Host / pathogen interactions

An immunological perspective
• Global evolution of infectious diseases

• Immunity to pathogens: revisited concepts
  – Resistance and tolerance
  – CMI and AMI for which pathogens
  – AMI: why protective? Always protective?

• Escape mechanisms
  – Recognition
  – Signalling
  – Destruction

• Genetic aspects
GLOBAL EVOLUTION OF INFECTIOUS DISEASES

Viral diseases
Anti-viral arms
Recent changes in infectious diseases
Viral infections

• Hit and run
  – Mainly cytolytic
  – Destroy cells in which they multiply
  – Highly infective and transmissible
  – Influenza, rhinovirus, measles
  – Resolution requires cell-mediated immune response
  – Survival strategies may exist for pox viruses or enteroviruses in external milieu or exogenous reservoirs
  – Infectiosity depends on fast mutations and seasonal impact allowing to change hosts (Influenza)

• Hit and stay
  – Long term residence in hosts
  – Latency (herpes) or persistent (hepatitis) infection
  – Equilibrium between commensalism or tolerance
Risk of infection of major viral diseases
## Vaccines

### Hit and run viruses

<table>
<thead>
<tr>
<th>Existing</th>
<th>Future</th>
<th>Hit and stay viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poliovirus</td>
<td>Respiratory syncytal</td>
<td>Hepatitis B</td>
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<tr>
<td>Measles</td>
<td>Parainfluenza</td>
<td>Varicella</td>
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<tr>
<td>Mumps</td>
<td>Dengue</td>
<td>Adenovirus</td>
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<tr>
<td>Rubella</td>
<td>West Nile</td>
<td>Epstein–Barr virus</td>
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<tr>
<td>Influenza</td>
<td>Severe acute respiratory syndrome</td>
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<tr>
<td>Hepatitis A</td>
<td>Bioweapons</td>
<td>HIV?</td>
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<tr>
<td>Yellow Fever</td>
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<td>Japanese encephalitis</td>
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<td>Rabies</td>
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<td>Rotavirus</td>
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<tr>
<td>Rotavirus</td>
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<tr>
<td>Smallpox</td>
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<tr>
<td>Tick B encephalitis</td>
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</tr>
</tbody>
</table>

### Alternatives

- Chemotherapeutics
- Chemotherapy/vaccine
- Gene silencing
Vaccine evolution

2000

- Killed
- Live attenuated
- Subunit

2020

- Prime boost
- DNA vaccines
- Immunotherapy
- Non replicating vectors
- Mucosal
- Subunit reverse vaccinology
- Subunit
Evolution of antiviral drugs

