Module 5: Immunity to pathogens

Lecture 29: Immunity to microbes (part I)

29.1 General features of immunity to microbes

- Microbial infections are best prevented by both innate and adaptive immune responses. The innate immune system takes care of early defense while the adaptive immune system offers a longer and potential response. In addition, adaptive immune responses are more specific and confer protection from repeated attacks by producing memory cells.

- As microbes differ a lot in their host attacking regime, their removal from the affected patient requires efficient effector systems. Adaptive immunity is developed in such a way that it permits the affected host to respond favorably to different types of microbes.

- The result of many microbial infections is decided by the balance between microbial schemes for withstanding immunity and the host immune responses. Microbes have adapted several ways to combat the immune response.

- Immunity against microbes performs almost similar to other defense mechanisms. Although it is essential for host survival but sometimes it may cause damage to the host tissue itself.

- Some microbes especially viruses have the potential to be latent. In such cases the host immune response does not allow the microbe to spread but the microbes survive in the latent form, i.e. infection may prevail under specific conditions like stress etc.

29.2 Immunity to bacteria

29.2.1 Immunity to extracellular bacteria

Extracellular bacteria are those that multiply and reside outside the host cell. These bacteria mainly affect the cells in two ways. They either attack by causing inflammation and tissue damage or by producing toxins.
29.2.2 Innate immunity to extracellular bacteria

Innate immunity to extracellular bacteria essentially involves three processes.

- **Stimulation of phagocytes** - Phagocytes take the help of surface receptors and Fc receptors to identify extracellular bacteria and its opsonization with the help of antibodies, respectively. Most of these receptors are associated with promotion of phagocytic activity and microbicidal activity.

- **Induction of inflammatory response** - Antigen presenting cells like dendritic cells in addition to phagocytes are stimulated by microbes and these cells secrete cytokines which are responsible for causing leukocyte infiltration at the site of inflammation.

- **Activation of complement system** - Both gram positive and gram negative bacteria stimulate alternative pathway of complement system and mannose expressing bacteria stimulate lectin pathway of complement system by binding to mannose binding lectin.

29.2.3 Adaptive immunity to extracellular bacteria

The immunity that plays major role against extracellular bacteria is the humoral or antibody mediated immunity as it prevents the infection by neutralizing the toxins. Usually polysaccharide antigens are prototypic thymus-independent antigens and humoral immunity is the basic line of defense against polysaccharide-rich encapsulated bacteria. The antibodies in such cases defend the body by neutralization, opsonization, phagocytosis and stimulation of complement system. Extracellular bacteria also stimulate the production of CD4+ helper T cells which induces inflammation and phagocytic activity. Besides this, these antigens may cause some mutational disorders and also the affected individual may have reduced immune response towards microbial infections.

29.2.4 Some important definitions

- **Septic shock** - It is the after effect of some gram positive and gram negative bacterial infections represented by intravascular coagulation.

- **Superantigen** - Some bacterial toxins or antigens stimulate non-specific activation of T-cells leading to polyclonal T-cell activation. These antigens are called superantigens.
29.2.5 Immune evasion by extracellular bacteria

1) Polysaccharide antigens or encapsulated bacteria are more lethal as compared to a strain devoid of capsule because they resist phagocytosis.
2) Capsulated bacteria inhibit alternate pathway of complement system due to the presence of sialic acid.
3) One more way of evading immune response by extracellular bacteria is due to the genetic edition of surface antigens. E.g. surface antigen of some specific bacteria is contained in their pili. Pili contain a protein antigen called “pilin” and this pilin undergoes gene variation. Pili are the structures of bacteria responsible for bacterial adhesion to host cells.

29.2.6 Immunity to intracellular bacteria

Some intracellular bacteria like pathogenic or facultative are able to multiply within the phagocytes, so their elimination from the patients requires modified strategies.

