Practical Aspects of the Mouse (and Human) Immune Systems

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Outline

• Innate and adaptive immune systems – brief intro
• How anti-cancer immune responses are generated
• Cancer antigens
• Dendritic cells
• T cells
• Cancer immune evasion
• Cancer immunotherapies – brief intro
The immune system

- Evolved to provide protection against invasive pathogens
- Consists of a variety of cells and proteins whose purpose is to generate immune responses against micro-organisms
- The immune system is “educated” to attack foreign invaders, but at the same time, leave healthy, self-tissues unharmed
- The immune system can sometimes recognize and kill cancer cells
- 2 main branches
  - Innate immune system – Initial responders
  - Adaptive immune system – Tailored attack
The immune system – a division of labor

Innate immune system

• Initial recognition of non-self (i.e. infection, cancer)

• Comprised of *cells* (granulocytes, monocytes, dendritic cells and NK cells) and *proteins* (antibodies and complement)

• Recognizes non-self via receptors that “see” microbial structures (cell wall components, DNA, RNA)
  
  • Pattern recognition receptors (PRRs)

• Necessary for priming adaptive immune responses
The immune system – a division of labor

Adaptive immune system

• Provides nearly unlimited diversity of receptors to protect the host from infection

• B cells and T cells

• Have unique receptors generated during development
  
  • B cells produce antibodies which help fight infection
  
  • T cells patrol for infected or cancerous cells
    • Recognize “foreign” or abnormal proteins on the cell surface
  
  • 100,000,000 unique T cells are present in all of us

• Retains “memory” against infections and in some cases, cancer.
Immune cells develop in the bone marrow

Figure 1.5 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)
How are cancer cells seen as “abnormal” by the immune system?

- **Oncofetal antigens** (ie. CEA in colon cancer)
- **Over-expressed antigens** (ie. WT-1 in AML)
How are cancer cells seen as “abnormal” by the immune system?

Neo-antigens
Mutational burden in tumors correlates with spontaneous immunity

Dendritic cells are important for priming anti-tumor T cells

- DCs - hematopoietic cells specially equipped for antigen presentation and T cell activation

- Classified in 2 groups
  - Conventional DCs
    - Antigen presentation
    - T cell activation
  - Plasmacytoid DCs
    - Type I IFN production
    - Important for immune responses against viruses

Colin et al. Nat Rev Immunol 2011
Dendritic cell activation

- DC receive signals through PRRs and other receptors (i.e. CD40) to become activated
  - Activation/licensing of DC results in:
    - HLA upregulation (enhanced antigen presentation to T cells)
    - Upregulation of costimulatory and cell adhesion molecules
    - Production of pro-inflammatory cytokines (IL-12, TNF-α, type I IFNs)
    - Alteration of chemokine receptor expression
    - Migration (to sites of inflammation)
  - Only licensed DC activate naïve T cells
  - Non-licensed DC induce peripheral tolerance (T cell deletion or anergy)

“Danger signals”
- Pathogen-associated molecular patterns (PAMPs)
  - Bacteria proteins
  - Viral DNA/RNA
- Damage-associated molecular patterns (DAMPs)
  - Products of dying cells

Types of PRRs
- Toll-like receptors (TLR)
- C-type lectin receptors
- NOD-like receptors (NLRs)
- RIG-I-like receptors

Receptors can be on the cell surface or intracellular (NLRs)

Adapted from Immunology 101 from SITC/NCI 2016
Dendritic cell activation

Microbial products
TNF family

MHC II
lysosome

IMMATURE DC
capture of antigens

- adsorptive uptake, eg, DEC-205, FcR
- macropinocytosis
- phagocytosis: microbes, dying cells

MATURE DC
stimulation of T cell immunity

- CD40, CD86
- CCR7
- IL-12
- High MHC - peptide

Steinman PNAS 2002
Dendritic cells sense “danger” signals released by dying cancer cells

T cells are activated by antigen-presenting cells (APCs)

Antigen – a substance recognized by receptors on immune cells

Cummings, B. 7th Ed. 2005
T cell activation 101

• Naïve T cell - a T cell that has not encountered its cognate antigen

• 2 signals (at least) are required to optimally activate a naïve T cell
  1. MHC-peptide : TCR (signal 1)
  2. B7 : CD28 (signal 2)
  Cytokines (signal 3)

• Activated T cells proliferate, differentiate into effectors and traffic to sites of inflammation (i.e. the tumor)

• In reality, things are more complicated…..
Positive and negative costimulatory receptors

Modulate magnitude of T cell activation and effector function

Positive costimulatory receptors:
- CD28 (classical)
- ICOS (inducible costimulator)
- CD27 (TNF family receptor)

Negative costimulatory receptors:
- CTLA-4 (cytotoxic lymphocyte antigen – 4)
- PD-1 (programmed death -1)
- TIM-3 (T cell immunoglobulin mucin -3)

Figure 8-22 Immunobiology, 7ed. (© Garland Science 2008)
Cancer immunotherapy makes its mark
Cancer immunotherapies

• Cancer vaccines
  • Peptide-based
  • Cellular-based (i.e. DC vaccines)

• Adoptive T cell therapy
  • Ex vivo expansion of tumor-infiltrating T cells and infusion into cancer-bearing hosts
  • Tumor Ag-specific TCR transduced T cell therapy
  • Chimeric antigen receptor (CAR) adoptive therapy (CD19)

• Immune checkpoint blockade
  • CTLA-4 blockade
  • PD-1 blockade

• Reversal of immune evasion
  • Treg depletion
  • IDO inhibition (1-MT and derivatives)
  • Prevention of tumor-induced T cell anergy (lymphodepleted host and adoptive T cell therapy)
What are the essentials of cancer immunology and immunotherapy?
CELLS AS DRUGS
New paradigms in tissue distribution and pharmacokinetics

Living cells can move ‘against’ concentration gradients and exhibit conditional function after integrating micro-environmental information.
At the center of the galaxy of increasingly successful cancer immunotherapies

T cell: Tumor cell

Checkpoint blockade anti-PD-(L)1, anti-CTLA-4

Cancer Vaccines

CAR/TCR/TIL-based treatments
General schema for growing naturally-occurring anti-tumor T cells

Rosenberg & Restifo
Science 2015
Immunotherapy - CAR T cell therapy

2nd generation CAR signaling

3rd generation CAR signaling

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Advantages of cell transfer therapy for treating metastatic cancer.

1. Administer large numbers of cells selected to have specificity for tumor antigens.

2. Identify exact T cell subpopulations and effector functions required for cancer regression in vivo.

3. Add and edit genes in transferred T cells to optimize their function or to confer new specificities to tumors.

4. ‘Lymphodeplete’ host prior to cell transfer to eliminate or reduce immunosuppressive elements of the tumor microenvironment.
Immunotherapy - Checkpoint blockade

Drake et al, Nat Rev Clin Oncol 2014
Conclusions

• The immune system, which developed to fight infections, can also recognize and kill cancer cells

• Cancers express antigens in the form of mutated or over-expressed proteins that can be seen as “foreign” to T cells of the immune system

• Although immune responses are generated against cancer in some patients, they are often suppressed and ineffective

• The 3 main types of immunotherapy for cancer are: cancer vaccines, adoptive T cell therapy and checkpoint blockade