USING THE IMMUNE RESPONSE TO ATTACK TUMORS AND VACCINATION.

Varad kulkarni
Molecular Immunology Seminar
Date: 19.06.2019
Using the immune response to attack tumors.

- A major problem in treating cancer is controlling metastasis.
- Discovery of protective immune responses to tumors.
- MHC molecules of tumor cells foreign to the mice are killed.
- Injection with irradiated tumor cells that cannot grow into mice.
Using the immune response to attack tumors.

• Mice are protected against later injection with lethal dose of viable cells of the same tumor.

• It indicates that the tumors express antigens that can become targets of a tumor-specific T-cell response that rejects the tumor.

• These **tumor rejection antigens** are expressed by experimentally induced murine tumors and are usually specific for an individual tumor.
Immune surveillance hypothesis - Immunological Editing.

- **Elimination phase**: In which the immune system recognizes and destroys potential tumor cells.

- **Equilibrium phase**: In which tumor Cells undergo changes or mutations that aid their survival as a result of the selection pressure imposed by the immune system.
Immune surveillance hypothesis

• Escape phase: Tumor cells that have acquired the ability to escape the attentions of the immune system and grow unrestrained become clinically detectable.

Eventually, one variant may escape the killing mechanism, or recruit regulatory cells to protect it, and so spread unchallenged.
Mechanisms of tumors to avoid immune recognition

- Tumors can have low immunogenicity.
- Cross-presentation of tumor-specific antigens.
- Antigenic change by which tumors lacking immunogenic antigens can expand.
Mechanisms of tumors to avoid immune recognition

• Direct suppression of T-cells.
• Creation of physical barriers.
Chimeric antigen receptor (CAR)

- Fusion receptors that contain extracellular antigen-specific domains fused to intracellular domains.
- These receptors are introduced into T cells via retroviral vectors to produce CAR T cells.
- The use of a CAR allows the T cell’s target specificity to be almost any molecule recognizable by an antibody rather than just peptide:MHC complexes.
Tumor-specific antigen recognition by monoclonal antibodies

- Tumor-specific antibodies of the correct isotypes can lyse tumor cells by recruiting NK cells.

- Antibody binding to the tumor cell and is endocytosed, the toxin is released from the antibody and can kill the tumor cell.

- The radioactive antibody-tumor cell will deliver a dose of radiation sufficient to kill the tumor cell.
Summery

• Some tumors elicit specific immune responses that suppress or modify their growth.
• Tumors evade or suppress these responses through a process known as immunological editing.
• Development of an effective vaccine against specific strains of cancer.
• Monoclonal antibodies have also been successfully developed for tumor immunotherapy.
• Current trend is to incorporate immunotherapy with other traditional anticancer treatments to take advantage of the specificity and power of the immune system.
Fighting infectious diseases with vaccination

• The goal of vaccination is the generation of long-lasting and protective immunity.

• The approach is via attenuated organisms with reduced pathogenicity, which would stimulate protective immunity but not cause disease.

• The second approach was the development of vaccines based on killed organisms and purified components.
Criteria for an effective vaccine

<table>
<thead>
<tr>
<th>Features of effective vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safe</strong></td>
</tr>
<tr>
<td>Vaccine must not itself cause illness or death</td>
</tr>
<tr>
<td><strong>Protective</strong></td>
</tr>
<tr>
<td>Vaccine must protect against illness resulting from exposure to live pathogen</td>
</tr>
<tr>
<td><strong>Gives sustained protection</strong></td>
</tr>
<tr>
<td>Protection against illness must last for several years</td>
</tr>
<tr>
<td><strong>Induces neutralizing antibody</strong></td>
</tr>
<tr>
<td>Some pathogens (such as polio virus) infect cells that cannot be replaced (e.g., neurons). Neutralizing antibody is essential to prevent infection of such cells</td>
</tr>
<tr>
<td><strong>Induces protective T cells</strong></td>
</tr>
<tr>
<td>Some pathogens, particularly intracellular, are more effectively dealt with by cell-mediated responses</td>
</tr>
<tr>
<td><strong>Practical considerations</strong></td>
</tr>
<tr>
<td>Low cost per dose, Biological stability, Ease of administration, Few side-effects</td>
</tr>
</tbody>
</table>
Fighting infectious diseases with vaccination

• Live-attenuated viral vaccines are usually more potent than ‘killed’ vaccines.

• Vaccines can be made safer by the use of recombinant DNA technology.

• Inactivated viruses cannot produce proteins in the cytosol of infected cells, thereby no viral antigen is presented by MHC I molecules.

• Live attenuated vaccines elicit a greater response and activate of CD4 T cells and cytotoxic CD8 T cells.

• Attenuated strains replicate poorly in human hosts and they induce immunity but not disease.
Fighting infectious diseases with vaccination

• The mutated genes are used to replace the wild-type genes in a reconstituted virus genome.

• The advantage of this approach is that mutations can be engineered so that reversion to wild type is virtually impossible.
Route of vaccination is important

• The ideal vaccination induces host defence at the point of entry of the infectious agent.

• Injections are painful and unpopular, expensive and need a trained injector.

• It does not mimic the usual route of entry of the majority of pathogens against which vaccination is directed.

• Presentation of soluble protein antigens by the oral route often results in tolerance, which is important for the food-borne and airborne antigens presented to the gut and respiratory tract.
Conjugate vaccines

- *H. influenzae*, have an outer capsule composed of polysaccharides that are species- and type-specific for particular strains.
- The most effective defence against this is opsonization of the polysaccharide coat with antibody.
- Conjugate vaccines take advantage of linked recognition to boost B-cell responses against polysaccharide antigens.
Upcoming strategies

• Vaccines based on peptides or purified proteins require additional components to mimic how real infections activate immunity.
• Such components of a vaccine are known as adjuvants, which are defined as substances that enhance the immunogenicity of antigens.
• Several other adjuvants are widely used experimentally in animals but are not approved for use in humans.
• Protective immunity can be induced by DNA-based vaccination.
• Current approaches are identifying how best to transfect DNA into these dendritic cell populations.
Summery

• Vaccination is arguably the greatest success of immunology, having eradicated or virtually eliminated several human diseases.
• It takes advantage of the immune system’s natural specificity and inducibility.
• Most effective vaccines are based on attenuated live microorganisms, but such vaccines carry some risk and are potentially lethal to immunosuppressed or immunodeficient individuals.
• New techniques are being developed to generate genetically attenuated pathogens for use as vaccines, particularly for malaria and tuberculosis.
Summery

• Many bacterial vaccines are based on components of the microorganism, including components of the toxins that it produces.

• Vaccines based on peptides, particularly very long peptides, are just emerging from the experimental stage and are beginning to be tested in humans.

• The development of oral vaccines is particularly important for stimulating immunity to the many pathogens that enter through the mucosa.
THANK YOU!!