Antivirals

1990

2004
Most emerging diseases are of animal origin.
Co-evolution

- Host susceptibility
  - Benefits of resistance
  - Costs of resistance
- Host resistance
  - Increased selection for pathogen infectivity
  - Increased selection for host resistance
- High pathogenicity
  - Costs of pathogenicity
  - Benefits of pathogenicity
- Low pathogenicity
  - Reduced selection for host resistance
  - Reduced selection for pathogen infectivity
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>co-evolution</td>
<td>Reciprocal, adaptive genetic changes between interacting species. Co-evolution can be studied in terms of paired phenotypic traits, such as resistance and infectivity, in terms of interacting host and pathogen molecules or in terms of genes or nucleotide sequences directly.</td>
</tr>
<tr>
<td>gene-for-gene</td>
<td>Co-evolution involving a single locus in the genomes of each of two interacting populations. The outcome of the interaction depends on the combination of alleles at these loci.</td>
</tr>
<tr>
<td>resistance</td>
<td>Genetic, biochemical or physiological characteristics of the host that inhibit pathogen establishment, survival or development. Resistance may be quantitative, so that hosts may be infected but resistant ones are harmed less, or qualitative, so that host infection is prevented. The majority of studies of host–pathogen co-evolution regard resistance as the latter.</td>
</tr>
<tr>
<td>infectivity</td>
<td>Genetic, biochemical or physiological characteristics of the pathogen that determine its ability to infect the host. High infectivity does not necessarily mean that symptoms of disease (pathology) appear more quickly, nor that the illness is more severe (virulence).</td>
</tr>
<tr>
<td>virulence</td>
<td>The direct or indirect reduction in host fitness attributable to pathogen infection, often measured as pathogen-induced host mortality. (Conflicting definitions exist, such as that of the infective capacity of pathogens (here termed &quot;infectivity&quot;) within plant-pathogen systems.)</td>
</tr>
<tr>
<td>compatibility</td>
<td>The ability of a given pathogen to infect a given host, as a consequence of the combined genetic, biochemical or physiological characteristics that determine infectivity and resistance.</td>
</tr>
<tr>
<td>trade-off</td>
<td>An unavoidable genetic constraint/negative correlation in which investment in one trait compromises investment in another.</td>
</tr>
<tr>
<td>local adaptation</td>
<td>Sympatric combinations (here, of host and pathogen) are more compatible than allopatric combinations.</td>
</tr>
<tr>
<td>dynamic polymorphism</td>
<td>A selection regime that results in the maintenance of two or more alleles at a locus in a population but with changing allele frequencies (often cyclic).</td>
</tr>
<tr>
<td>selective sweep</td>
<td>The process of an advantageous allele increasing to fixation under natural selection. Linked alleles may also go to fixation by ‘hitch-hiking’.</td>
</tr>
<tr>
<td>frequency-dependent selection</td>
<td>Dependence of relative genotypic fitnesses on genotype frequencies. Can be positive or negative. If negative, that is, if the fitness of alleles at a locus declines with increasing frequency, a stable or dynamic polymorphism may result.</td>
</tr>
<tr>
<td>balancing selection</td>
<td>Any form of selection acting to maintain alleles in a population, including frequency-dependent selection and heterozygote advantage.</td>
</tr>
<tr>
<td>positive selection</td>
<td>Spread of mutations owing to selection rather than drift.</td>
</tr>
</tbody>
</table>
Resistance and tolerance
CMI and AMI for which pathogens
AMI: why protective? Always protective?

IMMUNITY TO PATHOGENS: REVISITED CONCEPTS
Resistance versus tolerance

- Resistance will refer to the capacity to limit microbial burden

- Tolerance is defined as the ability to limit the health impact of a given pathogen burden

  - Schneider and Ayres, Nat Rev Imm 2008
Immune response can be damaging

• Hepatitis: cell mediated immunity destroys hepatocytes

• Granulomatous reaction to extracellular bacteria provoke massive oxidative stress that can lead to fibrosis

• Hyperactivated phagocytes / eosinophils can damage tissues
Immunity to pathogens

• Innate immunity versus Adaptive immunity based on various detecting mechanisms

• Effector mechanisms
  – Barriers, Exfoliation
  – Microbe destruction (C’, ROI, RNS, anti microbial peptides, enzymes …)
  – Opsonisation, clearance and detoxication
  – Phagocytosis and degranulation
  – Destruction of host reservoirs
  – Granuloma formation limiting diffusion
  – Control of replication (translation, aa deprivation, …)
  – Cell recruitment and cooperation
Current dogma

• Extracellular pathogens
  – Encapsulated bacteria, fungi, parasites, ...
  – Extracellular replication
  – Protective antibody-mediated immunity (AMI)

• Intracellular pathogens
  – Viruses, bacteria, some parasites
  – Cell host required for replication
  – Protective cell-mediated immunity (CMI)
  – Granuloma formation
Exceptions to the dogma?

