

transplant	graft
the person who gives the graft	donor
the person who receives the graft	recipient (host)
genetically identical animals (and graft)	singenic animals (singenic graft)
Transplantation within the same species	allogeneic or allo-transplantation
transplantation among different species	xenogen or xeno-transplantation
antigens that are targeted at rejection	alloantigens and xenoantigens
antibodies and T lymphocytes that react against these antigens	alloreactive and xenoreactive

Immunology of Transplantation

What is Transplantation?

- Replacement of non-functioning organs/tissues with healthy ones.
- Involves taking cells, tissues, or organs (graft) from a donor and placing them into a recipient (host).

Types of Transplantation

- Orthotopic Transplantation – Graft placed in its normal anatomical location.
- Heterotopic Transplantation – Graft placed in a different location.

Transfusion vs. Transplantation

- Transfusion: Transfer of blood cells or plasma between individuals.
- Transplantation: Transfer of organs, tissues, or cells.

The Challenge of Transplant Rejection

- Transplantation to a genetically non-identical individual leads to rejection.
- Caused by an adaptive immune response.
- Major barrier to successful transplantation.

Discovery of Transplant Rejection

- First observed in burn victims receiving skin grafts from unrelated donors.
- Within 1-2 weeks, transplanted skin underwent necrosis and detached.
- Led to experiments by Peter Medawar and others using animal models.

Types of Transplants

- Autograft: Transplant within the same individual (e.g., skin grafts, coronary bypass).
- Isograft: Between genetically identical individuals (e.g., identical twins).
- **Allograft**: Between genetically different individuals of the same species (most common).
- Xenograft: Between different species (e.g., pig-to-human transplants).

Risk of Rejection by Transplant Type

Type of Transplant	Donor and Recipient Relationship	Risk of Rejection	Immunosuppression Required?
Autograft	Same individual	None	No
Isograft	Identical twins	Very low	No
Allograft	Genetically different individuals of the same species	High	Yes
Xenograft	Different species	Very high	Yes (but still challenging)

Immune Responses to Allografts

Alloantigens trigger both cellular & humoral immune responses.

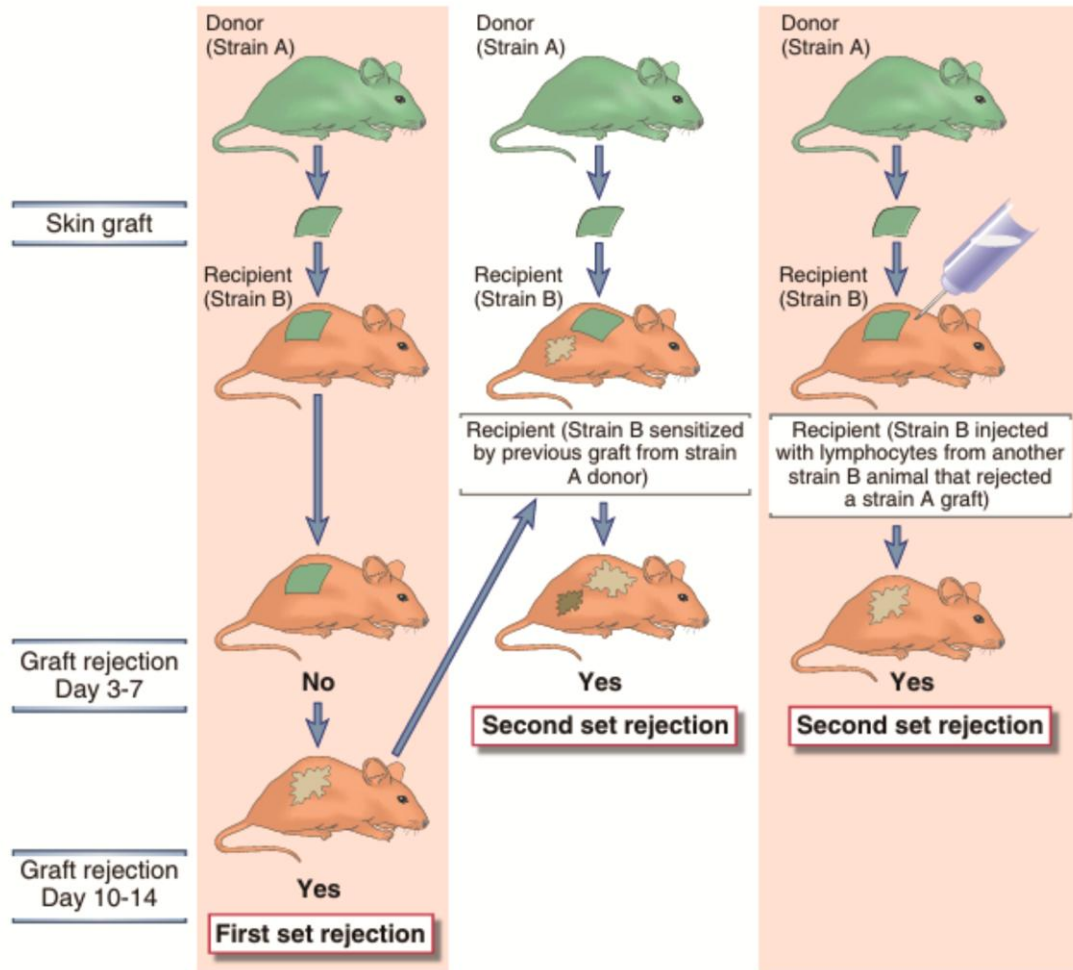
Key factors:

