Outline of Immunotherapies in Cancer

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History of Immunotherapy

History of lmmunotherapy

- In 1796 Dr. Edward Jenner realized cowpox protected against smallpox
  - Introduced the practice of vaccination

- lmmunotherapy has attracted new attention
  - Multiple new oncologic agents
  - lmmunotherapy may soon be another agent in the standard of care for treating cancer

History Of Immunotherapy

- William B. Coley : Father of Immunotherapy.
- Attempted to harness the power of the immune system for treating cancer in the late 19th century.
- Orthopedic surgeon : operated bone sarcomas.
- Patients with significant postoperative **wound infection**
  - spontaneous regression of their unresected tumours.

- 1891, Coley injected 1000 patients with mixtures of live and inactivated bacteria such as ***Streptococcus pyogenes* and *Serratia marcescens*** with the hope of inducing sepsis and strong immune and antitumour responses.

- Cocktail of bacteria : “Coley’s toxin”

- 1st documented active cancer immunotherapy intervention

The Next Revolutionary Wave

- Better understanding of the process of immune surveillance, by which innate immune cells eliminate cancer cells.

- T cell immune checkpoints: CTLA-4 and PD-1
- Propelled the field of immuno-oncology into its current era
- 2018 Nobel prize in Physiology or Medicine to Drs. Allison and Honjo.

Past Century

- Stages of cancer immunotherapy development
  - 1890- Cancer vaccine developed
  - 1960's - Tumor-specific monoclonal antibodies released
  - 1970-1980's - Clinical benefit of cancer immunotherapy does not fulfill expectations
  - Late 1990's - Several cancer immunotherapy drugs spur renaissance of interest

Tumor Immunotherapy Overview

What is the Immune System?

- A biological collection of organs, specific cells, molecules, and other components that protect body against foreign matter
- Immune cells and antibodies travel through the body to protect it from infectious pathogens and can also help protect against cancer cell proliferation

Innate Immunity

- Inherited physical and biochemical structures present from birth that protect the body from invading substances

- Innate immune defenses are **non-specific**

  - Respond to pathogens in a generic way
  - This system does not confer long-lasting immunity against a pathogen.

- The innate immune system is the dominant system of host defense in most organisms

Inflammatory Response

- The inflammatory response activates other components of the innate immune system's internal defenses
  - Phagocytes
  - Natural killer (NK) cells
  - Antimicrobial proteins
  - Cytokines (e.g., histamine, prostaglandins, etc.)
  - Kinins
  - Chemical reactions initiated by the complement system

Complement System

- The complement system
  - A group of 20+ proteins
  - Stimulates other immune system elements
  - Can also cause lysis of bacteria and certain other cells
  - Interferons and proteins are the two main types of non specific antimicrobial proteins

Adaptive Immunity

- Also called specific or acquired immunity
  - Develops upon exposure to a pathogen or foreign substance
  - Creates immunological memory
  - Substances causing this response are antigens

- The immune response can destroy anything containing the antigen, whether bacteria or cancer cells

- Adaptive immunity is highly specific to its molecular structural characteristics

  - This leads to an enhanced immune response to subsequent encounters with that same pathogen

Adaptive Immunity

- The process of adaptive or acquired immunity is the basis of vaccines

- By exposing the immune system to an inactivated form of a pathogen, vaccination protects the person from ever contracting the disease

Types of Specific Immune Response

Humoral Immunity

- Mediated by proteins, including antibodies, in the blood and other bodily fluids
- Produces a cascade of chemicals from the complement system
- Antibodies are produced by plasma cells {derived from Bcells)
  - Bind to specific antigens, inactivating them and/or marking them for destruction

Cellular Immunity

- Also called cell-mediated immunity
- Mediated by T cells
- May attack target cells directly or indirectly by activating other immune cells
  - Enhances the inflammatory response
- Cellular immunity primarily targets antigenic molecules and microorganisms

Immunotherapy

What is immunotherapy?

- The NCI defines immunotherapy as "treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases"

- Tumor immunotherapy Aims to

  - Augment the weak host immune response (active immunity)
  - Administer tumor-specific antibodies or T cells, a form of passive immunity

How Does it Work?