- Pathogens can have both extra and intracellular phases, notably in phagocytes (Plasmodium, streptococci, viruses)
- The presence of a polysaccharidic and anti-phagocytic capsule does not exclude an intracellular life (ex: M tuberculosis)
- S aureus, a typical extracellular bacteria can survive in neutrophils
- AMI can be efficient against intracellular bacteria such as B anthracis or Legionella pneumophila
Towards a new dogma

• Efficiency of CMI or AMI should rather be used as a criteria to define intracellular versus extracellular pathogens

• Most of these conclusions relies on the analysis of pathogens: what about commensals?

• Casadevall / Pirofski, Adv Immunol, 2006
CMI

• Innate mechanisms
  – Anti microbial peptides, ERO
  – Phagocytosis

• Adaptive mechanisms
  – Th1 -> intracellular pathogens (bacteria, protozoans, viruses)
  – Th2 -> helminthes
  – Th17 -> extracellular pathogens (bacteria, fungi)
AMI in a « protective framework »

- Innate immunity
- Acquired immunity
- Cell mediated inflammatory response
- Microbial burden
- Days to weeks
- Time
- Months to years
- IgM
- Cellular response
- IgG
- Pro-inflammatory
- Anti-inflammatory
- Antibody action
AMI

• Encompasses all protective effects associated with Ab being natural, passively transferred or acquired post-immunization

• Natural or preexisting Ab? What has been the triggering event?
  – Low affinity, crossreactive Ab but efficient!
    • Sensitivity of slgM mice to pneumococcal disease despite the fact that protection is usually considered associated with IgG!
    • Similar impact of natural Ab on Influenza or West Nile viruses
  – Supposed mechanisms: C’ or IgM mediated opsonisation

• Passively acquired Ab
  – Often used as anti-inflammatory preparations (anti-toxininc ?)
  – Rarely efficient on ongoing infection
  – Acquired Ab often appear once infection is controlled -> survival advantage upon reinfection
Mechanisms: double-edged sword!

- Double-edged sword of immune responses.
- C’ Lysis: Lysis through complement activation.
- Opsonisation: Enhancement of phagocytosis.
- Destruction: Inactivation of pathogens.
- Survival: Protection against immune attack.
- Protective Ab: Antibodies that protect against infection.
- Facilitating Ab: Antibodies that facilitate the immune response.
- Fc R: Fc receptor for antibody binding.
- C’ R: Cytosolic receptor for complement activation.
- CMI: Cellular-mediated immunity.
- IVIG: Intravenous Immunoglobulin.
- Effector cytokine (e.g., IFN): Cytokines that activate immune cells.
- Immunosuppressive cytokine (e.g., IL-10): Cytokines that suppress immune responses.
- Microbicid: Microbicidal activity.
- ERO: Erythrocyte rosette formation.
- Desensitization: Immune tolerance.

Diagram:
- Bug: Pathogen.
- C’: Complement component.
- Lysis: Mechanism of pathogen destruction.
- Opsonisation: Enhances phagocytosis.
- Destruction: Inactivation of pathogens.
- Survival: Protection against immune attack.
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- Desensitization: Immune tolerance.
What is a protective antibody?

- Ab reducing inflammation or enhancing weak immune response

- A question of timing?
  - Specific IgM contributes to neutrophil recruitment early in anti-\textit{S} pneumonialiae infection and to downregulation of chemokine expression in lung in late phase

- A question of host / microbe interaction?
  - Other Ab (\textit{C} neoformans) can provoke catastrophic cardiovascular collapse by acute release of proinflammatory and procoagulant factors or alternatively (Leishmania) contribute to virulence by promoting IL-10 secretion
Toxin-mediated diseases
Lack of strict correlation between immunity and protection

• Clostridium tetani or Corynebacterium diphteria provoke disease through toxin secretion without strong immunization

• Vaccination against toxins is efficient through neutralizing anti-toxin Ab

• Immunity is not long-lasting
Damage to the host?