29.2.7 Innate immunity to intracellular bacteria

Phagocytes and natural killer cells provide innate immunity to the intracellular bacteria. However some bacteria survive and multiply easily in the phagocytes, the phagocytes need to be stimulated by the secretions of these bacteria in order to clear the infection. The secretions from these bacteria are recognized by TLRs and cytoplasmic proteins of the NOD-like receptor (NLR) family so that they stimulate the phagocytes to degrade the invading bacteria. In addition to the intracellular bacteria, activated natural killer cells produce IFN-γ, which consecutively stimulates macrophages and cytokines. Although innate immunity provides protection from most of the bacteria but some intracellular bacteria like Listeria monocytogenes need cell mediated immunity in order to be eliminated from the body.

29.2.8 Adaptive immunity to intracellular bacteria

T cell-mediated immunity plays a significant role in providing protection against intracellular bacteria. CD4+ T-cells and CD8+ cytotoxic T lymphocytes are the two major forms of cell mediated immunity that participate in phagocytosis or killing of infected cells, respectively. Both the, CD4+ T-cells and CD8+ cytotoxic T lymphocytes work together to provide protection against the intracellular bacteria. Granulomatous
inflammation acts as a marker for most of the infections due to intracellular bacteria, which occurs because of T-cell and macrophage stimulation. Macrophage stimulation that occurs as an antigenic response towards intracellular microbes is sometimes able to cause tissue damage. The response shown by different patients towards the intracellular microbes decides the development of the disease and its consequence. One neat example of such type of response is shown by leprosy patients. Leprosy is a disorder caused by *Mycobacterium leprae* and it exists in two forms, the lepromatous and tuberculoid form. Lepromatous form is characterized by feeble cell-mediated immune response and high specific antibody titer while the tuberculoid form shows low specific antibody titer but very strong cell-mediated immune response. Although the reasons attributed to this type of response are still speculated and not yet verified, one of the factors that are given significance is regarding varied pattern of cytokine production and T-cell differentiation in patients.

### 29.2.9 Dodging of immune system by intracellular bacteria

Intracellular bacteria tend to dodge the immune system in many ways comprising evading into the cytosol or preventing phagolysosome fusion and by overpowering the reactive oxygen species by their microbicidal activity. These bacteria have the potential to cause chronic infections because they can survive the phagocyte mediated elimination and thrive for years in the body and may show reversion of the disease.
Lecture 30: Immunity to microbes (part II)

30.1 Immunity to Fungi

Mycoses is another term for fungal infections. Fungal infections are as important as other microbial infections but the lack of animal models for mycoses makes it less informed. Neutrophils and macrophages serve as the outstanding mediators of innate immunity against fungal infections. Neutrophils release lysosomal enzymes and fungicidal substances like reactive oxygen species, which phagocytose fungi to kill them within the cell.

Cell-mediated immunity is effective mechanism of adaptive immunity against fungal infections. It functions by preventing the spread of fungi to other tissues. Certain Fungi also evoke antibody response of protective value.

30.2 Immunity to viruses

Immune responses towards viruses either function by blocking the infection or by getting rid of infected cells. Type I interferons participate in innate immunity while neutralizing antibodies take part in the adaptive immunity.

30.2.1 Innate immunity to viruses

As mentioned above type I interferons inhibit the infection while the killing of infected cells is mediated by Natural killer (NK) cells. Type I interferons prevent viral replication by triggering an “antiviral state”. NK cells are significant in early stages of the infection because in later stages adaptive immune responses progress. NK cells kill the infected cells and also identify infected cells where the virus has shut off class I MHC expression as an evading mechanism from CTLs. The importance of evading mechanism lies in the fact that the liberation of NK cells from a normal state of inhibition occurs only when MHC class I expression is turned out and not active.

30.2.2 Adaptive immunity to viruses

High affinity antibodies produce adaptive immune response against viral infections by preventing virus binding to the host cells, and by CTLs which bring out elimination of infected cells by killing them. CTLs like CD8+ T-cells identify viral peptides by class I MHC molecule. Further virus infected cell is phagocytosed by the antigen presenting cells such as dendritic cells. Dendritic cells process the viral antigen and present it to
 naïve CD8+ T-cells. Some of the CD8+ T-cells replicate massively to kill the infected cells. In some cases the virus persists in the infected individual without active replication leading to latent infection. CTLs may lead to tissue injury even if the infectious virus is not dangerous to the body.

