Hemolytic disease of the newborn is caused primarily by clearance of fetal Rh+ red blood cells that have bound maternal Rh IgG.

Cytotoxic clearance of the IgG bound fetal blood cells occurs primarily via destruction by macrophages in the fetal spleen.

In contrast, RBCs bound by recipient IgM in transfusion reactions are agglutinated, then eliminated primarily by complement activation and hemolysis of the transfused RBCs

18-1

Important terms:

Hypersensitivity – immune responses that causes tissue damage

Autoimmune disease – immune responses to self-antigens

Immunodeficiency – insufficient immune response

18-2

Topics

- **Transplantation immunity**
- **Autoimmune diseases**
- **Immunodeficiency disorders**

18-3

Transplantation immunity

18-4

Transplantation immunity

- **Allografts**
- **Xenografts**
- **Genetically non – identical grafts cause rejections**
- **Type IV reaction – delayed cell-mediated**
  - **Immunological rejection of transplant**
    - **Killing of graft by sensitized cytotoxic T cells**
    - **Natural killer cells (ADCC)**
    - **MHC antigens major cause of rejection**
      - ***abundant on leukocytes = HLAs***
      - ***tissue typing minimizes incompatibility***

18-5

Transplantation immunity

- **Allografts**
- **Xenografts**
- **Genetically non – identical grafts cause rejections**
- **Type IV reaction – delayed cell-mediated**
  - **Immunological rejection of transplant**
    - **Killing of graft by sensitized cytotoxic T cells**
    - **Natural killer cells (ADCC)**
    - **MHC antigens major cause of rejection**
  - **Requires immunosuppression for successful transplants**
    - ***minor antigens cause rejection***
    - ***immunosuppressants may be needed indefinately***

18-6

Transplantation immunity

- Allografts
- Xenografts
- Genetically non – identical grafts cause rejections
- Type IV reaction – delayed cell-mediated
  - Immunological rejection of transplant
    - Killing of graft by sensitized cytotoxic T cells
    - Natural killer cells (ADCC)
    - MHC antigens major cause of rejection
  - Requires immunosuppression for successful transplants
    - Cyclosporin A, tacrolimus
    - interfere with cell signaling
    - inhibit clonal expansion of T cells
    - *specificity leads to fewer side effects than radiation and cytotoxicity inhibitors*

18-7

The fetus as allograft (Perspective 18.1 – page 452)

half the fetus' antigens are foreign (father's)
fetus is thus an allograft, but is not rejected. Why?

mother makes anti-Rh, anti-MHC antibodies
mother in fact has small number of fetal cells in circulation
therefore not due to lack of exposure to fetal antigen

trophoblast forms barrier as outer layer of placenta
no MHC molecules expressed
NK cells suppressed

"immunologically privileged" sites; do not drain via lymph
avoid APCs and immune stimulation
also produce immunosuppressive cytokines

pregnancy also causes immunosuppression in mother

18-8

Autoimmune disease

Negative selection eliminates self reactive lymphocytes
Autoimmune diseases caused by body responding to self antigens
MHC genes involved; genetically based

18-9

Autoimmune disease

- **Spectrum of autoimmune reactions**
- **Treatment of autoimmune diseases**

18-10

Table 18.4 Characteristics of Some Autoimmune Diseases

Disease (Known MHC Relationship)	Organ Specificity	Major Mechanism of Tissue Damage
Graves' disease (DR3)	Thyroid	Autoantibodies bind thyroid-stimulating hormone receptor, causing overstimulation of thyroid
Myasthenia gravis (DR3)	Muscle	Autoantibodies bind to acetylcholine receptor on muscle, preventing muscle contraction
Insulin-dependent diabetes mellitus (DR3/DR4)	Pancreas	T-cell destruction of pancreatic cells
Autoimmune hemolytic anemia	Red blood cells	Antibody, complement, and phagocyte destruction of red cells
Rheumatoid arthritis (DR4)	Widespread, especially joints	Lymphocyte destruction of joint tissues; immune complexes of IgG and anti-IgG *Type III Hypersensitivity*
Systemic lupus erythematosus (DR3)	Widespread (glomerulonephritis, vasculitis, arthritis)	Autoantibodies to DNA and other nuclear components form immune complexes in small blood vessels *Type III*

18-11

Treatment of autoimmune diseases

- **Immunosuppressants (eg cyclosporins)**
- **Anti – inflammatory drugs (eg steroids)**
- **Replacement therapy (eg insulin, thyroid hormone)**
  including transplantation of pancreatic insulin-producing cells for insulin-dependent diabetes

18-12

Treatment of autoimmune diseases

- Immunosuppressants (eg cyclosporins)
- Anti – inflammatory drugs (eg steroids)
- Replacement therapy (eg insulin, thyroid hormone)
- Feeding or oral tolerance (induce tolerance to antigen)
  - Feed insulin for diabetes
  - Collagen for rheumatoid arthritis
  - Cause local intestinal immune response,
    down regulation of antigen receptors
    deletion of immune cells

18-13

Immunodeficiency disorders

- Primary immunodeficiencies (genetic, inborn)
- Secondary immunodeficiencies (acquired, disease)

18-14

Primary immunodeficiencies

- Lack of B – cell function
- Lack of the different T – cell functions
- Lack of both T and B cell functions
- Defective phagocytes

18-15

Table 18.6 Some Primary Immunodeficiency Diseases for Which Genetic Defects Are Known

- Severe combined immunodeficiency (SCID) *no functional T, B cells*
- X-linked SCID
- MHC class II deficiency *
- CD3 deficiency
- CD8 deficiency
- X-linked agammaglobulinemia *no Ig*
- X-linked hyper-IgM syndrome
- Wiscott-Aldrich syndrome
- Ataxia telangiectasia
- * Chronic granulomatous disease
- * Leukocyte adhesion deficiency
- * Many complement deficiencies

18-16

Treatments for primary immunodeficiencies

eg SCID children
- *bone marrow transplants*
- *repair faulty genes*
  - *adenosine deaminase needed for B, T cell proliferation*
  - *replacement therapy with enzyme*
  - *collect T cells, introduce deaminase gene*

18-17

Secondary immunodeficiencies

- **Malnutrition**
- **Immunosuppressive agents**
- **Infections (measles, AIDS, SARS, promote secondary infections)**
- **Malignancies (multiple myeloma – from one B cell)**
  - **consumes immune resources**
  - **can't mount normal responses**

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