohler, Millstein & Jerne). One of the challenges for clinical use was the fact the antibodies were derived in rodents. “Humanization” was required to avoid rejection.

Antibodies can be used in many ways to directly target cancer cells:
- When they bind to their specific antigen on the surface of a cancer cell, they can help destroy the cells (via complement or antibody-dependent cell cytotoxicity (ADCC)).
- They can block cancer pro-survival factors from binding to their respective receptors (inhibit cancer cell survival and proliferation).
- They can serve as carriers for toxins or radioisotopes, to help specifically direct these death-inducing molecules to the cancer.

Antibodies can also be used in an attempt to make the T cell response to cancer more effective. Examples: blockade of immune checkpoints, neutralization of immune suppressive cytokines or other suppressive mediators.
Monoclonal Antibodies: Using them to Interfere with Immune Suppression by Blocking ‘Immune Checkpoints’

Immune checkpoints are inhibitory molecules that get expressed on T cells after they become activated; they are also expressed by some other immune cells. They are important as they help regulate the immune system. Unfortunately, cancers can hijack these pathways to ‘turn the T cells off’ so that they are unable to kill the cancerous cells. The PD-1 / PD-L1 (programmed death receptor-1) and CTLA-4 / B7 pathways are two of the checkpoints currently being targeted in the treatment of cancer.

Larsson et al. Retrovirology, 10:31, 2013
Monoclonal Antibodies that Block Immune Checkpoints Have now been FDA Approved

**CTLA-4** was the first checkpoint targeted by monoclonal antibodies. Ipilimumab was approved for treatment of metastatic melanoma in 2011.

**PD-1** specific antibodies: Pembrolizumab was approved for treatment of metastatic melanoma in 2014 (38% response rate). Nivolumab was approved in 2015 for non-resectable or metastatic melanoma and non-small cell lung cancer. PD-1 and PD-L1 specific antibodies have also been shown to have anti-tumor activity in at least 12 other cancer types.

Anti-CTLA-4 and anti-PD-1 antibodies have been combined to treat melanoma (Wolchok et al., New Engl J Med, 2013). Patients treated with the highest doses had the best response rate (53%).

Treatment with these antibodies does induce some acute toxicities, which can be severe and potentially life-threatening, but most of the toxicities can be managed.
Combined Blockade of Immune Checkpoints can have Synergistic Anti-Cancer Effects (Experimental)

A Experimental Design

B [n=5-12/group]

C [n=8-12/group]

D [n=5-12/group]

(J. ImmunoTherapy of Cancer, 2015)
Possible Ways to Overcome Cancer-Induced Immune Suppression by using Combinatorial Approaches

I. Treatment to reduce the numbers of cancer cells and disrupt the immune suppression

II. Infuse patient-derived immune cells to eliminate the remaining cancer cells

III. Vaccines or immune checkpoint protein blocking antibodies

Harvest some of the patient’s immune cells at the time of diagnosis or relapse

Activate, expand & possibly genetically engineer the cells (T or NK cells) to become potent cancer “killers”
Biomarkers of Cancer Immunity

Some potential biomarkers have been identified, but they need to be validated

- **The Immuno Score - Assessment of TILs**: The presence of T cell infiltrates (TILs) emerged as a stronger independent prognostic factor than clinicopathological criteria such as tumor size, depth of infiltration, differentiation and nodal status (Galon et al., 2006; Pages et al., 2005; Fridman et al., 2011; Galon et al., 2012).

- **Myeloid cells**: Tumor or peritumoral CD14\(^+\) monocytes is an independent prognostic factor for decreased survival in RCC patients (Gustafson et al., Clin Cancer Res. 2015).
Biomarkers of Cancer Immunity

- **B-cell signature:**
  - Immunoglobulin kappa chain (IGKC; plasma cell product) in the tumor stroma is a biomarker of prognosis and response to chemotherapy in patients with breast cancer, NSCLC and CRC (Schmidt et al., 2012). IGKC predicted responses to neoadjuvant therapy in breast cancer.
  - In ovarian tumor (Nielsen et al., 2012), and HNC metastasis (Pretscher et al., 2009) the presence of CD20⁺ B cells plus CD8 T cells correlated with increased patient survival.
**Take Home Messages**

1. Cancer cells can stimulate T cells, but the cancer avoids immune detection by a variety of mechanisms, including immune suppression. It is crucial that the immune suppression be blocked in order for the T cells, and other immune cells, to effectively kill the cancer cells.

2. Each cancer likely inhibits the immune system in different ways.

3. It is possible to develop treatments that can stimulate the immune system (immune therapies) to fight cancers. These treatments can consist of agents that directly activate immune cells or interfere with cancer-induced immune suppression to facilitate immune activation.

4. Immune therapies for cancers can be successful. However, they will typically need to be used in combinations with each other, or with other standard or novel therapies.
Questions?