30.2.3 How viruses deceive immune system?
Viruses have adopted numerous strategies for escaping the immune system.

- Viruses can change their surface antigens to avoid immune response. Generally surface glycoproteins containing T-cell epitopes undergo changes by point mutation or reassortment of genes especially in RNA viruses.
- Some viruses escape the immune surveillance by inhibiting the antigen presentation process and by inactivating the immunocompetent cells.
- Suppression of immunosuppressive molecules is also one of the strategies adopted by viruses.

30.3 Immunity to Parasites
Parasitic infections are mostly the infections caused by protozoa, ectoparasites and helminths. The parasitic infections are mostly chronic because of weak innate immunity. Besides weak immunity, parasites have a knack of evading host immune response very easily.

30.3.1 Innate immunity to parasites
Phagocytosis is the main innate immune response to parasitic infections but many parasites are able to escape the immune system. E.g. some helminths have thick teguments that enable them to evade the cytocidal mechanism of neutrophils and macrophages. Very few parasites have the potential to activate alternate pathway of complement system but the parasites that recoup from infected patients acquire resistance to complement mediated lysis.
30.3.2 Adaptive immunity to parasites
Parasites exhibit diverse adaptive immune response. Cell mediated immunity is the principal defense mechanism against parasitic infections. Stimulation of macrophages by Th1 cell derived cytokines is especially directed by cell mediated immunity to neutralize the antigens. Helminths are removed by IgE antibody and eosinophil-mediated killing as well as other leukocytes.

30.3.3 Immune evasion by Parasites
Parasites have varied mechanism to evade immune response due to some modifications.
- Parasites escape the immune system by preventing host immune response and by discounting their immunogenicity.
- They evade immune mechanism by bringing antigenic variation including changes in surface antigens by masking or shedding their antigens.
- One more way to evade immune response is by developing resistance to immune effector mechanisms.

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Parasite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigenic variation</td>
<td>Trypanosomes, Plasmodium</td>
</tr>
<tr>
<td>Prevention of host immune responses</td>
<td>Filaria, Trypanosomes</td>
</tr>
<tr>
<td>Shedding or masking antigen</td>
<td>Entamoeba</td>
</tr>
<tr>
<td>Acquired resistance to Complement</td>
<td>Schistosomes</td>
</tr>
</tbody>
</table>

30.4 Approach for vaccine development
Vaccination is an effective strategy for restraining infections. Remarkably potent vaccines are those that are successful in provoking high-affinity antibodies and memory cells. Most of the vaccines developed, function by inducing humoral immune response in the host.

30.4.1 Attenuated and Inactivated Bacterial and viral vaccines
Vaccines containing intact nonpathogenic microbes are made after attenuating the virus or by killing the microbes taking care of their immunogenicity. Attenuated viral vaccines prove beneficial because they evoke effective innate and adaptive immune responses. Live attenuated bacterial vaccines used nowadays offer protection but for small duration
while live attenuated viral vaccines elicit good response and long lasting immunity. Viral vaccines perform better because of their adaption in cell culture. However live viral vaccines always face a potent risk of reversion to virulence and hence safety is the main concern for such viruses. To minimize such risks inactivated vaccines are used such as influenza vaccine.

30.4.2 Purified Antigen (Subunit) Vaccines

Subunit vaccines are those that contain a purified antigen and also needs to be given along with an immunogenic enhancer called an adjuvant. Construction of subunit vaccine involves isolation of a specific protein from a virus or bacteria before administration. Diphtheria and tetanus are the best examples of subunit vaccines.

30.4.3 Synthetic antigen vaccines

This concept involves identification of an epitope or an antigen and designing it in the laboratory to be used in future as a vaccine.

30.4.4 Live viral vaccines involving recombinant viruses

Recombinant viruses involve the insertion of genes that encode an antigen into a noncytopathic virus, which provide immunity following its introduction to a susceptible host. They offer protection by eliciting both innate and adaptive immune response. However in some cases safety is the issue.