Histocompatibility genes determine recognition of transplanted cells.

Basic transplantation rules (from animal models):

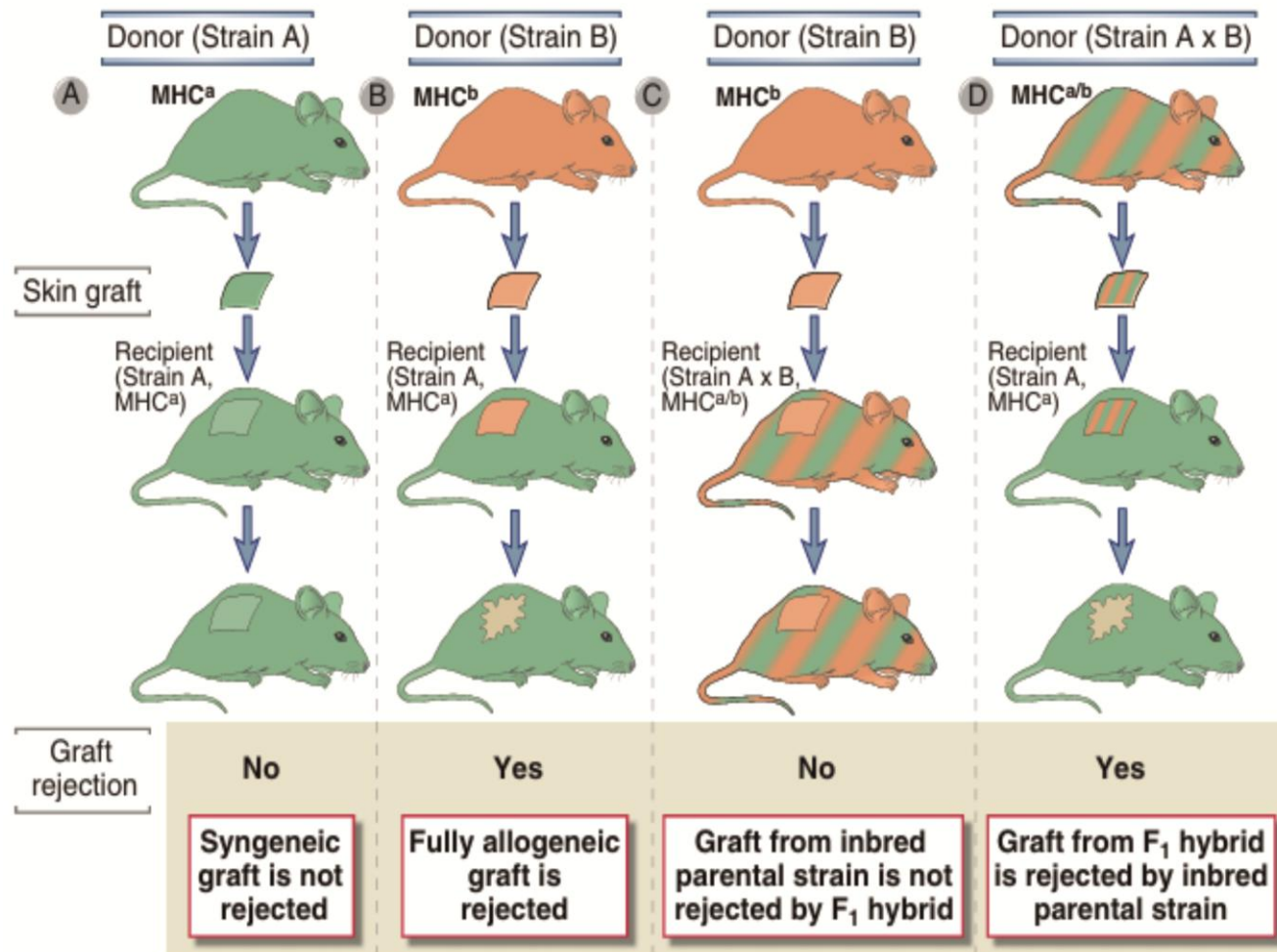
- Identical twins/inbred strains: No rejection
- Genetically different individuals: Rejection
- Offspring ($A \times B$)F1: Accepts grafts from A or B but rejected by parents