- Microbial pathogenesis is the outcome of an interaction between a host and a microbe.
- The relevant outcome of this interaction is damage to the host.
- Damage can be the result of host and/or microbial factors.
Antibody-mediated disease enhancement

- Enhancement of virus entry (Dengue virus)
  - Facts:
    - Hemorrhagic fever or shock syndrom mostly observed in children undergoing secondary infection with heterologous DENV serotype
    - Associated with situations where mothers and infants were not exposed to the same serotype or situations in which maternal Ab had declined to subneutralizing levels
    - Thus preexisting immunity can predispose to a more serious infection with a heterologous DENV serotype
  - Mechanisms:
    - IgG / FcgR mediated virus entry infecting more target cells and/or inducing immunosuppressive cytokine (IL-10?) inducti
    - Conformational changes induced on envelope proteins ?
    - Complement-mediated opsonisation ?

- Enhancement of viral replication through immune cell activation (Lentivirus)
  - Increased number of target CD4+ lymphocytes
  - Modification of viral envelopes (integration of cellular proteins involved in cell adhesion
  - Microbial cooperation
  - DC-mediated viral delivery to activated T lymphocytes
  - Vaccine-induced immune cell polarization towards Th2/eosinophil rich damaging responses
The failure of the Merck HIV vaccine

• Recombinant replication-incompetent adenovirus type 5 expressing well-conserved gag, pol, nef genes from subtype B strains of HIV

• Result: no reduction in viral load and rather increase in infection rate despite efficient CD8 immunity and AB induction
AMI with « intracellular pathogens »

- Observed with numerous intracellular bacteria (Brucella, Legionella, Listeria, Shigella, ...)

- Direct or indirect Ab effects

- Primary versus secondary responses
  - B cell deficient mice are resistant to Candida infection
    BUT resistance to reinfection requires acquired Ab -> Ab prime / maintain memory responses ?
AMI with intracellular pathogens

• Pathogens
  – Cryptococcus neoformans
  – Mycobacterium tuberculosis
  – Toxoplasma gondii
  – Chlamydia trachomatis
  – Listeria monocytogenes

• Arguments:
  – No greater susceptibility in B cell deficient mice
  – Variable effect of passive Ab administration but some AB are indeed protective!

• Mechanisms: still uncertain?
  – Nature of Ag
  – Modulation of immunomodulatory microbial Ag
  – Ig-mediated impact on Ag presentation (lysosomal fusion?)
  – Isotype preference
AMI via regulation of inflammation

- Proinflammatory effects
  - C’ activation (IgM > IgG)
  - Engagement of FcR
    - FcgR1 and RIII proinflammatory versus FcgRII anti-inflammatory
    - class specificity: IgG1 -> FcgRII, IgG2a/b -> FcgRIV
  - Phagocytosis and antigen presentation

- Antiinflammatory effects
  - Microbial clearance
  - IL-10 secretion
  - FcR-mediated inhibition (IgG > IgM ?)
  - Impact on Ag processing? -> determinant spreading?
AMI : impact on CMI

• C neoformans infection: efficacy of passive Ab depends on IFNg and T cells
• Friend leukemia virus: efficacy of passive Ab depends on MHC alleles
• LCMV: Sterilizing immunity requires T cells and Ab
• Salmonella typhimurium: efficacy of passive Ab depends on inherent host resistance
• S aureus: Ab-mediated pDC activation
Ig-dependent pDC activation by S. aureus
AMI: concentration dependence

• Passive Ab have variable efficiency depending on the dose

• Prozone effect: high Ab concentration aggravate disease
  – Reduction of ROI
  – Impact on cytokine response
  – C’ reticulation
AMI in damage-response framework?
Escape mechanisms

Variability
Subversion of cell-intrinsic innate immunity
Complement evasion
Latency
Subversion of cell-intrinsic innate immunity
Avoiding detection

