The immune system and cancer

Refs:

1. The Immune System in Cancer Pathogenesis:
Potential Therapeutic Approaches (Pankita H. Pandya,[1] Mary E. Murray,[2] Karen E. Pollok,[3] and Jamie L. Renbarger
2. Insights Into Mechanisms of Tumor and Immune System Interaction ()
3 ...

Joachim
P.Bio student

Introduction

- Currently , there is a significantly high cancer burden
  - 18.1 million new cases worldwide in 2020 (9.3 million in men and 8.8 million in women)
  - Projected to worsen over the years
- It’s now known that the immune system can be a formidable adversary against cancer
- The relationship between cancer and the immune system involves three basic principles
  - Detection of “nonself ” antigens
  - targeting and destroying the invader/cancer while protecting the host
  - Development of immunological memory

This presentation covers;

- Immune system overview
- Cancer biology overview
- Cancer and the immune system
  - Role of the immune system in cancer
    - Innate Immunity and Cancer
    - Adaptive Immunity and Cancer
  - Tumour antigens
  - How tumour cells escape from the immune system
  - H/O immunotherapy
  - Currently available immunotherapies and active lines of research

Immune system overview

- complex network of cells, tissues, and organs working for the body's defence
- comprises the innate and the adaptive immune system
- Innate:
  - nonspecific and immediate immune responses
  - includes physical barriers and cellular components (phagocytes and NK cells)
  - also utilizes soluble bioactive proteins such as cytokines and complement proteins
  - able to identify self and groups of pathogens by way of receptors like the TLRs
  - also plays a role in initiating and shaping the adaptive immune response,

