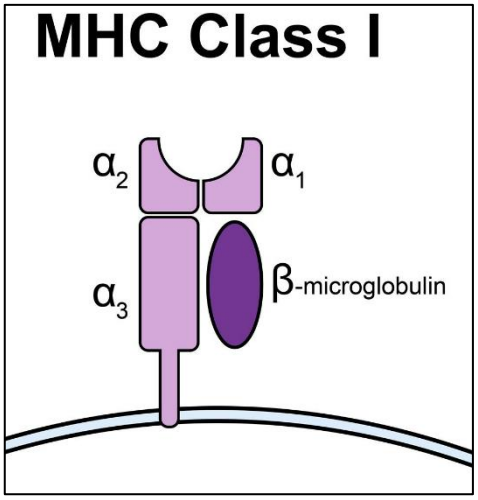
IMMU3202:
Immunology in Human Disease

Lectures:

Human leukocyte antigen (HLA) complex

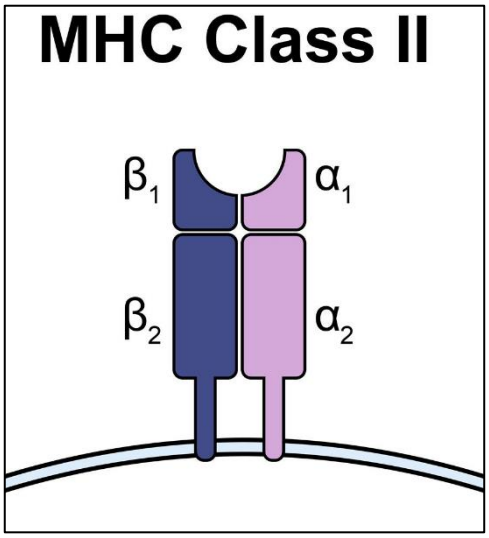
- Found on chromosome 6
- Plays a critical role in inducing immune response and with the complement system and other aspects of the innate and adaptive response
- 3 major regions within this locus
- Class 1 – HLA A, B and C
- Class 2 – classical loci R, P and Q and non-classical M
- Class 3 – Factor B and some cytokines
- HLA locus and prediction of certain genetic diseases



HLA Class 1

Peptide binding cleft is in the variable region – MHC class I is trimolecular that presents antigens to T cells

- 6-16 amino acids
- MHC class I = CD8 T cells
- Foreign peptide must bind to HLA molecule to be able to activate T cells – selected peptide residues fit different HLA alleles



HLA Class II

- 2 chains – alpha and beta chain form a peptide binding cleft
- About 30 amino acids
- DR, DP and DQ – classical types
- Much more restricted in the pattern of its expression – APCs and other cells that can express class II via stimulation with IFN-gamma
- MHC Class II = CD4 T cells

Types of genetic effects influencing immune responses to infection

Pattern of inheritance:

- Mendelian – autosomal dominant and recessive, X-linked
- Polygenic – cumulative effect of single nucleotide polymorphisms (SNPs) in multiple genes

Genetic spectrum and infection: spectrum of genetic effects on infection

Monogenic effects

- Single gene influences immune response - gene mutation leads to absent or non-functional protein

- Mendelian pattern of inheritance – autosomal recessive or x-linked
- Ex: primary immunodeficiency

(1) Global deficiency: absence of T or B cells

- T cell deficiency caused by absence of common gamma chain of IL-2 receptor
- Patients suffer from severe infections – pneumonia, meningitis, and bacteraemia

(2) Susceptibility to specific class of microbes

- Poor immune response to common pathogens. Ex: Mendelian susceptibility to mycobacterial infections (MSMD) or deficiency in IFN-gamma or IL-12 receptor or signalling
- Severe disease caused by non-tuberculous environmental mycobacteria such as M avium, M kansaii, M fortutium

Polygenic effects

- Influence of multiple genes on the immune response – gene mutations and allelic variations
- Can be blocks of variants separated by recombination hotspots
- Commonly single nucleotide polymorphisms (SNPs) - leading to loss of function of gene product or subtle change in function
- Region of the gene associated with disease is identified and then the individual gene is identified by fine mapping
- Individual genes may have Mendelian pattern of inheritance. Ex: requires SNP in both genes to lose function (autosomal recessive) or if protein acts as dominant negative mutant (autosomal dominant) - generally complex pattern of inheritance because the phenotype requires the effects of multiple variants
- **Family association studies**: risk of disease associated with one region, gene locus or allele inherited. Acts like a quantitative trait locus (QTL)
- **Case control studies**: Original candidate was HLA – assemble group of cases and controls and measure the frequency of gene variation in 2 groups. Predict that one gene product correlates with variation in immune responses to certain human diseases – risk of infection, autoimmune or allergic disease, response to vaccine.
- **Genome wide association studies***: risk of disease associated with variation in SNPs across whole genome. First find the regions on the chromosomes associated with disease and then fine map regions associated with that disease and identify the individual gene.