TLR
- Lipid A modifications and TLR4: Helicobacter pylori, legionella
- Flagellin and flagellated bacteria: evasion by proteobacteria, H pylori -> gut colonization
- Obligate intracellular pathogens: Coxiella burnetii for TLR2 versus 4 ??, inactivation of TRIF by Hepatitis C virus protease

CLR
- Phagocytosis by immature DC: MR, DC-SIGN, dectin-1 with different specificities for glycans: dectin-1 deficiency -> susceptibility to fungal infections; subversion of endocytic pathways to avoid degradation

NLR
- Two families: NOD and NALP
- Pox virus and inflammosome inhibition (Johnston Immunity 2005), Inflammatory caspases (inflammosome) Martinon Cell 2004 ?

RLR
- RIG-1, Mda5: dsRNA detection
- RNA viruses -> degradation of key signaling elements
- dsDNA: ZBP1
Bacterial evasion by modification of TLR agonists

Flagellin recognition sequence

LPS: acylation of lipid A
Viral escape

different for acute or persistent infections

• Replication: poor fidelity for RNA viruses, larger genomes for DNA viruses
• Sequestration in reservoirs (brain, stem cells, ...)
• Blockade of MHC presentation (proteosomal fragmentation, transport to ER, MHC loading, redirection)
• Cytokine evasion: mimics or antagonists
• NK cell evasion: CMV -> decoy analog of MHC (UL18) bonds CD94 and inhibits activation
• Inhibition of apoptosis via Bcl induction, caspase inactivation
• Ab and C’
Epitope variation
Restricting allele(s) present

A. Diverse CTL TCR repertoire
   - Restricting MHC molecule
   - Sustained CD4+ T cell response
   - No mutations
   - Clearance of infection

B. Narrow CTL TCR repertoire
   - Absent or weak CD4+ T cell response
   - Mutational escape
   - Compensatory mutations

C. Dysfunctional CTL response
   - Absent or weak CD4+ T cell response
   - No mutational escape

Restricting allele(s) absent

D. No CTL-mediated immune pressure
   - Non-restricting MHC molecule
   - High fitness cost
   - Reversion to ‘fitter’ sequence

E. No CTL-mediated immune pressure
   - Low fitness cost
   - Mutation persists
   - Equally ‘fit’ alternative
Antigen presentation pathways
Latent DNA viruses: EBV, CMV, ...
EBNA1: important for latency
Subversion of cell-intrinsic innate immunity

Disruption of IRF3-induced antiviral effector functions => Control of host cell translation

- ISG blocks eIF-3,
- PKR phosphorylates eIF-2
- 2’5’ oligoadenylate synthetase produces 2-5(A) which activates RNaseL
Interferon pathways
Major IFN-induced genes

- ISG15
- MxA
- OAS1
- OAS2
- OAS3
- OASL
- RNaseL
- PKR

Nature Reviews | Immunology
ISGylation of key intracellular proteins modifies cell responses by modulating the half life and activity of intracellular enzymes.
MxA proteins trap nascent viral nucleocapsides

Sensitivity to orthomyxovirus infection in Mx-deficient mice
OAS1-RNaseL antiviral pathway

OAS have polymerase activity on adenosine and permit synthesis of 2’,5’ oligomers activating RNase activity.
PKR-mediated translation inhibition

PKR phosphorylates eIF-2 preventing translation

PKR deficient mice have enhanced susceptibility to various RNA or DNA viruses (ex: HCV)
Regulation of IFN-dependent anti viral activity
Subversion of cell-intrinsic innate immunity
Disrupting cellular communications

• Convergence of early signals on signaling hubs involving NF-kB and MAPK
  
  – Myd88 (TIR/TIR domains) -> IRAK
    • NF-kB (direct transcriptional activator)
    • MAPK (indirect regulation of transcription factors via phosphorylation and control of chromatin assembly)
Viral inhibition of MAPK and NF-κB