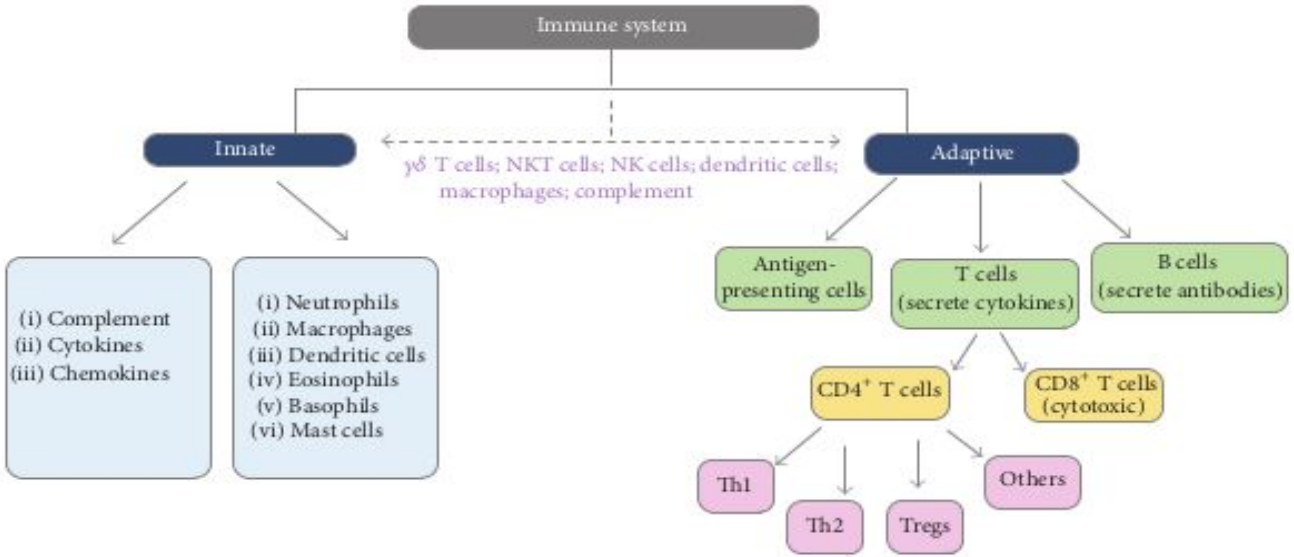
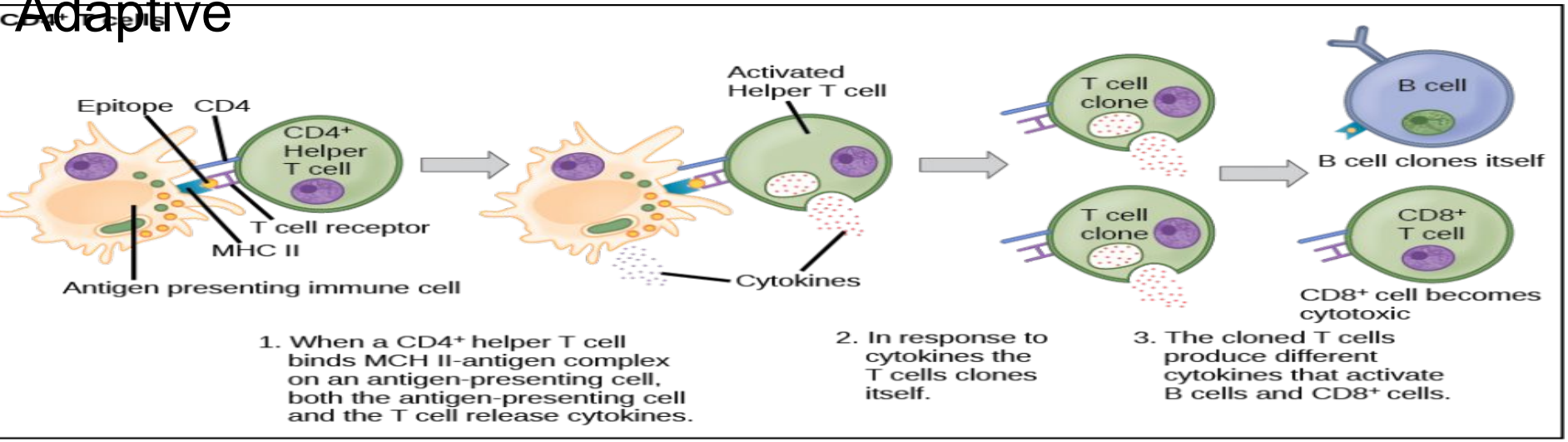
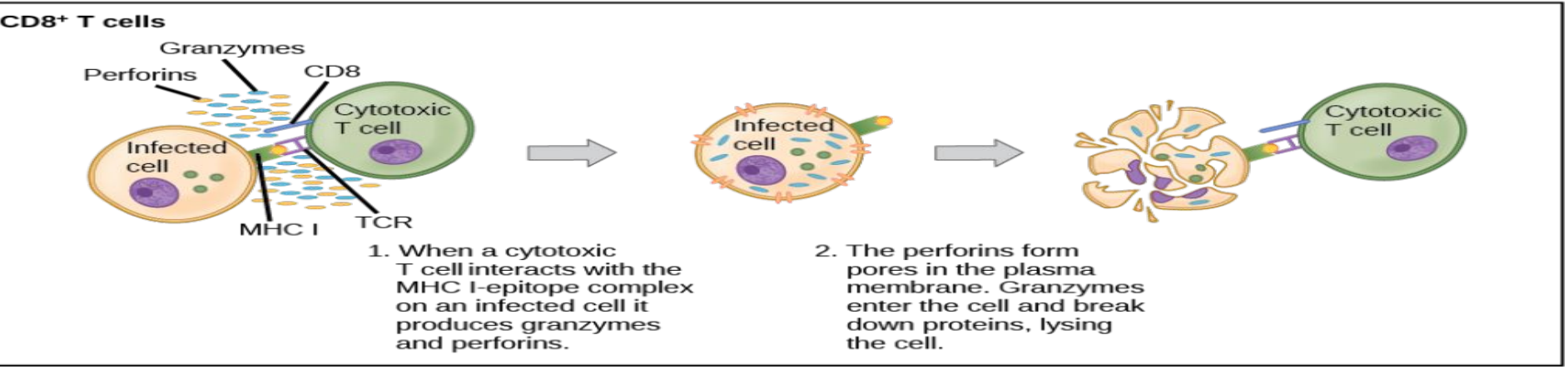


FIGURE 1: Overview of the immune system: innate and adaptive immunity. An evolutionary bridge between both forms of immunity is observed due to the presence of γδ T cells, NKT cells, NK cells, dendritic cells, macrophages, and complement proteins. The innate immune responses include cells and soluble components that are nonspecific, fast-acting, and first responders in inflammation. In contrast, adaptive immunity encompasses immune components that are more specific for targeted antigens and capable of forming immunological memory [25, 27, 38].

