Failures of the Body’s Defenses

1. Microbial mechanisms that subvert immune recognition/responses

-**Genetic variation:** Different strains (or serotypes) of *Streptococcus pneumoniae* have antigenically different polysaccharide capsules. Ab’s against capsular polysaccharide opsonizes the pathogen for subsequent phagocytosis. Infection with second strain (serotype) of *S. pneumoniae* results in no protection and disease as a result of no antigenic similarity in capsular antigenic structure compared to first strain.

- **Mutation/recombination** – escape from immunity: -**Antigenic drift** -> pt. Mutations in genes encoding key structure proteins ex. Flu virus – hemaglutinin epitopes. Occurs ~2-3 yrs, mild effect on disease as some cross-reactivity is retained. **Antigenic shift** -> more dangerous. Results in pandemics *reassortment* of segmented RNA genome ex. animal/human flu -> mix segments and the result = new pathogen, very lethal. Antigenic shift has been the cause of several flu pandemics over the last century.

- **Gene rearrangement** and antigenic variation (trypanosomes): -Ag variation -> programmed reorganization within DNA of pathogen ex. Trypanosomes -> cause sleeping sickness in Africa. Changes in major surface Ag repeatedly occur within host. How? -> parasite coated with one surface protein – variant specific glycoprotein (VSG); >1000 VSG genes and each different ** only one expressed at one time

-**Latency/persistence:**
  - Herpes simplex virus (HSV) infection results in persistence within the CNS (within trigeminal ganglion) in which virus enters a quiescent state i.e. virus does not replicate nor generate enough Ag to alert CTLs. In addition, neurons express very little MHC class I molecules further enabling the virus to remain quiescent.

  - Reactivation (stress, UV light, etc) leads to viral replication in neurons and spread to epithelium causing cold sores. At this time, virus can be passed from one person to another.

-**Sabotage/subversion of immune defense:** (see Fig. 11.6).

2. Inherited immunodeficiency disease
All primary immunodeficiency diseases are caused by dominant, recessive, or X-linked gene defects.

- **Dominant** defect – Show up in children who inherit a normal, functional allele from 1 parent and defective allele from other.
- **Recessive** defect – Manifested in patients who inherit the defective allele from both parents. Individuals who have 1 defective allele and 1 normal allele are healthy and called carriers.

- **X-linked diseases** – caused by recessive defects in genes on the X chromosomes. Because males only have one X chromosome, the disease occurs in all males that inherit an X chromosome with a defective allele. Disease occurs in females only when they inherit a defective X chromosome from both parents.

- **Example of Recessive and Dominant mutations in IFN-γ**: Dominant/recessive mutations and IFN-γ receptor on monocyte activation. IFN-γ receptors are composed of dimer of IFNγ R1 and IFNγ R2. Two such dimers need to be cross-linked by IFN-γ binding to IFNγ R1. Recessive mutant alleles of IFNγ R1 produce a mutant chain that does not reach the surface (second panel). Thus, only IFNγ R2 is present on the surface and cells cannot respond to IFN-γ. Heterozygotes for this mutation produce sufficient numbers of wildtype chain to allow for normal response. Dominant mutant alleles of IFNγ R1 generate a mutant chain lacking signaling domain (binding of Jak1). This chain can assemble into a dimer and bind IFN-γ but cannot signal. Heterozygotes for this allele (third panel) make a small number of functional receptors composed of wildtype chains but most are non-functional resulting in muted response to IFN-γ (as measured by TNF-α production).

- **Example of X-linked disease**: X-linked agammaglobulinemia – XLA. In XLA, **Bruton’s tyrosine kinase (BTK)** is defective. In patients with this disease, B cells become arrested at the pre-B cell stage because intracellular signals cannot be generated by the pre-B-cell receptor. Most patients with XLA are males because males have only 1 copy of the X chromosome. Heterozygous females are carriers of the disease trait although healthy. During development, female cells randomly inactivate one of their X chromosomes. Consequently, half of the developing B cells in a female carrier become arrested at the pre-B-cell stage.

- **Other inherited mutations that lead to phagocyte defects that result in enhanced susceptibility to bacterial infection**: (see Fig. 11.14).

**Treatment of genetic diseases**: **Transplantation of hematopoietic stem cells is used to correct genetic defects of the immune system.**

- Patient’s diseased hematopoietic system is destroyed by chemotherapy/irradiation. An infusion of bone marrow obtained from healthy HLA-matched donor is given. Over months, the hematopoietic stem cells in the graft reconstitute the patient with a healthy hematopoietic system.

- Donor and recipient must share HLA class I and II for protective T cell response to infection. After bone marrow transplantation, donor-derived thymocytes are positively selected on HLA molecules expressed on recipients thymic epithelium. Top panel: If none of the recipients HLA allotypes (red) are same as donors HLA allotypes (blue), the recipient will not generate a working T cell system & will suffer from severe combined
immunodeficiency. Why? T cells won’t be able to recognize Ag following infection because APCs will present through donor HLAs expressed on APCs derived from bone marrow transplant. Lower panel: If recipient and donor share HLA allotypes (indicated in blue), T cells will be able to respond following infection as they will recognize Ag presented by HLA’s on APCs. (See Fig. 11.18).