- Vaccinia Pox: protein interfering with TIR domain interaction, protein interfering with TRAF6 activation (blocks NF-κB but activates p38 to produce IL-10 (Blackburn Trends Mic 2006 -> viral persistence)

Bacteria exert epigenetic control on host immune responses

- Bacterial effectors and acetyltransferase activity
  - Yersinia infection: YopJ toxin -> limits TNF production by macrophages through interaction with MKK and IKK (Orth Science 1999, 2000, Mukherjee Science 2006) and acetylation of the kinases

- Bacterial effectors with phosphothreonine lyase
  - Shigella ospF gene translocates in nucleus and inhibits MAPK by dephosphorylation (Arbibe Nat Imm 2007) -> impact on the stability of NF-κB mediated IL-8 transcription by lack of MAPK-dependent histone H3 phosphorylation “epigenetic control”
Inhibition of MAPK activation by anthrax toxin

– Toxin diffuse in tissues and act at distance, interference with cell migration, protein translation and DNA replication

– Anthrax toxin: protective antigen, lethal factor and edema factor
  • Protective Ag binds to toxins and cell receptors to promote internalization in endosomes, acidification and formation of a channel which translocates toxins in the cytosol (Baldari Trends Immunol 2006);
  • Edema factor is a calmodulin-dependent adenylate cyclase increasing cAMP in cells;
  • Lethal factor is a protease cleaving MKK -> apoptosis induction in mac and DC (Park Science 2002, Boyden Nat Gen 2006)
Disruption of innate signaling pathways by microbial proteins
Complement activation
Complement regulation

- Glycoprotein C1 inhibitor (C1 INH) controls initial proteases
- Regulators of Complement Activation (RCA) control C3-dependent activation
  - CR1, factor H, C4BP, DAF, MCP (membrane cofactor protein)
  - Functions: destabilize C3 convertase (DAF), degrades C3b via factor I (iC3b)
- CD59 prevents MAC formation
Complement evasion

Complement binding proteins

• Recruitment / mimicking of RCA
  – Common to various pathogens
  – Efficient conserved regulators
  – Produced by host and thus non limiting, some are produced by pathogens (small pox, vaccinia pox)
  – Share short consensus repeats (SCR) allowing recruitment of different RCA
Complement evasion
Inhibition of C’ effectors

• Pathogenic proteases
  – Mainly reported in bacteria
  – Cleavage of Ig or C1q by pseudomonas
  – Cleavage of C5a by Serratia marcescens
  – Properdin degradation by Streptococcal pyrogenic exotoxin B (properdin stabilizes convertases on cell surfaces)
  – Cleavage of C3 by pseudomonas protease
  – iC3b degradation by Schistosoma mansoni protease (loss of CR3 binding)

• Microbial complement inhibitors
  – CD59 like protein in B burgdorferi: affinity for C8/C9 and inhibition of MAC
  – Transmembrane gC1 and gC2 from Herpes virus: bind C3b and accelerate the decay of the C3 convertase
  – Complement receptor in Schistosoma and Trypanosoma preventing C2/C4 association to form the C3 convertase

• Highjacking complement to enter cells
  – HIV and EBV express proteins binding C’ receptors
Staphylococcus aureus
a master of complement evasion

- Opportunistic pathogen, extracellular
- Persistent in vivo
- Gram+ cell wall resistant to MAC formation
- SpA protein binds Ig Fc, blocks C1q and FcR binding
- Protease -> plasmin activation -> IgG cleavage
- Inhibition of C3 activation, C5
Complement evasion
Passive mechanisms

- Inhibition of MAC mediated cell lysis: a property of Gram+ cell wall
Blocking cell recruitment
S aureus resists opsonisation
S aureus modulates adaptive immunity
GENETICS OF INFECTIOUS DISEASES
Genetics of infectious diseases