30.4.5 DNA vaccines

This founds the basis of most fundamental work being done in current times. DNA vaccine strategy involves inoculation of a plasmid containing complementary DNA encoding a protein antigen. DNA vaccines elicit both humoral and cell mediated response even without any adjuvant administration but their effectiveness needs more experimentation and verification.

30.4.6 Adjuvants

Adjuvants are the immunogenic substances that do not provide immunity by themselves but enhance the immunogenicity of the vaccines to which they are administered with.
30.4.7 Passive immunization

Passive immunization is another way of providing protective immunity. This can be done by transfer of specific antibodies and are useful in cases like snake bite. Passive immunity does not offer long lasting memory because it is short lived and does not generate memory.

<table>
<thead>
<tr>
<th>Type of vaccine</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live attenuated or killed bacteria</td>
<td>Bacillus Calmette-Guerin, Cholera</td>
</tr>
<tr>
<td>Viral vectors</td>
<td>Clinical trials of HIV antigens in Canarypox vector</td>
</tr>
<tr>
<td>Live attenuated viruses</td>
<td>Polio, rabies</td>
</tr>
<tr>
<td>Subunit vaccines</td>
<td>Tetanus toxoid, diphtheria toxoid</td>
</tr>
<tr>
<td>Conjugate vaccines</td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>Synthetic vaccines</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>DNA vaccines</td>
<td>Clinical trials ongoing for several infections</td>
</tr>
</tbody>
</table>
Lecture 31: Transplant immunology (Part I)

Transplantation is a method of treating the patient with malfunctioned organ or tissue with the healthy one. The organ to be taken is called graft from a healthy individual referred as donor. The individual who receives the graft is called recipient. The transplantation is called orthotropic if the graft is used for an identical anatomical position and heterotropic if used in a different anatomical location. The blood from one individual can be transferred to another individual of same blood group and the process is called as transfusion. The method of transplantation can turn into rejection if the graft belongs to a genetically different individual. The phenomenon of rejection is a large and one of the challenging areas of research in the field of immunology. The immunology behind a tissue or cell rejection is due to the adaptive immune response. One major concept to remember here is an inbred strain of animal is genetically identical because of the homozygous nature of all the genes except the sex chromosome.

A graft transplanted from one part of body to other of a same individual is called autologous graft.

A graft transplanted from one individual to a genetically identical individual is called syngeneic graft.

A graft transplanted from one individual to a genetically different individual is called allogeneic graft (allograft).

A graft transplanted between individuals of two different species is called xenogeneic graft (xenograft).

The substances recognized as foreign by the host immune system in an allograft are called alloantigens and the lymphocytes and antibody against those are called alloreactive. Similarly, for xenograft the substances are called xenoantigens and counteracting immunity is called xenoreactive.
31.1 Immunity to allograft

Polymorphic genes called histocompatibility genes are responsible for the recognition of foreign transplant cells, and are very diverse among the individuals of same species. Some of the basic rules of transplantation are as follows

- Cells and organ transplanted between genetically identical individuals are not rejected.
- Cells and organ transplanted between two genetically non identical or different individuals are always rejected.
- The offspring of two different inbred animals usually do not reject the organ or tissue from either of the parents.
- The parents of an offspring belonging to two different inbred strains usually reject the graft taken from the offspring.

![Figure 31.1 Genetics of graft rejection in mice:](image-url)
The molecules responsible for rejection of transplants are well known to be major histocompatibility complex (MHC). The alloantigen from a foreign donor is presented to the T cell by MHC molecules. The alloantigens are presented by typically two ways, direct and indirect.

In **direct presentation**, MHC molecules from the donor is directly presented to host T cells to elicit the cell mediated immune response without the involvement of host antigen presenting cells or MHC molecule.

In **indirect presentation**, the alloantigens are captured and processed by host antigen presenting cells and presented to T cells to elicit the immune response.