Immune Responses to Allografts



- First and second set allograft rejection
- Graft rejection demonstrates adaptive immune features: memory, lymphocyte mediation, and specificity
- Transferring lymphocytes from a sensitized strain B mouse to another strain B mouse also causes second-set rejection, proving lymphocyte involvement.

MHC molecules are the primary cause of graft rejection.



- Graft rejection is determined by MHC genetics.
- Grafts from parent A or B are accepted by (A × B)F₁ offspring (C), but grafts from the offspring are rejected by either parent (D).
- This occurs because grafts are rejected only if they express an MHC type not present in the recipient.
- **MHC products drive rejection**

Role of MHC in Rejection

- MHC molecules are the primary cause of graft rejection.

MHC (HLA) is:

- Highly polymorphic (varies among individuals).
- Codominantly expressed (inherited from both parents).

MHC molecules

Three genes for α chain of MHC molecule class I on each chromosome:

$3 \times 2 =$ maximum 6 different products of class I on each cell

MHC I class- HLA-A;HLA-B;HLA-C

Three genes for α chain and three or four genes for β chain (which can be combined) of MHC class II on each chromosome.

MHC II class- HLA-DP; HLA-DR; HLA-DQ

maximum 16 different MHC class II molecules

MHC molecules

Question:

Why would one person's T lymphocytes recognize another person's MHC molecules?

fact (paradox):

The reaction to foreign MHC is one of the strongest immune reactions

Explanation :

Allogeneic MHC molecules displaying peptides of an allogeneic cell can look like its own MHC with a foreign peptide – **cross reaction**

Immune Response to Transplants

- MHC (HLA) molecules present self & non-self antigens.
- MHC mismatch → Higher risk of rejection.
- HLA matching is crucial for kidney, bone marrow, and heart transplants

Mechanisms of Alloreognition

Direct Alloreognition:

- Recipient T cells recognize intact donor MHC.
- Leads to acute rejection (**fast, strong response**).

Indirect Alloreognition:

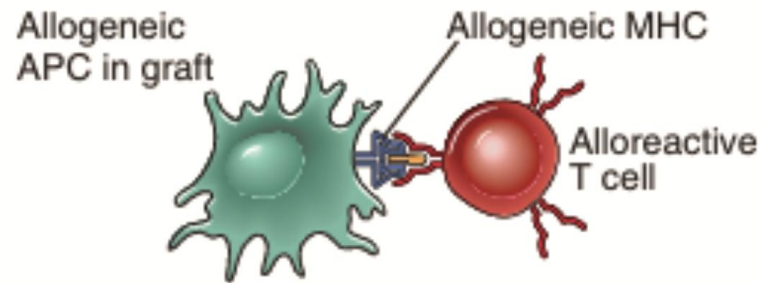
- Donor MHC fragments presented by recipient APCs.
- Leads to chronic rejection (**slow, fibrosis**).

Mechanisms of Allorecognition

Mechanism	How it Works	Immune Cells Involved	Type of Rejection
Direct Allorecognition	Recipient T cells recognize intact donor MHC molecules	CD8+ cytotoxic T cells, CD4+ helper T cells	Acute rejection (fast, strong immune response)
Indirect Allorecognition	Recipient APCs process donor MHC fragments and present them to T cells	CD4+ T helper cells, B cells (antibody response)	Chronic rejection (slow, leads to fibrosis)