- Microbial theory of disease: cause of infection -> microbe
- Causes of intrafamilial heterogeneity -> genetics of susceptibility, immunodeficiency?
- Clinical: mendelian genetics
- Epidemiological: susceptibility loci
- Evolutionary: consequences of past infection in the genetic make up of populations
- Reverse genetics: KO, KI versus forward genetics: natural mutations, random mutagenesis
- Advantage and Limits of mouse genetics: controlled experimental conditions but lack of definition of natural functions of genes in a natural ecosystem
Human genetics of infectious diseases

Evolutionary time

Impact on population fitness

Clinical genetics

Epidemiological genetics

Evolutionary genetics
Clinical genetics of infectious diseases

Ex: Primary immunodeficiencies

• Some are rare, monogenic, familial and confer predisposition to multiple, recurrent, opportunistic and fatal infections in infancy
• Others are more frequent and confer susceptibility to a single infection, phenotype seen both in mouse or human models although some have no mouse equivalent:
  – Properdin and C’ defect in invasive Neisseria infection
  – X-linked lymphoproliferative disease and EBV
  – Epidermodysplasia verruciformis and papillomavirus
  – ApoL1 deficiency and trypanosomiasis
• Examples
  • Role of Th1 cells: critical for resistance to mycobacteria, redundant for most other microbes (penetrance variable depending on the gene defect)
  • Role of TLR: ? main sensors of microbes but IRAK4 deficiency susceptible to pneumococcal disease mainly, TL3-deficiency to herpes simplex encephalitis (Picard Science 2003, Zhang Science 2007)
  • Private (TLR3?) versus public (RAG-1) genes?
Epidemiological genetics of infectious diseases

• Interaction of genetic factors with environment
• Autosomal recessive deficiencies and susceptibility
  – DARC -> Plasmodium vivax
  – Glycosphingolipid P antigen -> parvovirus B19
  – CCR5 -> HIV
  – Fucosyltransferase 2 -> norovirus
• Linkage studies within families versus association studies between polymorphism and phenotype
• Common infectious diseases reflect polygenic inheritance
  – 5q31-33 for levels of Schistosomiasis mansoni infection
  – 8q12 for pulmonary tuberculosis
Extreme polymorphism of HLA genes and high heterozygosity at the population level result from a long process of balancing and positive selection.

Mendelian deficiencies in HLA expression confer vulnerability to a large number of pathogens.

Certain HLA alleles confer vulnerability to specific infections.
Homozygosity for the 32 CCR5 allele confers almost complete mendelian resistance to R5-tropic HIV-1, with little cost to fitness.

HIV-infected individuals heterozygous for the 32 CCR5 allele show delayed progression to AIDS.