Adaptive


CD4⁺ cells
Epitope
CD4
CD4⁺ Helper T cell
T cell receptor
MHC II
Antigen presenting immune cell
Activated Helper T cell
Cytokines
T cell clone
T cell clone
B cell
B cell clones itself
CD8⁺ T cell
CD8⁺ cell becomes cytotoxic
1. When a CD4⁺ helper T cell binds MCH II-antigen complex on an antigen-presenting cell, both the antigen-presenting cell and the T cell release cytokines.
2. In response to cytokines the T cells clones itself.
3. The cloned T cells produce different cytokines that activate B cells and CD8⁺ cells.


CD8⁺ T cells
Granzymes
Perforins
CD8
Cytotoxic T cell
Infected cell
MHC I
TCR
Infected cell
Cytotoxic T cell
1. When a cytotoxic T cell interacts with the MHC I-epitope complex on an infected cell it produces granzymes and perforins.
2. The perforins form pores in the plasma membrane. Granzymes enter the cell and break down proteins, lysing the cell.

Cancer biology overview

- characterized by uncontrolled cell growth, invasion into surrounding tissues, and potential metastasis to distant organs
- Cellular Transformation:
  - Mutations in normal cells usually affecting genes involved in cell cycle control, DNA repair, apoptosis, and signaling pathways (oncogenes)
- Tumor Formation
  - Benign
  - malignant
- Genomic Instability
- Tumor Microenvironment

Hallmarks of cancer

1. Self-sufficiency in growth signals
2. Insensitivity to growth inhibitory signals
3. Evasion of cell death
4. Limitless replicative potential
5. Development of sustained angiogenesis
6. Ability to invade and metastasize
7. *Reprogramming of energy metabolism*
8. *Evasion of the immune system*

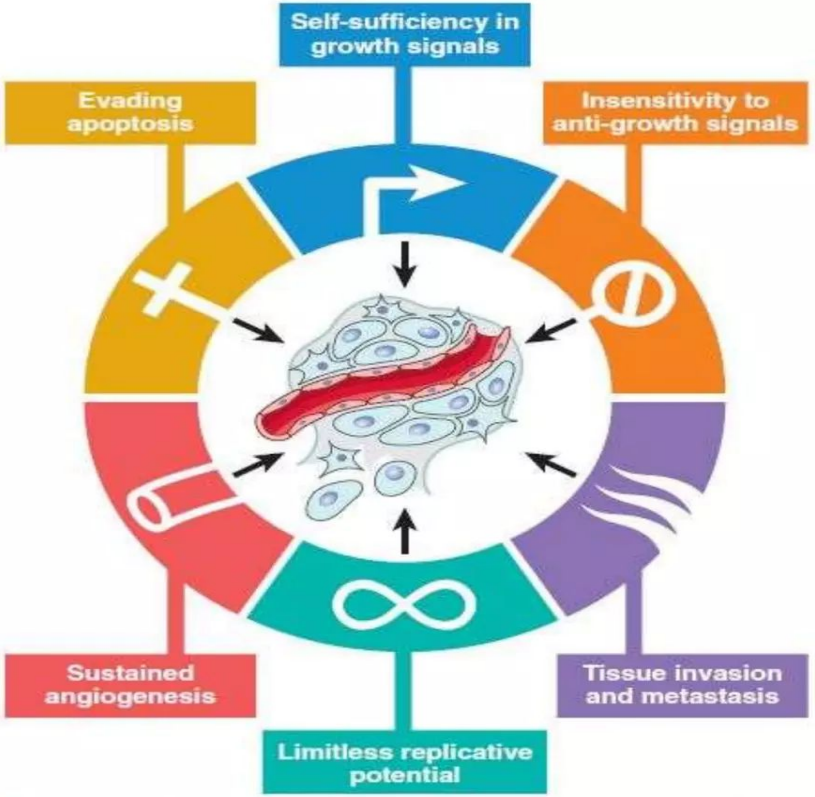


Figure 5–18 Six hallmarks of cancer. Most cancer cells acquire these properties during their development, typically by mutations in the relevant genes.

(From Hanahan D, Weinberg RA: The hallmarks of cancer. Cell 100:57, 2000.)