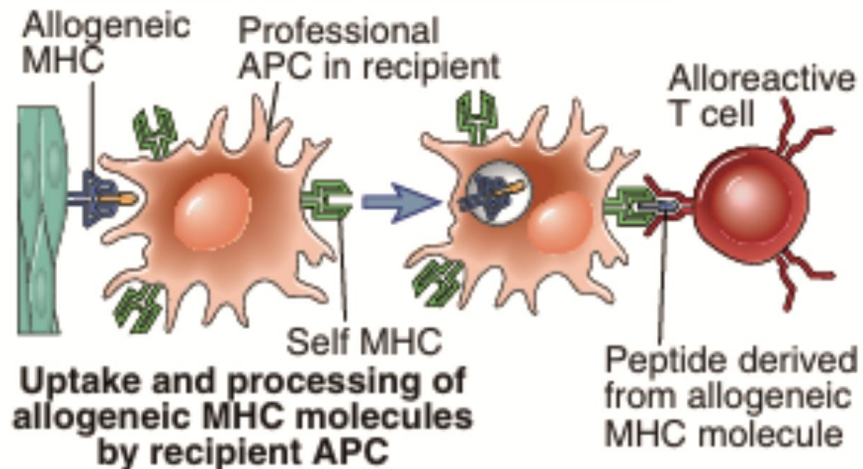
Mechanisms of Allorecognition

A Direct alloantigen recognition



T cell recognizes unprocessed allogeneic MHC molecule on graft APC

B Indirect alloantigen presentation

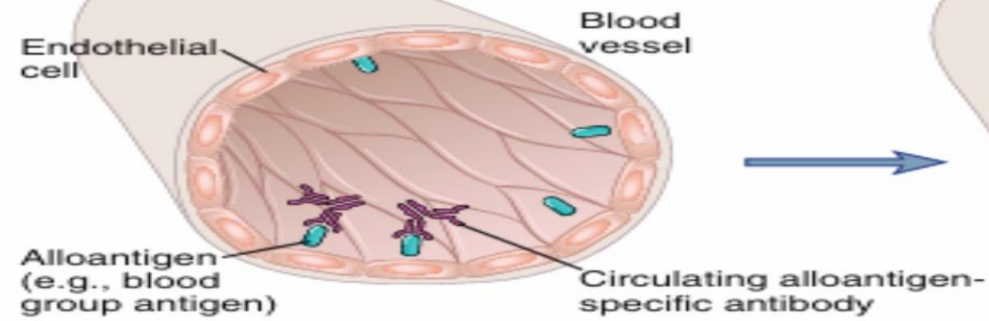


Presentation of processed peptide of allogeneic MHC molecule bound to self MHC molecule

Types of Transplant Rejection

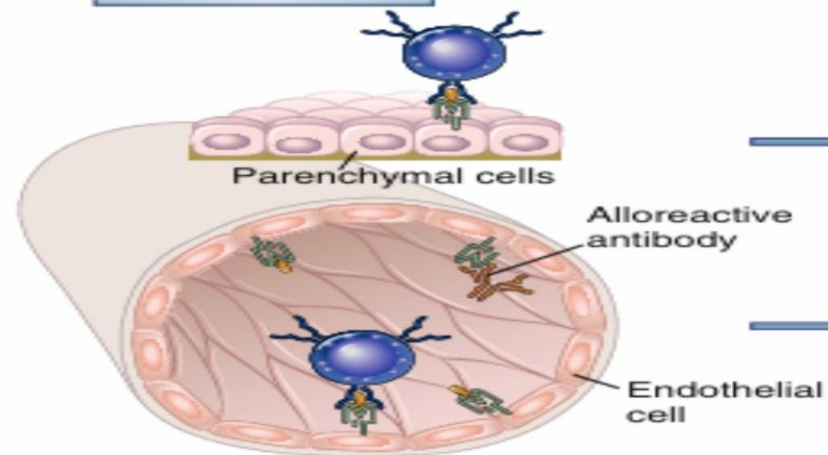
Type	Onset	Cause	Mechanism	Outcome
Hyperacute	Minutes to hours	Preformed antibodies (ABO, HLA mismatch)	Complement activation, thrombosis	Irreversible, graft must be removed
Acute	Days to weeks	T cells & antibodies attack donor antigens	Inflammation, endothelial damage	Can be reversed with immunosuppressants
Chronic	Months to years	Persistent low-grade immune response	Fibrosis, vascular damage	Irreversible, may require re-transplantation

