L4: Nanomedicine in Immunotherapy

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Body has two main branches of immunity, innate and adaptive. Innate immunity is the first line of defense. Phagocytes such as dendritic cells and macrophages will non specifically take up certain suspected pathogens and destroy them. The adaptive immunity is acquired immunity that is largely run by the B cells and T cells. For adaptive immunity, these cells become specific to certain foreign proteins, called antigens, after exposure, and will actively seek to destroy that antigen in a targeted manner.

The adaptive immunity is further broken down into two branches, humoral and cellular immunity. Humoral immunity is governed by the B cells, and generally works to combat antigens that are present in the bodily fluids via antibody production. Cellular immunity is produced through T cells, which focus on seeking out and destroying cells that are infected or mutated, and therefore express the antigen it is specific for.
During antigen presentation, the immature dendritic cell will take up the antigen and present it on the major histocompatibility complex (MHC) complexes. There are two MHC complexes, MHC-I which is present on all nucleated cells, and MHC-II, which is present only on antigen presenting cells. The APC will present the antigen on both the MHC-I and MHC-II complexes. The APCs will then interact with both CD4+ helper T cells via MHC-II, and then interact with CD8+ T cells through MHC-I.
Activation of B Cells

- Antibodies are produced only by B lymphocytes.
- Humoral immune responses are initiated by binding of antigen to membrane bound antibody on B cells. Activated B cells secrete soluble antibodies of the same specificity as the membrane receptors.
- Antibody responses are specialized and enhanced by signals from helper T cells.
Activation of T Cells

- CD4 and CD8 “co-receptors” recognize MHC molecules (class II or class I) at the same time as the TCR sees the peptide-MHC; CD4 and CD8 provide necessary activating signals for T cells.
- CD28 is a receptor for “costimulators” expressed on APCs.

General Immunotherapy Approaches

Nonspecific

- Antigen-specific
  - Tumor lysate
  - Viral vector
  - Peptides
  - Mature DCs
  - CTL
  - T cell
  - DC

- Vaccination
  - Inject DCs

- Adoptive T cell transfer
  - Conditioning
  - TCR/CAR
  - Ag presenting cells

- Cytokine therapy
  - IFN-γ
  - TRAIL
  - CD8+ T cell

- Checkpoint blockade
  - Anti-PD-L1 antibody
  - PD-L1
  - PD-1
  - T cell
  - Tumor cell

Sources:
- Dranoff. Nat Rev Cancer, 2004
What is a Vaccine?

A vaccine is a substance that is administered to produce or increase immunity against one or more antigens. This is done by introducing an antigen along with stimulatory factors to force the innate immune system to program a cytotoxic T cell response.
Vaccine Mechanism

- Introduce antigen to antigen presenting cells (usually dendritic cells).
- Antigen is presented on the major histocompatibility complex (MHC) complex and interact with T cells.
- Activated T cells scan cells in the body and destroy target pathogens or cells.
How do these different parameters affect the ability of nanoparticles to interact with and modulate the immune system?
An effective coating material helps to reduce nonspecific interactions in complex biological environments such as in circulation or in the subcutaneous space.

(2) Nanoparticle material

- Quantum Dots
- Liposomes
- Iron oxide NPs
- Carbon nanotubes
- Gold NPs
- Polymeric NPs
- Dendrimers
- Micro- and nanobubbles
- Upconverting NPs
- Iron-platinum NPs
- Nanoclusters
- Functionalized NPs
Nanoparticle carriers enable the colocalization of antigen and adjuvant, enhancing antigen-specific immune response.

Fang et al. Small, 2015 (top); Fischer et al. JACS, 2013 (bottom).
Dendritic cells can be specifically targeted via cell surface receptors, leading to enhanced uptake.
(5) Physical Properties

Lymph nodes are an important network of organs in immunity.

Nanoparticles smaller than 50 nm have been shown to accumulate much more rapidly in draining lymph nodes compared with nanoparticles over 50 nm in size.