BASIC IMMUNOLOGY and ORGAN TRANSPLANTATION

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Host defense against infection

is 1-nonspecific or

2-specific (immune system)
NONSPECIFIC

- Starts in the blood by
  - 1) leucocytes phagocytosis and
  - 2) activation of the complement system both classic and alternative
• **Phagocytosis** occurs mainly by leucocytes, which is considered to be the most important cell for phagocytosis.

• It also occurs by macrophages, but leucocytes are more efficient and more in number.
• **In tissues**, macrophages engulf and phagocytose the bacteria.

• The secretion of monokines and other mediators of inflammation (platelet activating factor and leukotrienes), complement activation *(classic by IgM and IgG) or alternative by endotoxin of Gm-ve* …

• All these will lead to recruitment of PMNL
• **PMNL** appear early and the bone marrow responds to **IL3** (colony stimulating factor) by releasing more PMNL.

• Half life time is **12 hours** in the circulation and **24 hours** in the tissues. Because of quickness of release of PMNL from the bone marrow, some are still premature and have some bands.
Two types of Phagocytes can be differentiated

1. *circulating* = granulocytes and monocytes
2. *fixed* = macrophages
PMNL have 3 functions

1) **chemotaxis** = migration by many chemotactic factors
   the most important is C5A

2) **Phagocytosis** = occurs by adherence then opsonisation.
   the most potent opsonins are C3B
   *IgM is the best immunoglobulin to fix complement*

3) **intracellular killing**
• PMNL have receptors for IgGs, C3B, ..
SPECIFIC FUNCTION

• HUMORAL (B CELL)

• CELLULAR (T CELL)
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<tr>
<th>AFFERENT</th>
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<tbody>
<tr>
<td>Antigen presenting cell</td>
<td><strong>CD4</strong></td>
<td>-CD8</td>
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<td>-B Lymphocytes</td>
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Humoral B Lymphocytes

- **B lymphocytes** will originate and grow in the Bone marrow. IL7 for early development.
- They produce Immunoglobulins in response to antigens.
- The B cells when activated are called Plasma cells (have more condensed Golgi apparatus).
• The immunoglobulins (IgG, IgM ...) released by the B cells act as receptors for the B cells and link them to the Antigen.

• The Antigen then becomes opsonised by the B cells.
• The Antibody bound surfaces also activates a destructive enzymatic cascade known as the Complement system.

• The **activation of the Complement** causes multiple effects e.g opsonisation, chemotaxis, membrane attack complex, Stimulation of factor XI of coagulation, fibrinolysis, Kallikerin..
• **B cells** (unlike T cells) do not need MHC to recognize antigen.

• **Immunoglobulins (IgG, IgM,...)** act like receptors for B cells, just like T cell receptors for T cells.
• **IgM** is the first to appear but later changes to other more specific IgG or IgM.

• **IgA** is the mucosal immune antibody

• **IgE** for mast cell mediated immunity

• The cytokines responsible for B cells activation are **IL2**, **IL4**, **IL6**, and **IL7** for early maturation.
• Hyperacute rejection is related to preformed natural antibody on Donor endothelium
Cell Mediated Immunity

T lymphocytes

• T lymphocytes originates in the bone marrow but mature in the Thymus.

• Acquire a specific receptor T cell receptor = TCR.

• T cells can not recognize antigens without a TCR. The antigen has also to be associated with MHC II (HLA II) to be recognized by the T cell receptor.
• The TCR is antigen specific and has alpha, beta subdimer and an essential part is CD3

• All TCR have CD3

• The TCR also has either
• CD4 or CD8
• Resting (non activated) T cells do not express IL2 receptors.

• Only when stimulated by a specific antigen with MHC II at the T cell receptor, they then express IL2 receptors and bind the IL2 to become active in inducing more T cells to express IL2 receptors.