A Hyperacute rejection



Complement activation, endothelial damage, inflammation and thrombosis

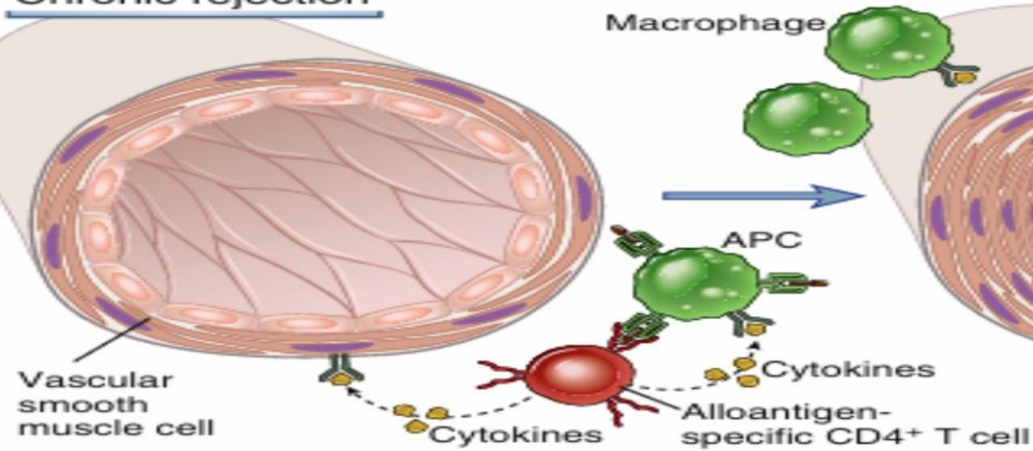
B Acute rejection



Parenchymal cell damage, interstitial inflammation

Endothelialitis

C Chronic rejection



Chronic inflammatory reaction in vessel wall, intimal smooth muscle cell proliferation, vessel occlusion

Donor and recipient compatibility tests

- **ABO Blood Group Compatibility**
- **HLA Typing**

To determine the HLA alleles of the donor and recipient.

HLA-A, HLA-B, HLA-C; HLA-DR, HLA-DQ, HLA-DP.

- **Crossmatching**

To detect pre-formed antibodies in the recipient that could react with the donor's cells.

Immunosuppressive Therapy

- Calcineurin Inhibitors: Block IL-2, prevent T-cell activation (Cyclosporine, Tacrolimus).
- Corticosteroids: Reduce inflammation (Prednisone, Methylprednisolone).
- Anti-Proliferative Agents: Inhibit lymphocyte proliferation (Mycophenolate mofetil, Azathioprine).
- Monoclonal & Polyclonal Antibodies: Target T/B cells (Basiliximab, ATG, Rituximab).