- Intended to augment or restore the body's own immune function by some means.
- May be quite different from the traditional cancer treatments of chemotherapy/targeted therapy, radiation, and surgery, which intend to act directly upon the targeted tumor

Immunotherapies

Components of Immunotherapy

- New cancer immunotherapies include multiple modalities:
  - Vaccines
  - Growth factors
  - Checkpoint inhibitors
  - Monoclonal antibodies
  - Cytokines
  - Several targeted and nonspecific agents

Vaccines

Mechanism

- Introducing a non-infectious version of a disease causing microbe into an individual, thereby providing a better stimulus for the **activation of disease-specific T cells** and the development of **immunological memory**.

- Memory immune cells are able to rapidly kill microbes and prevent infection

- More effective for Infection but not against cancer and chronic infectious diseases such as HIV.

Vaccines

- Promoting intense, cancer-specific, T cell immune response
- Vaccines derived from autologous or allogeneic tissue
  - **Autologous vaccines** use tumor cells from patient receiving vaccine
    - Contains all tumor antigens present in tumor, and is MHC matched with the patient
  - **Allogeneic vaccines** prepared with tumor cells from others
    - Easier to manufacture in quantity
    - May lack unique patient antigens

Vaccines: Sipuleucel-T

- Only first FDA approved therapeutic cancer vaccine.

  - Sipuleucel-T : An autologous vaccine approved for metastatic prostate cancer.

  - Sip-T elicit anti-tumor activity via activation of T cells that are specific for prostatic acid phosphatase (PAP), an enzyme found on the surface of 95% of prostate cancer cells.

Vaccines: HPV Vaccine

- Development of virally induced tumors can be blocked by preventive vaccination with viral antigens or attenuated live viruses
  - HPV vaccines promise to reduce the incidence of HPV-induced tumors

Specific/Targeted Immunotherapies

- Tumor-specific monoclonal antibodies (MABs) act via direct or indirect immune response resulting in cell death

- MABs are produced from single B cell clone and consist of multiple identical copies.

- MABs work through various mechanisms of action to elicit cell death
  - Blocking signaling pathways necessary for tumor growth
  - Triggers immune-mediated cytotoxic response
  - Blocking angiogenesis

Antigen Non-specific Immunotherapies

- Do not target cancer cells specifically
- Stimulate the immune system in a more general way that may lead to a better immune response against cancer cells
- Non-specific cancer immunotherapies may be administered as:
  - Monotherapy
  - Adjuvant therapy to boost the immune system and potentiate other agents, such as vaccines

Antigen Non-specific lmmunotherapies

- These agents include Cytokines
  - Five classes of cytoklnes are important in immunity
    - Interleukins
    - Interferons
    - Tumor necrosis factors
    - Colony-stimulating factors
    - Chemokines

Cytokines

- Binding of a cytokine to a cell can have a variety of different effects
  - Inducing production of more cytokine molecules
  - Promoting or inhibiting cytokine activity
  - Activating or suppressing target cell activity, proliferation, or differentiation

Cytokines

- Cytokines as Cancer Immunotherapy

  - Recombinant versions of some cytokines are produced commercially for cancer and other disorders

  - Interleukins, interferons, and colony-stimulating factors

Immuno-stimulatory Agents

- Potential mechanisms of these therapies vary
    - Direct anti-tumor effects
        - Reversal of immune suppression
        - Activation of innate immunity
    - Antigen-non-specific T cell activation

Immuno-stimulatory Agents

- CpG oligonucleotides
  - Potent stimulators of both innate and adaptive immune systems
  - Currently being examined for cancer immunotherapy
  - Nonspecific immune stimulation
  - Activates macrophages and promotes macrophage-mediated killing of tumor cells
  - Used as adjuvant may stimulate T cell responses
  - BCG is currently used to treat bladder cancer

Immuno-stimulatory Agents: MABs

- Some commercially available MABs
  - Rituximab
  - Ipilimumab
  - Tositumomab
  - Adalimumab
  - lbritumomab tiuxetan

Immuno-stimulatory Agents

- Agonistic CD40
  - CD40 is a tumor necrosis factor receptor expressed on APCs such as:
    - Dendritic cells (DC)
    - Bcells
    - Monocytes
    - Many non-immune cells
    - A wide range of tumors
  - Agents currently in research
  - May be combined with vaccines and chemotherapy in the future

Immuno-stimulatory Agents: Enzyme Inhibitors

- Targeted therapies inhibit signaling enzymes, allowing tumor growth

- May be called different names based on enzymes they block

Immuno-stimulatory Agents: Enzyme Inhibitors

- Tyrosine kinase inhibitors (TKls) include:

  - Axitinib
  - Dasatinib
  - Erlotinib
  - Gefitinib
  - lmatinib
  - Pazopanib
  - Sorafenib
  - Sunitinib

