Properties of Cytokines

Cytokines, chemokines and growth factors can be placed into several structurally & functionally related families

- Growth Factors (direct hematopoiesis and endothelial cell growth/activation)
- IL-1 Family (e.g., IL-1 & "Toll-like")
- TNF Family (e.g., TNFα, CD40L, FasL)
- TGF-β Family (e.g., TGF-β)
- Chemokines (e.g., CC and CXC families)
- Hematopoietins / a.k.a. Four Helix Bundle (e.g., IL-2, IL-4, IL-6, IL-10, IL-12, IFNγ, IFNα/β)

Let’s digress to review TCR signaling for an important clinical pearl!

TCR-mediated Signal Transduction: A Tyrosine Kinase Cascade
Cyclosporin A (CyA) & Tacrolimus (FK506) are two important drugs that block calcineurin activation and NF-AT activation, thus IL-2 production! They are therefore potent immunosuppressive drugs.

IL-4, IL-5 and IL-6 are Th2 cytokines and promote humoral immunity.

Pathophysiology of the balance between Th1 and Th2

Rheumatoid arthritis
type I diabetes mellitus
multiple sclerosis

Allergy
graft-vs-host disease

A. Host Defense
B. Disposal of Waste
C. Regulation of the Immune Response

Functions of Complement

Disposal of Waste
Immune Complex Removal
Apoptotic Cell Debris Removal
Phagocytosis: An Evolutionarily Conserved Mechanism to Remove Apoptotic Bodies and Microbial Pathogens

Immunological Consequences of Phagocytosis

- Clearance of pathogens
- Death of pathogenic microbe
- Resolution of infection
- Persistence of pathogenic microbe
- Failure of resolution of infection
- Clearance of apoptotic corpses
- Suppression of inflammation
- Tolerance
- Inappropriate inflammation
- Break in tolerance

Requirement of Activating FcRs in Immune Complex-mediated Glomerulonephritis

- Glomerulonephritis is blocked in γ chain-deficient NZB/NZW (lupus-prone) mice. Pathological features include mesangial thickening and hypercellularity evolving into end-stage sclerotic and crescentic changes.

Summary

1. Phagocytosis is a component of innate and acquired immunity. It is the principal means of destroying pathogenic bacteria and fungi. Phagocytosis initiates the process of antigen presentation.
2. Many phagocytic receptors recognize a diverse array of microbial pathogens. Some pathogens (e.g., S. pneumoniae) require opsonization for their clearance.
4. Phagocytosis is an essential component of development and tissue remodeling. Ingestion of apoptotic bodies is immunologically "silent" and is normally accompanied by a suppression of inflammation.
5. Failure of this mechanism may result in autoimmunity.
6. Fc receptors come in two basic types: activating (ITAM-associated) and inhibitory (ITIM-associated).
7. The relative expression of activating and inhibitory Fc receptors determines the outcome of a given engagement of Fc receptors.
8. Fc receptor-driven pathology includes formation and deposition of immune complexes, which play a major role in autoimmunity.
Receptors Important in The Systemic Response to Infection

The (Primary) Acquired Immune Response is Initiated by Innate Immune Recognition

Chemokines Direct Trafficking of Immune Cells
Autoimmune diseases: classification according to the class of the susceptibility MHC allotype and lineage of autoantigen specific T-cells mediating injury

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8</td>
<td>CD4</td>
</tr>
<tr>
<td>HLA-A,B, or C</td>
<td>HLA-DR, DQ, or DP</td>
</tr>
</tbody>
</table>

- Psoriasis
- Psoriatic arthritis
- Reiter’s syndrome
- Ankylosing spondylitis
- Lupus erythematosus
- Multiple sclerosis
- Pemphigus vulgaris
- Rheumatoid arthritis
- Psoriatic arthritis
- Psoriatic arthritis
- Reiter’s syndrome
- Ankylosing spondylitis
- Lupus erythematosus