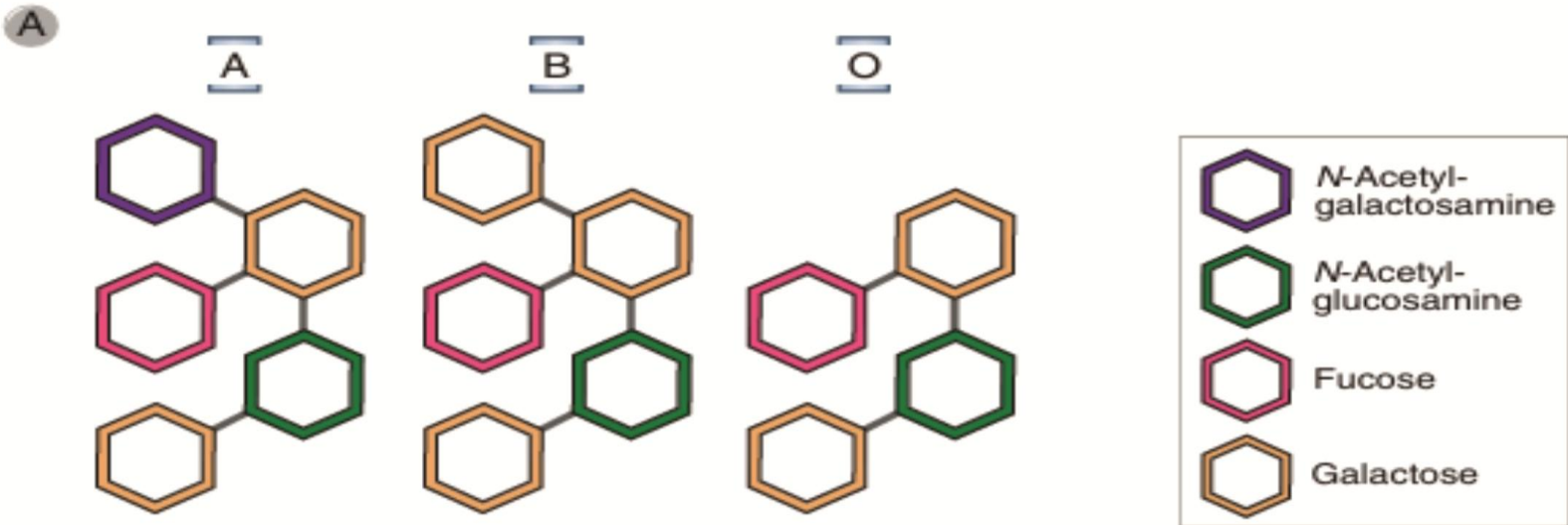
Future of Transplantation

- Tolerance Induction: Train the immune system to accept the graft.
- Chimerism: Mixed donor-recipient immune cells → Reduced rejection.
- Gene Therapy: Modify donor/recipient cells to prevent rejection.
- Cellular Immunotherapy: Tregs, dendritic cells, and CAR-T to suppress immune attacks.

Conclusion

- Transplant success depends on immune compatibility.
- Immunosuppression is essential but has side effects.
- New strategies like gene therapy & chimerism aim to eliminate rejection.
- The future of transplantation focuses on tolerance & personalized therapies.

Transplantation of blood cells (transfusion)



B

	Group A	Group B	Group AB	Group O
Red blood cell type	Type A 	Type B 	Type AB 	Type O
Antibodies present	Anti-B 	Anti-A 	None	Anti-A and Anti-B
Antigens present	A antigen 	B antigen 	A and B antigen 	None

- ABO antigens are carbohydrates on membrane glycoproteins or glycosphingolipids, expressed on erythrocytes, endothelial cells and many other cells
- Type O: Universal donor (can donate to any blood type).
- Type AB: Universal recipient (can receive from any blood type).
- Type A: Can donate to A or AB.
- Type B: Can donate to B or AB.

Hematopoietic STEM Cell Transplantation

- Also known as bone marrow transplantation.

Sources of stem cells:

- Bone marrow aspiration.
- Mobilized stem cells from peripheral blood (via colony-stimulating factors).

Pre-transplant preparation:

Recipient's bone marrow is depleted to create space for new stem cells.

Post-transplant:

Stem cells repopulate bone marrow and generate all blood cell types.

Clinical Uses of Stem Cell Transplantation

- **Main Applications:**
 - **Leukemia treatment:** Grafted cells help destroy residual cancer cells.
 - **Chemotherapy recovery:** Bone marrow transplantation rescues the patient from side effects.
 - **Genetic blood disorders:** Used to treat inherited diseases affecting blood cells, such as:
 - ADA deficiency
 - X-linked SCID
 - Beta-thalassemia major & sickle cell disease

Graft-Versus-Host Disease (GVHD)

Cause: Grafted **mature T cells** attack host alloantigens.

Occurs in:

- **Bone marrow transplants** (when the host is immunocompromised).
- **Solid organ transplants** with high T cell content (e.g., small bowel, lung, liver).

Major limitation of bone marrow transplantation.

Immunity to Tumors

Overview of Tumor Immunology

Cancer is a leading cause of morbidity & mortality worldwide.

- **Characteristics of Malignant Tumors:**

Uncontrolled proliferation & invasion of tissues.

Resistance to apoptosis.

Ability to metastasize.

- **Immune Surveillance Hypothesis (Burnet, 1950s):**

The immune system detects and eliminates transformed cells before they develop into tumors.

- **Evidence:** Higher tumor rates in immunocompromised individuals.

- **Goal of Tumor Immunology:**

Understand immune recognition of tumors and develop immunotherapies.

General Features of Tumor Immunity

Immune responses to tumors show adaptive immunity traits:

- **Specificity & memory** – T cells can recognize and respond to tumor antigens.
- **Tumor-infiltrating immune cells** (T cells, NK cells, macrophages) correlate with better prognosis.

Why does the immune system fail to stop tumor growth?

- Tumor cells resemble normal cells → **weak immune response**.
- **Rapid tumor growth & immune evasion** overwhelm the immune system.
- Some tumors **actively suppress immune responses**.

Tumor Antigens & Their Classification

- **Tumor-specific antigens (TSA):** Found only on tumor cells.
- **Tumor-associated antigens (TAA):** Found on tumor & normal cells but abnormally expressed in cancer.

Clinical relevance:

- Identifying tumor antigens helps in diagnosis & immunotherapy development.
- Used in tumor vaccines & antibody-based therapies.