• This is why IL2 inhibitors e.g Cyclosporin (mainly used in kidney) and (Tacrolimus=Prograf =FK506) (mainly used in liver) FK506 are important.
• T helper cells (Th1, Th2) have CD4
• T cytotoxic cells (Tc1, Tc2) have CD8
For CD8 to act on targets, an MHC I has to be present

• Interferon Gamma increases the expression of MHC I (HLA I) on the cells to be attacked.
Immune Response (Afferent & efferent)
Antigen presenting cells

- Are B Cells, macrophages and dendritic cells, Langerhans cells. They ingest antigens, process them, then express them on their surface for TCR, in association with MHC II (HLA II).
• **Major Histocompatibility Complex (HLA)**
  - transmembrane glycoproteins which are encoded by the short arm of chromosome 6
  - have a high degree of sequence polymorphism

  – **Type I:** A, B, C.
    - Present on all nucleated cells, including T cells, B cells and platelets and are targets for cytotoxic CD 8 T cells = efferent limb of the immune response

  – **Type II:** DR, DP, DQ
    - Present only on B lymphocytes, monocytes, macrophages and some activated T cells but not on unstimulated T cells. It is the afferent limb of the immune response
- B lymphocytes
- Macrophages
- T cells activated

CD4

HLA II

D DR

CD8

HLA I

C B A

all nucleated cells
Why HLA matching is NOT commonly followed

- HLA matching test takes time. Remember that organ ischemia time (graft is not perfused) is more important than HLA matching for the graft to survive and function in the recipient. No preservation solution is ideal.

- Early long term graft survival is equal in HLA matched or mismatched, long term (> 5 years) graft survival, however, is better in matched transplants.

Necessity of transplantation is more pressing e.g. end stage liver disease
• HLA cross matching is highly recommended for **living related kid Tx**. It may also be done for Cadaveric kid since it may increase the long term graft survival.

• > 5 mismatching is a relative contraindication

• **DR** and **DQ** are the more important
Graft survival; HLA matched/mismatched
Complications of Transplantation

- **Hyperacute rejection**: 1% preformed antibodies. Occurs immediately after release of clamp and is irreversible. No treatment available.

- Should be prevented by conducting the **Final Lymphcytotoxic cross match** to detect IgG antibodies directed against class I MHC.

- Positive Cross match is a contraindication.
Cross match; panel /final
• **Acute rejection**
  T cell mediated, treated with steroids initially with 90% success rate.

• Occurs any time after day 5 of Transplantation as unexplained function deterioration.

• Organ is infiltrated with T cells. (diagnostic)
• **Chronic rejection** seen after 1 or 2 years as gradual deterioration of function

• Chronic rejection is called;

• *Broncholitis obliterans* in lung
• *Vanishing Bile duct syndrome* in Liver
• *Endarteritis obliterans* in heart
Complication of transplantation

- **Infection**
  - **First month** = usual post op infection
  - **2 to 6 month** = opportunistic infection e.g. CMV – Pneumocystis – Aspergillosis
  - **After 6 months** = low incidence of infection
• **Malignancy**
  • Skin tumors  SCC > BCC (cardiac transplant)
  • B cell Lymphoma (EB virus infection) =
  • Post Transplant Lymphoproliferative Disorders = PTLD - discontinue IL II inhibitors
  • give Gancyclovair for EB virus infection
• **Cardiovascular disease**
Question

- The most common cause of mortality within the first year after renal Tx is
  - A. Malignant tumors
  - B. Cardiovascular disease
  - C. Sepsis
Early and late mortality after Renal TX

- **EARLY (1st YEAR)**
  - Sepsis 45%
  - CVS 35%

- **LATE (2-17 YEARS)**
  - CVS 35%
  - Malignancy 20%
  - Sepsis 19%
Brain dead Donor

- Avoid hypotension and hypoxia
- Dopamine, norepinephrine
- Thyroxine, insulin, steroids, vasopressin
Kidney Transplantation

RENAL Transplantation;

- Most common indications are: Diabetes, glomeruronephritis
- Cadaveric and Living related TX.
- HLA is used in living related
Complications of Renal Tx

- Arterial or Venous thrombosis.
- Ureter leak or stenosis
- Lymphocele \( \rightarrow 15\% \)
Question

• Three weeks after LRRT, a 35 years old male presents ipsilateral leg and abdominal wall edema and cyanosis of the leg. Normal kidney function. The most appropriate is
  • A. Lower limb duplex and start Heparin
  • B. Renal Ultrasound and biopsy
  • C. Renal Ultrasound and Aspiration
  • D. Renal Ultrasound and exploration
• Ultrasonography is the first test Renal Biopsy for rejection

• **US of transplanted kid can detect ;**
  • 1) Vascular anastomosis problems ( Artery or Vein)
  • 2) Ureter anastomosis
  • 3) Size of kidney(enlarged in rejection) or fluid collection around the kidney (lymphocele)
Causes of Oliguria after renal Transplantation;