Stages to progression of autoimmune disease

1. Genetic Predisposition
   - MHC allele
   - (+ other genes?)
2. Initiation of Immune Recognition
   - Event
   - (+ other genes?)
   - Autoimmunity
   - Autoimmune Disease
3. T cell clonal Expansion, Spreading
   - B cell help
   - Effector mechanisms
   - Inciting event /failure of tolerizing mechanism

T-Cell Anergy vs T-Cell Activation

- Pathological Mechanism of Rejection
  - **Hyperacute**
    - Minutes to hours
    - Preexisting antibodies (IgG)
    - Intravascular thrombosis
    - Hist of blood transfusion, transplantation or multiple pregnancies
  - **Acute Rejection**
    - Few days to weeks
    - CD4 + CD8 T-Cells
    - Humoral antibody response
    - Parenchymal damage & Inflammation
  - **Chronic Rejection**
    - Chronic fibrosis
    - Accelerated atherosclerosis
    - 6 month to 5 yrs
    - CD4, CD8, Th2
    - Macrophages

- **Primary Graft Failure**
  - 0 - 30 days
  - Host NK Cells
  - Lysis of donor stem cells

- **Secondary Graft Failure**
  - 30 days – 6 months
  - Autologous T-Cells
  - CD4 + CD8
  - Lysis of donor stem cells

Immune Mechanisms of Solid Organ Allograft Rejection
**Mechanism of T-Cell Inactivation**

(CTLA-4/B7 Interaction)

**ORAL TOLERANCE**

- ORAL ADMINISTRATION OF A PROTEIN ANTIGEN MAY LEAD TO SUPPRESSION OF SYSTEMIC HUMORAL AND CELL-MEDIATED IMMUNE RESPONSES TO IMMUNIZATION WITH THE SAME ANTIGEN.
- POSSIBLE MECHANISMS:
  - INDUCTION OF ANERGY OF ANTIGEN-SPECIFIC T CELLS
  - CLONAL DELETION OF ANTIGEN-SPECIFIC T CELLS
  - SELECTIVE EXPANSION OF CELLS PRODUCING IMMUNOSUPPRESSIVE CYTOKINES (IL-4, IL-10, TGF-β)

**REGULATORY T CELLS (CD4+)**

- TH3 CELLS: A POPULATION OF CD4+ T CELLS THAT PRODUCE TGF-β. ISOLATED FROM MICE FED LOW DOSE OF ANTIGEN FOR TOLERANCE INDUCTION
- TR1 CELLS: A POPULATION OF CD4+ T CELLS THAT PRODUCE IL-10. CAN PRODUCE SUPPRESSION OF EXPERIMENTAL COLITIS IN MICE
- CD4+CD25+ REGULATORY T CELLS: A POPULATION OF CD4+ T CELLS THAT CAN PREVENT AUTOREACTIVITY IN VIVO.

**INDUCTIVE LYMPHOEPITHELIAL TISSUES: PEYER’S PATCHES**

**EFFECOR SITES: LAMINA PROPRIA AND INTRAEPITHELIUM**

**Inflammatory Bowel Disease:**

Immunological Features

- HUMORAL IMMUNITY: MASSIVE INCREASE IN THE NUMBER OF PLASMA CELLS AND IN IgG PRODUCTION (IgG2 in CD and IgG1 in UC)
- IMBALANCE OF PRO-INFLAMMATORY (TNF-α, IL-1, IL-8, IL-12) AND ANTI-INFLAMMATORY CYTOKINES (IL-10, IL-4, IL-13)
Immune response to HIV-1 and effects of HIV infection

**HIV strain early in infection**
- R5 is almost always the sexually transmissible form of the virus
- Primary isolates from newly infected individuals are usually R5
- R5 strains mainly replicate in monocytes. Activated and memory T cells are infected, but at lower efficiency (old term = MT-tropic or monocytotropic)
- Therefore much of the viral load in earlier phase of HIV infection is in the monocytes and macrophages and the numbers of CD4 T cells remains stable, but decreased