Immuno-stimulatory Agents

- Proteosome inhibitors
  - Proteasomes are found in all cells
  - Help degrade excess protein

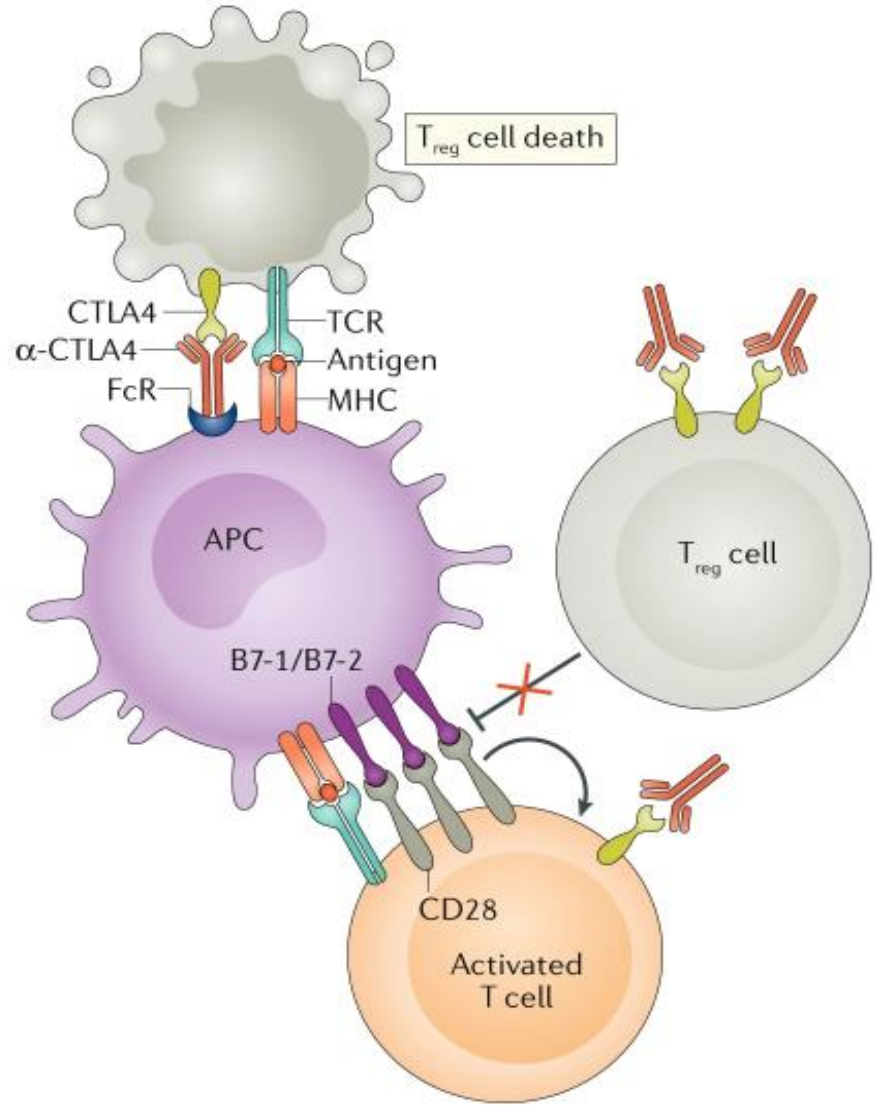
- Proteasome inhibitors cause a build-up of unwanted proteins in the cell Makes cancer cells die Bortezomib is a proteasome inhibitor used to treat multiple myeloma

- Signal-transduction inhibitors and multi-targeted kinase inhibitors

Checkpoint inhibitors

- CTLA 4 : Cytotoxic T lymphocyte antigen-4
- CTLA-4) and programmed cell death protein 1 (PD-1) are the canonical immune-checkpoint receptors.
- Together they show ligand–receptor interactions between T cells and APCs that modulate the T cell response to antigen.

CTLA 4 Mechanism



Cytotoxic T lymphocyte antigen 4 (CTLA4)-blocking antibodies (α-CTLA4), especially when bound to an Fc receptor (FcR) on an antigen-presenting cell (APC), can promote antibody-dependent cellular cytotoxicity (ADCC). $CD4^{+}CD25^{+}$ regulatory T (T_{reg}) cells express higher amounts of CTLA4 than conventional T cells and are therefore more prone to α-CTLA4-induced ADCC than conventional T cells. In addition, α-CTLA4 can bind to CTLA4 on the surface of the T_{reg} cell and prevent it from counter-regulating the CD28-mediated co-stimulatory pathways that are playing a role in T cell activation. At the same time, α-CTLA4 can also promote T cell responses by blocking CTLA4 on the surface of conventional T cells as they undergo activation. TCR, T cell receptor. Adapted from ©2019 Fritz, J. M. & Lenardo, M. J. Originally published in *J. Exp. Med.* https://doi.org/10.1084/jem.20182395 (ref.[135]).