![Figure 31.2 Direct and indirect recognition of allogeneic antigens:](image)

Direct alloantigen recognition

- Alloantigen displayed by MHC in graft
- Allogeneic MHC in graft
- Alloreactive T cell

Indirect alloantigen recognition

- Alloantigen MHC in graft
- Presentation of allogeneic MHC by antigen presenting cells
- Peptide from allogeneic MHC
- Alloreactive T cell
31.2 Activation of alloreactive lymphocytes

The alloantigens stimulate the B and T cell response similar to that of a protein antigen. Alloantigens can be recognized by T cells either by direct or indirect way and trigger a T cell immune response. Naïve lymphocyte migrates to lymph node after sensitization and differentiates into an effector cells that migrate back to the graft in order to induce rejection. Usually many of the T lymphocytes responding to alloantigens are memory T cells. In addition to alloantigen recognition by T lymphocyte, costimulatory molecules such as B7-1 also activate proliferation of lymphocytes. Similar to the processing of a protein antigen, the alloantigens that are processed by MHC class I can activate the CD8+ T cell response and those processed by MHC class II can activate CD4+ specific immune response.
Lecture 32: Transplant immunology (Part II)

32.1 Inhibition of allograft rejection

The rejection of the allograft in a recipient having fully functional immune system is inevitable. It has been a challenging task to prevent the rejection of allograft in a recipient. An important area of research in the field of immunology is to avoid the rejection of an allograft and allow it to survive without any immune reactivity.

Many strategies have been adopted to avoid the rejection

I. Immunosuppressive drugs can be used to prevent graft rejection. Cyclosporine can inhibit the transcription of genes responsible for T cell activation and IL-2 secretion. Rapamycin inhibits the growth factor responsible for T cell activation.

II. Some antimetabolites that have the potential to kill the activating T lymphocyte can be used to prevent the alloreactive response.

III. Inhibition of costimulatory molecule is another strategy to prevent the rejection of the allograft.

IV. Anti-inflammatory drugs such as corticosteroids are frequently used to create an immunosuppressive condition in an individual and allow the survival of graft.

32.2 Xenogeneic transplantation

Transplantation of an organ from a different species has been a great interest for the scientist working on different human disease models. Transplantation of organs from pigs to human is an interesting outcome of the transplantation immunology. Pigs are preferred species for transplantation in human as compared to other species because of the anatomical compatibilities. However, the presence of natural antibodies such as IgM to the xenograft causes a hyperacute reaction in the recipients. The natural antibodies are mostly directed towards the carbohydrate present over the cell surface. Xenograft can also be rejected by T cell mediated immune responses similar to what is observed for the allograft.
32.3 Blood transfusion

Blood transfusion is also a kind of transplantation in which blood is transferred from one individual to other having same blood group. The concept of blood grouping was put forth by Karl Landsteiner, who divided the blood into A, B, and O based on the presence of specific antigens. A, B, and O are the carbohydrate moiety present over the surface of blood cells. An individual having blood group A contains type “A” antigen and antibody against type B, so it will show rejection against blood group B. Same is true for blood group B antigen, which contains antibody against A. The blood group AB contains antigen against both A and B and do not produce antibody against any antigen hence the person of blood group AB can take blood from any individual hence called as universal recipient. The blood group O contains no antigen over its surface and produces antibody against both A and B hence can give the blood to any blood group individual and is called as universal donor. Individual having blood group AB can give blood to only AB individuals while blood group O individuals can only accept blood from an O group individual.

Table 32.1 Blood group antigens:

<table>
<thead>
<tr>
<th>Antigens on RBC</th>
<th>Blood group A</th>
<th>Blood group B</th>
<th>Blood group AB</th>
<th>Blood group O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Against</td>
<td>A</td>
<td>B</td>
<td>Both A and B</td>
<td>None</td>
</tr>
<tr>
<td>Accept blood from</td>
<td>A and O</td>
<td>B and O</td>
<td>A, B, AB and O</td>
<td>Only O</td>
</tr>
<tr>
<td>Donate blood to</td>
<td>A</td>
<td>B</td>
<td>AB</td>
<td>A, B, AB and O</td>
</tr>
</tbody>
</table>

32.3.1 Other blood group antigens

The ABO blood group may be modified by the enzymes involved in the modification of the surface glycoproteins. The enzyme glycosyltransferase plays an important role in the terminal carbohydrate addition in the blood group antigens. The modification in which a different enzyme fucosyltransferase incorporates a fucosyl group at any other terminal position of the blood group antigen, results in the formation of Lewis antigen. Lewis
antigen has a capacity to bind with E and P type selectin, making it a useful tool for immunologist.