Role of the immune system in cancer

Immunosurveillance Hypothesis (1909):

- suggested by Paul Ehrlich in the early 20th century
- in his hypothesis, Ehrlich proposed that the immune system has the ability to recognize and eliminate cancer cells as part of its normal function.
- he suggested that the immune system acts as a surveillance system, constantly monitoring the body for abnormal cells, including those with cancerous potential.
- contradictory reports based on studies conducted by Burnet and Thomas and Stutman's group brought the concept of immunosurveillance to the forefront in oncology and due to these and other inconsistent reports from studies highlighting the immunosurveillance mechanisms in cancer, the concept was largely rejected

Three major phases comprise the immunoediting process in cancer pathogenesis: elimination, equilibrium, and escape

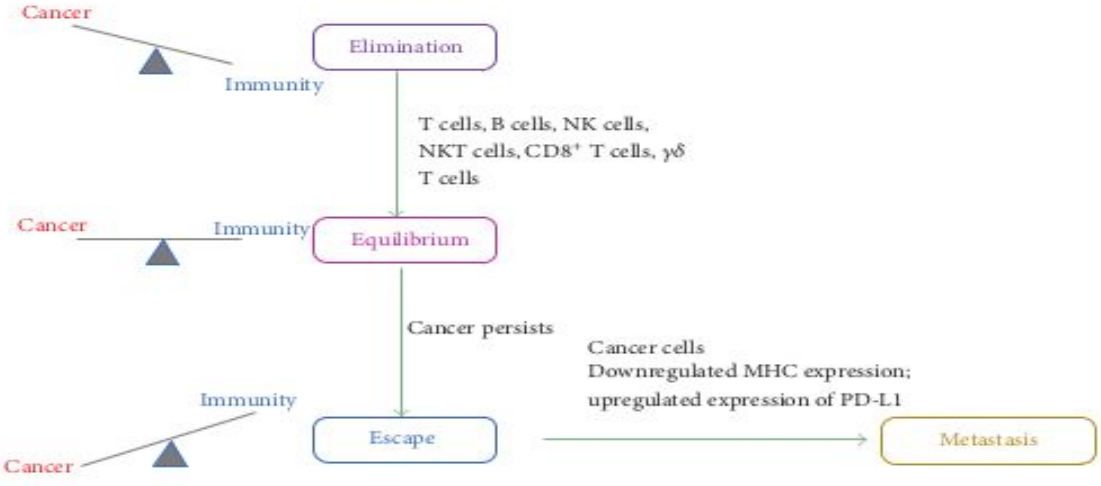


FIGURE 2: The cancer immunoediting process. There are three phases in the cancer immunoediting process: elimination, equilibrium, and escape [4]. Elimination phase involves effector function of the immune cells to target and eradicate cancer. In the equilibrium phase a balance is obtained between progression of cancer and cancer elimination by the immune system. If the cancer persists then it overwhelms the immunity and escapes to go on and metastasize to the other organs [4, 40, 53].

Innate

- phagocytes facilitate immediate host protection by engulfing cells that express non-self-antigens
- NK cells use major MHC class I proteins which are universally expressed on surfaces of all nucleated cells.These NK cells secrete perforin and granzyme to induce apoptosis of cells that have abnormal or altered MHC class I expression
- aberrant MHC class I expression leads to activation of NK cells via activating receptors present on NK cell surface such as NKG2D which bind to surface glycoproteins, that may be present on the tumors

- MHC I expression becomes altered in cancer cells and this leads to activation of NK cells via activating receptors present on NK cell surface leading to NK-induced apoptosis which can occur by several mechanisms such as
  - TNF-α- dependent release of cytoplasmic granules (perforin and granzymes) that form pores in cell membranes;
  - by antibody-dependent complement cytotoxicity due to the presence of anti-body receptor (CD16) on NK cell surface;
  - and by the release of cytokines such as IFN-γ which mediates activation and maturation of antigen-presenting cells such as dendritic cells

- neutrophils are known to promote cancer progression via Proteases such as neutrophil elastase present in neutrophil granules facilitate growth of cancer cells
- Other proteases in the neutrophil granules assist in cleaving extracellular matrix proteins, thus allowing cancer invasion and metastasis