CTLA 4

- Inhibition of CTLA4 enhances T cell clonal responses to tumour-associated neoantigens and a high neoantigen burden portends a favourable response to anti-CTLA4 therapy

- Apart from boosting effector T cell responses, anti-CTLA4 therapy depletes local intratumoural T_{reg} cells through antibody-dependent cell-mediated cytotoxicity.

- Ipilimumab: human IgG1κ anti-CTLA4 mAb
- FDA approval in 2011 for non-resectable stage III/IV melanoma following evidence that it elicited potent tumour necrosis.
- Tremelimumab: IgG2 isotype form of a CTLA4-blocking antibody: Yet to get FDA Approval

PD1-PDL1 **biological function**

- PD1: First identified in 1992 as a putative mediator of apoptosis
- Role in restraining immune system hyperactivation, analogous to CTLA4
- Type 1 transmembrane glycoprotein within the immunoglobulin superfamily, PD1 exhibits a 20% and 15% amino acid identity to CTLA4 and CD28, respectively.

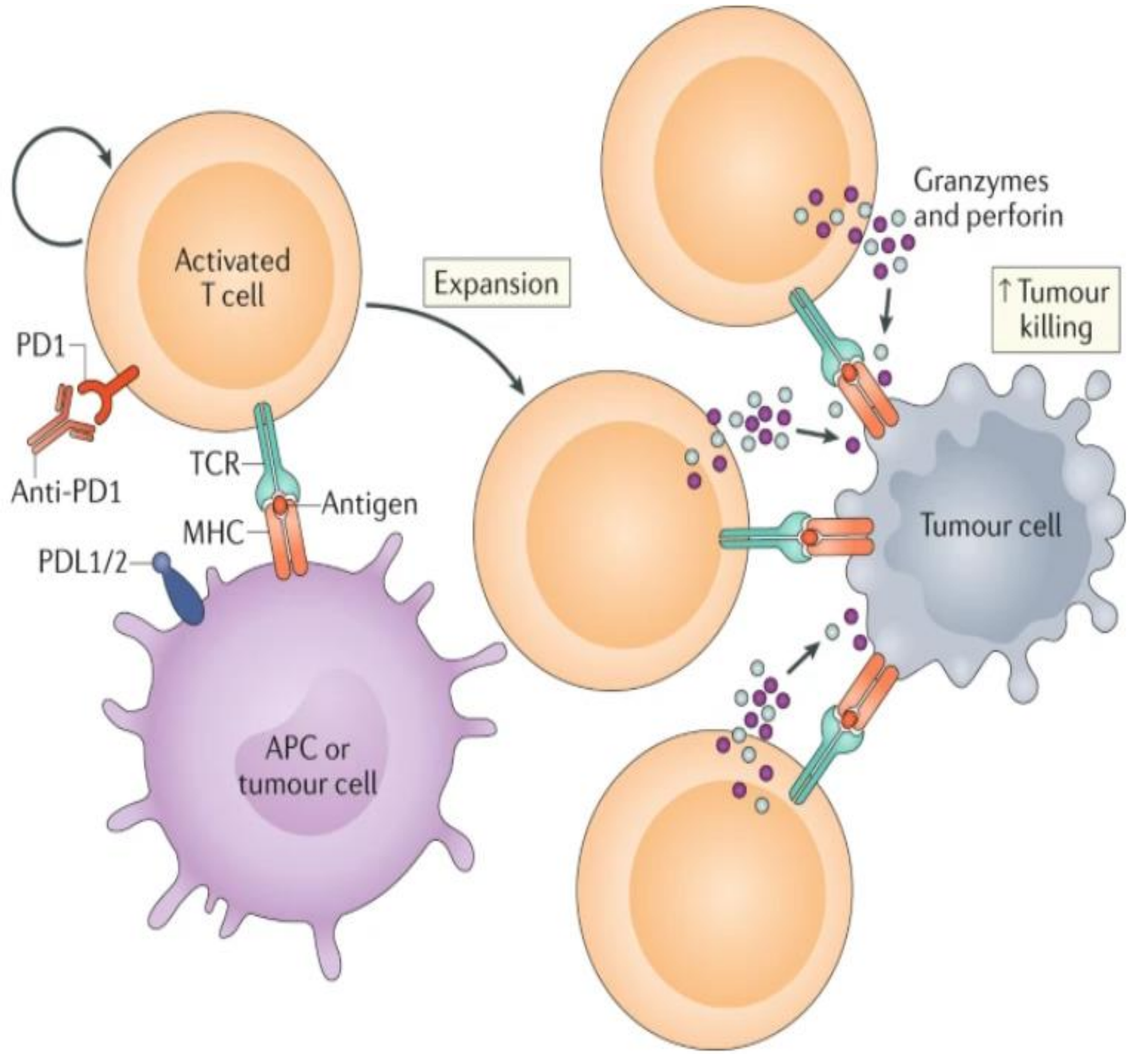
- Human PD1 is expressed on T cells after TCR stimulation and binds the B7 homologues PDL1 (also known as B7-H1)