Another important blood group antigen is called Rh factor, named after Rhesus monkey from which it was first identified. The person can be Rh+ or Rh- based on the presence or absence of Rh factor in the blood cells. The Rh- mother carrying an Rh+ child can be sensitized by the Rh+ factor circulating through the placenta in her blood. Since Rh factor will act as an antigen in mother’s body and she will produce an IgG antibody against Rh factor. Any subsequent pregnancy can lead to abortion because of the destruction of the blood cells by antibodies against Rh factor; such condition is called *erythroblastosis fetalis*.

### 32.4 Graft versus host diseases

Graft versus host disease (GVHD) occurs when a host is unable to reject the graft due to some form of immunosuppression. GVHD is usually caused by the antibody against MHC molecules of the host. GVHD is initiated by the grafted T cells that recognize the host alloantigens and mount an immune response in the form of effector T cell. The condition may be acute or chronic based on the severity of mounted immune response. Acute may be fatal while chronic GVHD leads to dysfunction of the affected organs. Natural killer cells, cytokines, and cytotoxic T lymphocytes are the major players of GVHD.
Lecture 33: Tumor immunology (part I)

33.1 Immune surveillance

The concept of immune surveillance was given by Macfarlane Burnet in 1950’s. According to his definition of Immune surveillance physiologic function of the immune system is to identify cancerous or precancerous cells and remove them from the body before they cause any harm.

General features of tumor immunity

- One of the most important features is that tumors elicit specific adaptive immune responses. This can be proved due to the presence of T lymphocytes, natural killer cells and macrophages in the surroundings of the tumor cells.
- Tumor immunity is not sufficient to stop the growth of tumors. This study pattern undoubtedly raises questions about the concept of Immune surveillance.
- Outside source can be used to stimulate immune system to prevent and destroy the tumor cells.
Figure 33.1 Schematic representation of tumor immunity:

Mice treated surgically for chemical induced carcinogen gets immune to tumor growth following the injection of same tumor cells. Similarly, transfer of CD8+ cells to a recipient mice having tumor transplant rejects the tumor growth. However transplantation of same into a syngeneic mouse turned into a tumor mass.
33.2 Tumor antigens

These are the antigens produced in tumor cells. Tumor antigens are classified based on how they express. Oncogenes and mutated tumor suppressor genes are identified as tumor antigens.

- **Tumor specific antigens** – are the ones that do not express on normal cells but only on tumor cells.
- **Tumor associated antigens** - are the ones that express on tumor as well as normal cells.
- **Antigens of oncogenic viruses** - Oncogenic viruses such as Epstein – Barr virus, human papillomavirus and papovaviruses are associated with certain types of cancers in humans and animals. The end products of these oncogenic viruses act as tumor antigens and induce immunogenic response. This concept of immune response against virus induced cancers has paved way for the synthesis of vaccines against the tumor causing viruses.
- **Oncofoetal antigens** - These are the proteins that are highly expressed in cancer cells as well as in foetus undergoing development but are absent in the adult cell.
- **Tissue specific differentiation antigens** - These are tissue specific molecules expressed only on normal cells of origin and are not expressed on cells from other tissues.

33.3 Immune response to tumors

Tumor Immune response mostly occurs in two forms either by innate immune response or by adaptive immune response.