32 is a recent mutational event under positive selection in the European population.
<table>
<thead>
<tr>
<th>Major parasitic infections</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Parasitic disease</th>
<th>Parasite</th>
<th>Vector</th>
<th>Population infected (million)</th>
<th>Deaths (000s)</th>
<th>Countries affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>African trypanosomiasis (sleeping sickness)</td>
<td>Protozoan Trypanosoma brucei, rhodesiense, gambiense</td>
<td>Bloodfeeding tsetse flies</td>
<td>0,3</td>
<td>48</td>
<td>Sub saharan Africa</td>
</tr>
<tr>
<td>American trypanosomiasis (Chagas disease)</td>
<td>Protozoan Trypanosoma cruzi</td>
<td>Bloodfeeding Assassin bugs</td>
<td>13</td>
<td>14</td>
<td>Central and South America</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>Protozoan Leishmania donovani, major, braziliensis</td>
<td>Sandflies (phlebotomes)</td>
<td>12</td>
<td>51</td>
<td>5 continents</td>
</tr>
<tr>
<td>Malaria</td>
<td>Protozoan Plasmodium vivax, malariae, ovale, falciparum</td>
<td>Bloodfeeding female Anopheles mosquito</td>
<td>300-500</td>
<td>1000,00</td>
<td>Africa, Asia, South America</td>
</tr>
<tr>
<td>Schistosomiasis (bilharziasis)</td>
<td>Trematode flatworms: Schistosoma haematobium, intercalatum, mansoni, japonicum, mekongi</td>
<td>Aquatic snails</td>
<td>200</td>
<td>200</td>
<td>Africa, Asia, Mediterranea</td>
</tr>
<tr>
<td>Lymphatic filariasis (elephantiasis)</td>
<td>Parasitic nematode worms</td>
<td>Bloodfeeding female mosquito</td>
<td>120</td>
<td>0</td>
<td>Africa, Asia, South America</td>
</tr>
<tr>
<td>Onchocerciasis (river blindness)</td>
<td>Parasitic worm of the family Filiariidae</td>
<td>Blackflies</td>
<td>18</td>
<td>0</td>
<td>Africa, South America, Yemen</td>
</tr>
<tr>
<td>Amebiasis</td>
<td>Protozoan parasite Entamoeba histolytica</td>
<td></td>
<td>40-50</td>
<td>100</td>
<td>India, South America, Africa</td>
</tr>
<tr>
<td>Soil trasmitted Helminthiases</td>
<td>Ascaris lumbricoides, Trichuris trichiura, Ancylostoma duodenale, Necator americanus</td>
<td></td>
<td>800-1200</td>
<td>135</td>
<td>China, Southern India, Southeast Asia, Africa and Latin America</td>
</tr>
</tbody>
</table>
Schistosomiasis

• Immunity
  – Sterile immunity against worms
  – Clinical immunity -> Protection against clinical signs

• Genetics: two major loci
  – 5q31-q33: control of infection levels -> cytokine cluster, Th2 / IgE Ab / eosinophil active against larvae, IL-13 polymorphism
  – 6q23: control of liver fibrosis
Schistosomiasis
Evolution of Schistosomiasis

**ACUTE**
- Katayama fever
- Th1: TNF, IL-1, IL-6
- Intestinal hemorrhages
- Mainly in newly exposed individuals
- IL-4 deficient mice: Lethal disease
  - Treatment with uric acid (ROS scavenger)

**CHRONIC**
- Concomittant with egg appearance
- Th2 response (IL-4 dependent), reduced inflammation
- Mostly in in utero exposed babies
- Prolonged Th2 responses -> liver fibrosis (IL-13)
- Th1 effectors: anti-fibrotic
Granuloma: variable composition

Liver
T cells, mast cells, eosinophils

Intestine
Macrophages

Infiltrating Cells

Nature Reviews | Immunology
Vanin-1 and Schistosomiasis

Symmers fibrosis

- Chronic oxidative stress
- IL-4/13 > IFN\(\gamma\)

A Dessein et al
Schistosomiasis

**Acute**
- Th1 > Th2 granuloma
- Unexposed individuals
- Intestine
- Hemorrhages
- IFNγ, IL-12, TNF

**Chronic**
- Th2 > Th1 granuloma
- In utero exposed individuals
- Liver
- Fibrosis
- IL-4, IL-13

**Vanin-1 KO**

*LETHALITY*
Schistosomiasis

Acute
Th1 > Th2 granuloma
Unexposed individuals
Intestine
Hemorrhages
IFNγ, IL-12, TNF
LETHALITY
IL-4R KO in MΦ
Wasting disease

Chronic
Th2 > Th1 granuloma
In utero exposed individuals
Liver
Fibrosis
IL-4, IL-13
Evolutionary genetics of infectious diseases

• Evolutionary footprints of natural selection exerted by past infections -> how natural selection shaped the variability of host defense genes (ex HLA, KIR) Abi-Rached JEM 2005 ?

• Selection
  – Positive selection of advantageous alleles
  – Heterozygote advantage (balancing selection)
  – Negative selection
  – Neutrality

• HbS and malaria

• Caspase 12 deficiency and resistance to sepsis (Xue Am J Hum Gen 2006)