- PDL2 (also known as B7-DC), which are present constitutively on APCs and can be induced in non-haematopoietic tissues by pro-inflammatory cytokines.

PD1-PDL1 **Biological function**

- Predominantly modulates effector T cell activity within tissue and tumors
- Therefore more widely expressed than CTLA-4
- It is induced on activated T cells, B cells, macrophages, dendritic cells and Tregs
- The potent inhibitory signal is provided through its interaction with programmed death-ligand 1 (PD-L1) and/or PD-L2, whereby PD-1 inhibits kinases involved in T cell activation

PD1-PD-L1 axis



Activated T cells express programmed cell death 1 (PD1), which engages with its specific ligand (PDL1 or PDL2) to dampen activation. Blocking of the PD1 axis through the administration of an anti-PD1 (or anti-PDL1 or anti-PDL2) antibody prevents this inhibitory interaction and unleashes antitumoural T lymphocyte activity by promoting increased T cell activation and proliferation, by enhancing their effector functions and by supporting the formation of memory cells. Consequently, more T cells bind to tumour antigens presented on tumour cells by MHC molecules via their T cell receptors (TCRs). This ultimately leads to the release of cytolytic mediators, such as perforin and granzyme, causing enhanced tumour killing. APC, antigen-presenting cell. Adapted from ©2019 Fritz, J. M. & Lenardo, M. J. Originally published in *J. Exp. Med.* https://doi.org/10.1084/jem.20182395 (ref.[135]).

PD1-PDL1

- Overexpression of PDL1 or PDL2 in cancer cell lines was found to constrain the $CD8^+$ T cell cytotoxic antitumour response
- Blockade of PD1 suppressed the growth of transplanted myeloma cells
- Neutralizing the PD1 axis using mAbs or secreted PD1 extracellular domains reversed these effects and enhanced T cell cytotoxicity towards tumour cells

PD1-PDL1

- PD1 inhibition not only augments antitumoural immunity but also limits haematogenous seeding of B16 melanoma and CT26 colon carcinoma metastases

- PD1/PDL1 blockade can both enhance tumour cytolysis and limit metastasis

- In 2014, the humanized and fully human anti-PD1 mAbs pembrolizumab and nivolumab (both IgG4) became the first FDA-approved PD1-targeted therapeutics for refractory and unresectable melanoma

Other lmmunotherapies

- Killer T cell andregulatory T cell manipulation Lymphokine activated killer cell (LAK cell)

- White blood cell stimulated to kill tumor cells

- Adoptive therapy with autologous LAK cells and *in vivo* administration of IL-2 or chemotherapeutic drugs has yielded results in mice, with regression of solid tumors

Other lmmunotherapies

- Variation of adoptive therapy isolates tumor-infiltrating lymphocytes (TlLs) from inflammatory infiltrate in and around solid tumors
  - TlLs are obtained from surgical resection specimens and expanded by culture in IL-2
  - TlLs may be enriched for tumor-specific cytotoxic T lymphocytes (CTLs) and for activated NK cells

- TIL therapy for metastatic melanoma being used in various cancer centers

Other Immunotherapies

- Other drugs boost immune system in a non-specific way, similar to cytokines

- Unlike cytokines, these therapies are not naturally found in the body

- Known as immunomodulating drugs
    - Thalidomide
    - Lenalidomide
    - Pomalidomide
- Thought to work by boosting immune system: Exact mechanism unknown

Thank You