Adaptive

- comprised of several components that can either eradicate cancer cells or promote their proliferation
- targeting antigens specific to the cancer cells by exploiting the effector functions of antibodies, T cells, B cells, and antigen-presenting cells
- Within this central dogma of cancer immunity, there are several regulatory factors that act as immune checkpoints in the context of adaptive immune responses to mediate either cancer progression or regression.
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- during the first encounter with antigen/MHC class II on the antigen presenting cells(APCs), it is critical to have two signals delivered between the APC and T cell for activation : antigen-bound MHC class II interacting with the T cell receptor and costimulatory signals including CD28, ICOS, and CD80 /CD86
  - The ICOS ligand on APCs interacts with ICOS receptor on T cells, whereas CD28 on T cells interacts with CD80 (B7.1)/CD86 (B7.2) on APCs for costimulation
- If these costimulatory signals are not present when activating the naïve T cells, then they will not differentiate or proliferate
- Lack of an appropriate costimulatory signal ultimately results in a weak T cell response and a state of immune tolerance to cancer cell-associated antigens; thus adaptive immunity is shut down and cancer progresses

- Similarly, immune tolerance is also initiated by CTLA4 on T cells binding to the CD80/CD86 proteins on APCs which mediates downregulation of immune responses
  - CTLA4 is also expressed by several cancers/tumors and this mechanism corresponds with immune tolerance as seen in cancer progression
- T cells also have a cell surface receptor molecule known as programed cell death protein 1 (PD-1) which can bind to its ligand, PD-L1, on APCs and mediates immunosuppression
- PD-1 expression has also been reported in multiple other immune cells such as B cells, NK cells, monocytes, dendritic cells, and Tregs
  - Similar to expression of CTLA4, this PD-L1 protein is also expressed by various types of cancer cells which may be a mechanism for how these cancers escape immunity

- Immune responses within the tumour microenvironment can also be suppressed by Tregs

These innate and adaptive immune responses in oncogenesis serve to be the underlying basis for immune surveillance, cancer immunoediting and immunotherapy in general

immune system cells involved in anti-tumour response

- Cytotoxic T Lymphocytes (CTLs)
- Helper T Cells (Th Cells)
- NK cells
- Macrophages
- Dendritic cells
- B cells
- Tregs

Qn : **What are the basic mechanisms of anti-tumour immunity for each of the cells listed?**

Tumour antigens

- novel or over-expressed proteins expressed by tumours that may be recognized by the immune system
- Classification;
  - Initially as **Tumor-Specific Antigens** (TSA), and **Tumor-Associated Antigens** (TAA), which are present on some tumor cells and also some normal cells
  - Currently, based on their molecular structure and source
    - Products of Mutated Oncogenes and Tumor Suppressor Genes
    - Products of Other Mutated Genes
      - Overexpressed or Aberrantly Expressed Cellular Proteins
      - Tumor Antigens Produced by Oncogenic Viruses
      - Oncofetal Antigens
      - Altered Cell Surface Glycolipids and Glycoproteins
      - Cell Type-Specific Differentiation Antigens

Examples of tumour antigens

Tumor antigen	Tumor in which it is found	Remarks
Alphafetoprotein (AFP)	Germ cell tumors Hepatocellular carcinoma	
Carcinoembryonic antigen (CEA)	Bowel cancers	Occasional lung or breast cancer
CA-125	Ovarian cancer	
MUC-1	Breast cancer	
Epithelial tumor antigen (ETA)	Breast cancer	
Tyrosinase	Malignant melanoma	normally present in minute quantities; greatly elevated levels in melanoma
Melanoma-associated antigen (MAGE)	Malignant melanoma	Also normally present in the testis
abnormal products of ras, p53	Various tumors	

Certain tumor antigens are thus used as tumor markers. More importantly, tumor antigens can be used in cancer therapy as tumor antigen vaccines.[2]

How do tumour cells escape from the immune system?

- Downregulation of Antigen Presentation
- Loss or Altered Expression of Tumor Antigens
- Immune Checkpoint Activation
- Induction of Immunosuppressive Molecules
- Recruitment of Immunosuppressive Cells
- .....

Currently available immunotherapies and active lines of research

- monoclonal antibody therapy — Rituximab(CD 20)
- Immune Checkpoint Inhibitors — Pembrolizumab, nivolumab, atezolizumab (Block the inhibitory signals (checkpoint pathways such as PD-1/PD-L1 and CTLA-4))
- CAR-T Cell Therapy: (Genetically modify a patient's own T cells to express chimeric antigen receptors (CARs) targeting specific cancer antigens)
- Cancer vaccines
- Cytokine Therapies

active lines of research