Identification of Tumor Antigens

- **CD8+ T cell recognition of tumor antigens:**

Tumor-reactive CTLs from cancer patients used to identify tumor-derived peptides.

- **Methods for tumor antigen discovery:**

cDNA library screening – Identifies genes encoding tumor-specific peptides.

SEREX (Serologic Analysis of Recombinant cDNA Expression):

Detects **antibody responses** to tumor proteins.

- **Example:** Melanoma antigens identified using T cells from patient tumors.

Tumor Antigens – Products of Mutated Genes

Oncogenes & Tumor Suppressor Genes:

- Mutations in **Ras, Bcr/Abl, p53** produce abnormal proteins.
- Recognized as **tumor antigens** by immune cells.

Mechanism:

- Mutated proteins enter **MHC class I & class II pathways** → stimulate **T cell responses**.

Clinical Insight:

- **CD8+ & CD4+ T cells** can target these mutated proteins.
- **Potential targets** for immunotherapy (e.g., Ras & p53 vaccines).

Tumor Antigens – Abnormally Expressed Proteins

Tumor cells overexpress normal proteins → trigger immune response.

Examples:

- **Tyrosinase** – Involved in melanin production (expressed in melanoma).
- **Cancer/Testis Antigens (MAGE proteins):** Found in tumors & normal testes but not other somatic tissues.

Clinical Relevance:

- Targets for tumor vaccines (e.g., **tyrosinase-based melanoma vaccine**).

Oncogenic Virus-Derived Tumor Antigens

Viral proteins act as tumor antigens → elicit immune response.

Examples:

- **EBV (Epstein-Barr Virus)** → B cell lymphoma, nasopharyngeal carcinoma.
- **HPV (Human Papillomavirus)** → Cervical cancer.
- **HTLV-1 (Human T-cell Leukemia Virus)** → Adult T cell leukemia.

Vaccination Strategies:

- **HPV vaccine** prevents cervical cancer.
- **Hepatitis B vaccine** reduces liver cancer risk.

Oncofetal & Glycoprotein Tumor Markers

Oncofetal Antigens:

- Expressed in fetal development & tumors but not normal adult tissues.

Examples:

- **CEA (Carcinoembryonic Antigen):** Colorectal, pancreatic, breast cancer.
- **AFP (Alpha-Fetoprotein):** Liver & germ cell tumors.

Altered Glycolipids/Glycoproteins:

- Overexpressed in cancer, used as **diagnostic markers & therapy targets**.

Examples:

- **MUC-1 (Breast cancer).**
- **CA-125 (Ovarian cancer).**
- **Gangliosides (Neuroblastomas, melanomas).**

Immune Responses to Tumors

Both innate & adaptive immunity contribute to tumor defense.

Key immune effectors:

- **Innate immunity:** NK cells & macrophages.
- **Adaptive immunity:** CD8⁺ T cells (CTLs) & antibodies.

Enhancing tumor-specific immune responses.

Overcoming tumor immune evasion mechanisms.

NK Cells in Tumor Immunology

- Discovered in 1975, NK cells are key players in immune surveillance and anti-tumor immunity.
- They recognize and kill cells with missing or incomplete MHC class I expression (common in tumors).
- Activating (KAR) and inhibitory (KIR) receptors regulate NK cell activity.
- Antibody Therapies: Targeting KIR receptors to enhance NK cell activity.
- NK Cell Infusion: Expanding and reinfusing NK cells into patients.
- CAR-NK Cells: Genetically engineered NK cells with chimeric antigen receptors.

LAK Cells in Tumor Immunology

- LAK cells are a mixture of NK and NKT cells activated by IL-2 and anti-CD3 antibodies.
- They exhibit strong cytotoxic activity against tumor cells in the lab.
- Limited efficacy as monotherapy in clinical settings.
- Low Clinical Efficacy: Limited anti-tumor activity in patients.
- Need for Combination Therapies: Better outcomes when combined with other treatments.
- Complex Production: Requires IL-2 and anti-CD3 antibody stimulation.

CIK Cells in Tumor Immunology

- CIK cells share characteristics of NK and T cells.
- They are expanded using $\text{IFN}\gamma$, anti-CD3 antibodies, and IL-2.
- Exhibit strong nonspecific cytotoxicity, especially against hematological malignancies.
- Hematological Cancers: Promising results in treating leukemias and lymphomas.
- Solid Tumors: Limited efficacy but potential in combination therapies.
- Ongoing Research: Improving CIK cell expansion and targeting.