Strong association with autoimmune diseases and the HLA locus

- Ankylosing spondylitis – autoimmune diseases affecting the spine
- Type 1 diabetes
- Graves disease
- Rheumatoid arthritis
- SLE

Association with HLA and drug hypersensitivity:

- Abacavir – anti-retroviral drug for HIV (HLA-B)
- Dapsone – anti-leprosy (HLA-B)

Genes associated with type 1 diabetes

- HLA Class II: strongest association with HLA-DQ 3.2
- PTPN22: phosphatase that reduces signalling in lymphocytes
- CTLA-4: inhibitory molecule on T cells
- IL2R-alpha chain: high affinity IL-2 receptor
- Interferon-induced helicase I protein: signals viral infection
- Insulin: not adequately tested in GWAS
- PTPN11: phosphatase is involved in insulin and immune signalling

Genes associated with Rheumatoid arthritis (RA)

- HLA-DRB1 locus:
  Allele in protein tyrosine phosphatase non-receptor 22 (PTPN22) – turns off signalling in T cells and macrophages. Confirmed in type 1 diabetes too and explains 50% of genetic risk for RA
- CTLA4, IL2R-alpha and genes in TNF signalling pathway also likely to be involved

HIV

HIV is the most common infective cause of immunodeficiency and MHC class I is important here because HIV is an intracellular virus.

HIV transmission

Dendritic cells:

- Binding of HIV virus dependent on CD4 and CCR5 co-receptors on the cell-surface
- R5 or M-tropic virus are the initial infecting virus
- DCs carry virus to the lymph node and transfer the infection to T cells – **rapid**

CD4 T cells:

- Dependent on CD4 and CCR5 or CXCR4 co-receptors on T cells – co-receptors allow infection of the T cells
- HIV DNA integrates into T cells which are long-lived

Some individuals can control HIV better because of genetic changes.

Genetic control of HIV infections

Delta-32 CCR5: allele for 32 bp deletion in CCR5 – truncated non-functional molecule that does not support infection of cells with HIV-1

- Homozygous (2x copies of delta 32): < 1% = high level resistance to HIV infection, even following multiple exposures
- Heterozygous (wt and 1x copy of delta 32): 15-20% = doesn't prevent infection but slower rate of disease progression
- decreased CCR5 on cell surface (dominant negative mutant)
  compound heterozygotes with different mutation in CCr5 confers resistance to HIV

Mutations in other chemokine receptors may also influence disease progression.

Genetic control of HIV progression

Non-progressive disease:

- HLA*B5701 and B5703 strongly associated, HLA*B27, HLA*5801, B1503, B14, Bw4
- These haplotypes are more efficient at binding HIV peptides and stimulate HIV-1 specific CD8+ CTL against multiple epitopes

Provides selective pressure on HIV for selection of mutants with non-HLA class-1 binding peptides in these individuals and populations. With time, it is predicted that there will be a reduced association of these HLA class I haplotypes with non-progression.

Kaposi's sarcoma is a tumour of endothelial cells caused by Human Herpesvirus (HHV-8), associated with HIV/AIDs.

Sporadic childhood KS – whole exon sequencing identified a splice-site mutation in STIM1

Tuberculosis

- Multiple factors determine disease included nutrition, environment, HIV co-infection, genetics and environment.
- Transmission by aerosol -mycobacterium tuberculosis

Genetic susceptibility to TB

- Monozygotic twins have greater concordance of TB and leprosy than dizygotic twins
- Higher rates in African Americans than Caucasians -independent of socio-economic status
- Mendelian susceptibility to mycobacterial infections: rare AR condition with risk of NTM or BCG. IL-12/IFN-gamma axis
- Polygenic basis for susceptibility to TB: case control studies, GWAS, testing of mouse susceptible genes in humans

Leprosy

- Mycobacterium leprae - Spectrum of leprosy
- HLA alleles and control of this infection have been related
- Large number of lesions and mycobacteria present in 6+, but 0 is tuberculoid
- Tuberculoid = pauci-bacillary, lepromatous = multibacillary
- Genes: HLA-DR + NOD-2 pathway of innate immunity similar to Crohn's disease

Meningococcus- Neisseria Meningitidis

- Complement C5 deficiency so cannot form membrane attack complex – higher risk of disseminated Neisseria infections
- Classical primary immunodeficiency (PID)
- Complement factor H and CFH protein 3 implicated
- N. meningitidis avoids complement mediated killing by binding CFH and variants in CFH determines invasive disease