**CD8 T-cell Response to HIV-1**
- Establishes asymptomatic phase of infection
- The CD8 T-cell responds to HIV-peptides by activation, clonal expansion, and differentiation to effector status
- Specific lysis of HIV-infected target cells (macrophages and CD4 T cells) via perforin pathway and/or apoptosis via upregulation of fas ligand
- Strong inhibition of viral infectivity by release of chemokines (MIP-1α/β, RANTES) that bind to CCR5 and block coreceptor dependent entry of R5 HIV-1
- Release of IFN-γ and secondarily TNF-α, decrease LTR-driven transcription

**Thwarted immunosurveillance (2)**
Dendritic cells used as a “Trojan Horse”
- Immature DCs, typically located in the submucosa express a C-type lectin DC-SIGN
- HIV-1 envelope binds to DC-SIGN with high affinity
- The virions are internalized and remain in acidic endosomal compartments while the DC matures
- Intact infectious virions are reexpressed on the surface when the DC enters the lymph node

**Viral Response near end of asymptomatic period**
- Rate of viral infection and potential mutations increases. Definitive viral escape occurs when virus is no longer presented by MHC to available CD8 T cell clones
- Continual generation of env mutations
- Selection against R5 variants by CD8 T-cell CCR5 chemokines that blocks infection is finally bypassed
- Change in cellular tropism by env mutations leads to X4 phenotype (CXC4, T-tropic)
- Enhanced T-tropism of X4 leads to more significant impairment of CD4 T-cell compartment

**Another reason for CD4 T cell loss**
CD4 T cell activation initiates HIV replication
HIV replication initiates CD4 T cell activation
T cell activation causes, among other effects, a marked increase in cyclin T1, NFAT and NFκB

Loss of the “epitope war”
EBV Latency, Immortalization and the Role of T Cells

EBV genomes exist in latent form intracellularly as circular plasmids; also EBV genome can integrate into cellular genome

Immortalization (Burkitt’s Lymphoma)

Latent infection

Depressed T cell function

EBV genome

EBNA

CR2

Endocytosis of the EBV-CR2 complex

HLA

MHC II

FcR

B Cell

IgE-mediated Inflammation

Early Phase

Time course: Minutes after antigen challenge
Example: Acute asthma
Cause: Mediators released by cells attracted to area of inflammation
Cells involved: Mast cells, basophils

IgE-mediated Inflammation

Late Phase

Time course: Hours after antigen challenge
Example: Chronic asthma
Cause: Mediators released by cells attracted to area of inflammation during and after the early phase
Cells involved: Eosinophils, Basophils, Neutrophils, Lymphocytes

Control of IgE Production (Candidate Genes)

I. Localization to specific chromosomes
   a. Chromosome 5q - Promoter variants for IL-4 (IL-3, -5, -9, -13 and GM-CSF)
   b. Chromosome 11q
      β Subunit of FcεRI (High affinity IgE receptor)
   c. Others
II. HLA linkage to specific antigen responses

“Hygiene Hypothesis”

- Observation (one of a number of examples) – Children raised in rural areas close to animals and exposed to endotoxin in dust have a lower incidence of atopic disease
- Theory – Endotoxin acting on Toll-like receptors influences the cytokines that APC’s secrete as they present antigen so as to favor a Th1 instead of a Th2 response
**IgE Receptor Cross-linking on Mast Cell**

**Inflammatory Mediators**

**Mast Cells and Basophils**
- Histamine
- Leukotrienes C₄, D₄, E₄
- Platelet Activating Factor (PAF)
- TNF-α, IL-4, IL-13

**Mast Cells Only**
- PGD₂
- Tryptase (Used to detect anaphylaxis)
- IL-5, -6

**Arachadonic Acid Metabolism**

**Some Results of Immunotherapy**

Specific IgE Decrease
Specific IgG Increases
Conversion from a Th2 to a Th1 Response
↓ IL-4

↑ IL-2, IFN-γ
Decreased eosinophil accumulation
Decreased mediator response
Non-specific decrease in basophil sensitivity