• A- Foley catheter blocked
• B- Arterial thrombosis
• C- Rejection (Acute or hyperacute)
• D- Acute tubular necrosis
Question

- 5 weeks After CRT from a 60 years old healthy donor, a 50 years old patient showed gradual rise in Creatinine to 4, then remained stable. Renal US normal. Renal Bx shows dilated tubules, flat tubular epithelium. The most likely explanation is
  - Hyperacute rejection
  - Acute rejection
  - Acute tubular necrosis
• **Liver Transplantation**

• The recipients are arranged according to the degree of illness (coma, encephalopathy, coagulopathy, pulmonary hypertension)

• **MELD**: Model for End Stage Liver disease (0-40); less than 17 = no transplant yet

• Creatinine, bilirubin, INR...

• Fulminating liver failure = immediate transplant
Veno venous bypass (Anhepatic phase)
Adult to adult, use R lobe
Adult to children < 5 years

segments 2 and 3
- **INDICATIONS OF Liver Tx:**
  - *Liver failure from:*
  - 1) Hepatitis C is common
  - 2) Non Alcoholic hepatic steatosis (NAHS) will be the most common
  - 3) Alcoholic Cirrhosis.
  - 4) Sclerosing Cholangitis..
  - 5) Biliary atresia in pediatric patients
  - 6) Tumors ? Fibrolamellar carcinoma (Best prognosis) and some Hepatocellular carcinoma Stage I or II A in cirrhosis Milan criteria; if resection is not feasible for HCC → liver transplant is good option for tumors less than 5 cm or 2 tumors 3 cm each. Patient is given a MELD of 22
• It could be done with incompatible Blood groups (results are mixed) and even in the presence of preformed antibodies.

• Hyper acute rejection is rare with Liver TX

• Acute rejection occurs in 50 %

• Chronic rejection (vanishing bile duct syndrome) is also common
Complications of liver TX

- **1- Bleeding** *(portal hypertension, coagulopathy)*
- **2- Portal vein thrombosis may go unnoticed***
- **3- Primary Graft Nonfunction** ? 2- 5% → retransplantation
- **4- Biliary tract complications**
- **5- Sepsis** *(most common cause of early death)*
- **6- Hepatic artery thrombosis** typically presents with bile duct stricture or leak. Most require retransplants
Pancreas Transplantation

- **indication:** Diabetics
- **Methods of TX:**
  - Drainage of Duodenum into the urinary bladder. Or into the small bowel
- **Complications:**
  - Vascular thrombosis
  - Allograft pancreatitis
Lung and Heart

• **Lung transplantation**
  
  Broncholitis obliterans is the most common complication

  Most lung transplants are **unilateral**.

  In cystic fibrosis **Bilateral** lung transplant is needed to avoid infection in the new lung

Heart transplantation

  Atherosclerosis of the new heart coronary arteries is the limiting long term complication
New Immunosuppressive drugs
mTOR inhibitor

- Normally Mtor is cell receptor which stimulates;
- Cell growth and proliferation. Where mTOR regulates protein metabolism by ribosomes.
- mTOR also produce enzymes essential for glycolysis which is essential for cancer cells.
- mTOR also stimulates angiogenesis

- RAPAMYCIN (sirolimus) is the classic mTOR inhibitor (immunosuppressive – drug eluting stent – anticancer)
mTOR inhibitor

mTOR
An important target with multiple biologic effects

Cell Proliferation
Tumor Angiogenesis
Cell Metabolism

Inhibition of mTOR by AFINITOR has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and/or in vivo studies.
AFINITOR side effects

- Non infectious pneumonitis
- Viral bacterial infections
- Oral ulcerations
3 years after renal Tx, a patient required distal small bowel resection. He has been on steroids and Cyclosporin, he starts to develop rejection. The most appropriate step is

1- increase steroids
2- start OKT3
3- increase cyclosporin
4- start antilymphocytic globulin
Question

10 years after renal TX, a patient presents with SOB, Chest CT with 10 cm mid line opaque lesion. The most appropriate is

A. start antibiotics after culture, bronchoscopy
B. Fine needle Aspiration
C. Excision, + Chemotherapy
D. Incision biopsy, + chemo
- Okt3
- CD4
- Cyclosporin/tacrolimus
- IL2
- CD8
- mtor
- Sirolimus (rapamycin)