NK, LAK, and CIK Cells: Antigen-Independent Tumor Killers

- NK, LAK, and CIK cells are immune cells with antigen-independent cytotoxic activity.
- They can directly destroy tumor cells without prior recognition of specific antigens.
- These cells are powerful tools in cancer immunotherapy.

Macrophages: Key Players in Tumor Immunology

- Discovered by Ilya Mechnikov in 1883, macrophages are innate immune cells.
- They play a dual role in tumor progression, depending on their activation state.
- Crucial in both anti-tumor immunity and tumor promotion.

M1 vs. M2 Macrophages in Tumor Progression

M1 Macrophages:

- Classically activated, pro-inflammatory, and anti-tumor.
- Dominate in early tumor stages, stimulating immune responses.
- Anti-tumor → Secrete **TNF, ROS, NO** → Tumor killing.

M2 Macrophages:

- Alternatively activated, pro-tumor, and immunosuppressive.
- Promote tissue remodeling, angiogenesis, and tumor growth in later stages.
- Pro-tumor → Secrete **VEGF, TGF- β** → Angiogenesis, tumor progression.

Adaptive Immunity – CD8+ T Cells & Antibodies

CD8+ Cytotoxic T Lymphocytes (CTLs):

- Recognize tumor antigens via MHC class I.
- Kill tumors via perforin/granzyme & Fas-FasL pathways.
- Cross-priming by dendritic cells enhances tumor recognition.

CD4+ Helper T Cells:

- Provide cytokines (IFN- γ , TNF) to enhance CTL & macrophage responses.

Antibodies:

- Target tumor antigens → Activate complement & antibody-dependent cytotoxicity (ADCC) via NK cells.
- Example: Anti-EBV antibodies in EBV-associated lymphomas.

Tumor Immune Evasion Mechanisms

Intrinsic Tumor Evasion:

- **Antigen loss variants:** Tumors stop expressing immunogenic antigens.
- **MHC downregulation:** Prevents CTL recognition.
- **Antigen masking:** Glycoproteins hide tumor antigens.
- **Checkpoint inhibition:** Tumors exploit **CTLA-4 & PD-1/PD-L1** to suppress T cells.
- **Immunosuppressive cytokines:** Tumors release **TGF- β** to inhibit T cells & macrophages.

Extrinsic Evasion (Cellular Suppression):

- **Tumor-associated macrophages (M2):** Promote tumor angiogenesis.
- **Regulatory T cells (Tregs):** Suppress anti-tumor T cell responses.
- **Myeloid-Derived Suppressor Cells (MDSCs):** Block CTL activation.

Cancer Immunotherapy – Boosting Immune Responses

Active Immunotherapy (Stimulating Host Response):

- **Tumor vaccines:** Use tumor antigens or antigen-loaded dendritic cells.
- **Checkpoint blockade: Anti-CTLA-4 & Anti-PD-1 therapies** remove immune suppression.
- **Cytokine therapy:** IL-2, IFN- α to enhance T cell & NK cell function.

Passive Immunotherapy (Transferring Immune Effectors):

- **Monoclonal antibodies:** Target tumor antigens (e.g., **Rituximab** for B-cell lymphoma).
- **Adoptive T Cell Therapy:**
 - LAK cells (IL-2–activated NK cells).
 - Tumor-Infiltrating Lymphocytes (TILs).
 - CAR-T therapy (genetically engineered T cells).

Immune System's Role in Promoting Tumors

Chronic Inflammation Increases Cancer Risk:

- **Infection-driven cancers:**
 - **Helicobacter pylori** → Gastric cancer.
 - **Hepatitis B & C viruses** → Liver cancer.

Inflammatory diseases & cancer:

- **Barrett's esophagus** → Esophageal cancer.
- **Crohn's disease** → Colorectal cancer.

Immune System's Role in Promoting Tumors

How Inflammation Promotes Tumors:

- **M2 Macrophages** → Secrete **VEGF & TGF- β** → Angiogenesis & tissue remodeling.
- **Neutrophils & Mast Cells** → Release **DNA-damaging free radicals** → Mutations in oncogenes.
- **NF- κ B Activation** → Drives **tumor survival & proliferation**.
- **B cells secrete factors** that enhance tumor growth.

Potential Target for Therapy:

- **Anti-inflammatory drugs** (e.g., COX-2 inhibitors, TNF blockers) may help control cancer-promoting inflammation.