33.3.1 Innate immune response to tumors

**Natural killer cells (NK cells)**

Around 15% of mammalian blood lymphocytes are composed of NK cells. NK cells can be activated by interferons from virus infected cells or by IL-12 from activated macrophages. NK cells are large, granular, and non-phagocytic cells that are derived from bone marrow. NK cells can kill certain tumor cell lines and are quite effective in eliminating the cells that diminish class I MHC expression. Studies also indicate that patients with deficiency of NK cells are more likely to suffer from EBV- associated
lymphomas. NK cells express CD56 and CD16 antigen receptors over their surface. Activation of NK cells by antigen antibody reaction through CD16 kills the target cells.

**Macrophages**

Macrophages can prevent the spread of cancer based on their activation state. Activated macrophages can kill transformed cells more efficiently than the normal cell. M1 cells especially treat the tumor cells like an infectious organism and produces cytokine tumor necrosis factor (TNF) to kill the tumor but M2 macrophages on the other hand are associated with tumor progression.

### 33.3.2 Adaptive immune response to tumors

**T-lymphocytes**

The basis of adaptive tumor immunity is to destroy tumor cells by CD8+ CTLs. Functioning of CD8+ cell requires cross presentation of the tumor antigen by the dendritic cells. Although CD8+ CTLs have a substantial role to play in killing the transformed clones but not much is known about the efficacy of CD4+ helper T-cells in tumor immunity.

**Antibodies**

These are known to kill tumors either by stimulating antibody-dependent cell mediated cytotoxicity or by the activation of complement system. Even though there is some immune response by antibodies in which NK cells mediate the destruction of tumor cells but antibody response towards tumors is not quite effective in most of the tumor cases.
Figure 33.2 Immune response to tumor:

- **T cells**
  - Interferon-γ and IL-2
- **Macrophages**
- **Tumor cells**
  - Interferon-γ
  - TNF-α and IL-12
- **NK cells**
Lecture 34: Tumor immunology (part II)

34.1 Evasion of immune response by tumors

Immune evasion by tumors can be divided into intrinsic or extrinsic mechanisms based on how these mechanisms are mediated.

34.1.1 Intrinsic mechanism of immune evasion by tumor cells

➢ Tumor cells are highly prone to mutation due to increased mitotic rate and hence the antigen expression may change at times and within a particular period tumor cells may lack or be deficit of the antigens that generate immune response.

➢ Immune system may not have access to the tumor cells because of antigen masking effect of glycocalyx molecules. Glycocalyx molecules help in hiding the tumor cells from the immune system by getting expressed in higher amounts in tumor cells.

➢ Tumor cells may prevent the immune response by associating with molecules that destroy the immune system.

➢ Some of the released products from the tumor cells may prevent the immune response. e.g TGF-β inhibits lymphocytes and macrophages.

➢ Tumor cells do not express class II MHC molecules so they may not elicit effective T cell immune response.

34.1.2 Extrinsic cellular suppression of anti-tumor immunity

➢ M2 macrophages are associated with progression of tumor growth and thus these macrophages may suppress the T-cell response to the tumor cells.

➢ T-Cell immunity can be lowered by the presence of regulatory T cells.

➢ Myeloid – derived suppressor cells (MDSCs) are detrimental to T cell response and may recruit regulatory cells to suppress the immune response.

34.2 Immunotherapy for tumors

Immunotherapy has a potential role in transformed cells because it is less harmful than other known treatments for cancer (chemotherapy, radiotherapy and surgery). Some of the roles that immunotherapy can play are mentioned below

➢ Treatment of patient with cytokines and costimulators may help to increase the immunity against tumor.

➢ Tumor antigens can be used as a vaccine for the infected individuals.
➢ Tumor immunity can be augmented by blocking the inhibitory pathways.
➢ Stimulation of immune response can be done by local administration of polyclonal activators of lymphocytes.
➢ Another way of inducing immune response is to transfer antibodies and other immune effectors passively.
➢ Adoptive cellular immunotherapy can be approached which involves transfer of cultured immune cells in the host body.
➢ In some patients transfer of hematopoietic stem cell transplants combined with alloreactive T cells help in elimination of tumor.
➢ Monoclonal antibodies which are tumor specific may prove useful in some cases.
Figure 34.1 Adoptive transfer of antibodies in immunotherapy for cancer: