

Lecture 1: Foundations of Immunology (Review/Refresher) Dr. Alia Alubadi

1. Innate vs. Adaptive Immunity

- **Innate immunity**
 - Present from birth; non-specific; rapid response (minutes–hours)
 - No immunological memory (classically) — though "trained immunity" in monocytes/NK cells is an emerging exception worth flagging for discussion
 - Recognition via **Pattern Recognition Receptors (PRRs)**: Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors, C-type lectin receptors
 - Recognizes **PAMPs** (pathogen-associated molecular patterns) and **DAMPs** (damage-associated molecular patterns)
 - Physical/chemical barriers: skin, mucosa, mucus, antimicrobial peptides, commensal microbiota competition
 - Soluble mediators: complement, acute phase proteins, interferons
- **Adaptive immunity**
 - Antigen-specific; slower to develop (days) on first exposure
 - Generates immunological memory → basis for vaccination
 - Mediated by T and B lymphocytes bearing clonally distributed receptors (TCR, BCR) generated via **V(D)J recombination**
 - Clonal selection and clonal expansion as the organizing principle
- **Bridging concept**: Dendritic cells and other antigen-presenting cells (APCs) are the functional bridge — innate recognition events (PRR engagement) shape the character of the adaptive response (Th1 vs. Th2 vs. Th17 skewing). This bridging concept will recur throughout the course whenever we discuss immunopathology, since **most immune-mediated tissue damage arises from miscommunication or dysregulation at this innate–adaptive interface**.

Comparative note: Relative reliance on innate vs. adaptive mechanisms varies by species and life stage — e.g., neonatal rely heavily on passive transfer of maternal antibody (colostral IgG) because adaptive competence is immature at birth. Relevant later when discussing secondary immunodeficiencies.

2. Cells of the Immune System

Learning focus: Functional identity of each cell type, not just morphology — what does each cell *do* when it encounters antigen or danger signals?

Cell Type	Lineage	Key Functions	Immunopathology Relevance
Macrophages	Myeloid	Phagocytosis, antigen presentation, cytokine production	Central to granulomatous inflammation, chronic inflammatory disease,

		(TNF- α , IL-1, IL-6), tissue remodeling	M1/M2 polarization imbalance
Dendritic cells (DCs)	Myeloid/lymphoid	Professional APCs; capture antigen in periphery, migrate to lymph nodes, prime naïve T cells	Determine Th-subset polarization; central to tolerance vs. autoimmunity balance
Neutrophils	Myeloid	First responders; phagocytosis, NETosis (neutrophil extracellular traps), respiratory burst	Drivers of acute inflammatory tissue damage; NETs implicated in autoimmune flares
Lymphocytes (T & B)	Lymphoid	Antigen-specific recognition and effector/memory responses	Core effectors of adaptive immunopathology (autoimmunity, hypersensitivity)
NK cells	Lymphoid (innate)	Kill virus-infected and tumor cells without prior sensitization; "missing self" recognition via killer-cell receptors	Important in early antiviral defense and tumor immunosurveillance
Mast cells / Basophils / Eosinophils	Myeloid	Granule-mediated effector functions; central to Type I hypersensitivity and antiparasitic defense	Directly relevant to allergic and parasitic immunopathology (upcoming lecture)

Discussion prompt for seminar: Which of these cell types would you expect to dominate the histopathology of an acute vs. chronic lesion, and why does that timing matter diagnostically?

3. Antigen Presentation (MHC I/II)

Learning focus: MHC restriction as the molecular basis for T cell recognition — this is foundational for understanding autoimmune breakdown later in the course.

- **MHC Class I**
 - Expressed on nearly all nucleated cells
 - Presents **endogenous antigens** (cytosolic/viral proteins processed via the proteasome, loaded via TAP transporter in the ER)
 - Recognized by **CD8+ cytotoxic T lymphocytes (CTLs)**

- Key surveillance mechanism for intracellular pathogens and neoplastic cells
- **MHC Class II**
 - Restricted to professional APCs (DCs, macrophages, B cells) and some activated/epithelial cells depending on species and inflammatory state
 - Presents **exogenous antigens** (phagocytosed/endocytosed material processed in endolysosomal compartment)
 - Recognized by **CD4+ helper T cells**
- **Cross-presentation:** Some DC subsets can present exogenous antigen via MHC I — critical for priming CTL responses against antigens the DC did not directly synthesize (e.g., tumor antigens, some viral antigens)
- **Species/genetic note:** MHC in different species has different nomenclature (SLA in swine, BoLA in cattle, DLA in dogs, FLA in cats) but conserved function. MHC polymorphism underlies differential disease susceptibility across breeds/lines — a recurring theme in comparative immunopathology.
- **Clinical link forward:** Aberrant MHC II expression on non-professional

4. Humoral Immunity:

Antibodies are normally protective. However, antibodies may become pathogenic through several mechanisms.

Antibody against cell-surface antigens

Antibodies can:

• Activate complement	• Promote phagocytosis
• Cause cell destruction	• Alter receptor function

B Cells, Antibody Structure/Function, Isotypes

- **B cell activation**
 - T-dependent activation: requires cognate help from CD4+ Tfh cells via CD40–CD40L interaction → germinal center reaction → somatic hypermutation, affinity maturation, class switch recombination
 - T-independent activation: repetitive epitopes (e.g., bacterial polysaccharides) can activate B cells without T cell help — typically produces lower-affinity, less durable responses
- **Antibody structure**
 - Basic monomer: two heavy chains + two light chains, held by disulfide bonds
 - **Fab region:** antigen-binding specificity (variable regions, hypervariable CDR loops)
 - **Fc region:** determines effector function (complement fixation, Fc receptor binding on innate cells)
- **Isotypes and function**

Isotype	Key Features	Function
IgM	Pentameric; first antibody produced	Potent complement activation; early response marker
IgG	Monomeric; multiple subclasses	Opsonization, complement fixation, placental/colostral transfer, long-term memory
IgA	Dimeric (secretory form)	Mucosal immunity; neutralization at mucosal surfaces
IgE	Monomeric; binds FcεRI on mast cells/basophils	Type I hypersensitivity, antiparasitic immunity
IgD	Monomeric; naïve B cell surface marker	Poorly understood effector role; primarily a B cell receptor co-expressed with IgM

5. Cell-Mediated Immunity: T Cell Subsets

Subset	Master Transcription Factor	Signature Cytokines	Primary Function	Dysregulation Consequence
Th1	T-bet	IFN- γ , IL-2, TNF- α	Intracellular pathogen defense; macrophage activation	Excess $\rightarrow$ chronic inflammatory/granulomatous disease
Th2	GATA3	IL-4, IL-5, IL-13	Antiparasitic immunity; B cell help for IgE/IgG1	Excess $\rightarrow$ allergic disease, asthma-like pathology
Th17	ROR γ t	IL-17, IL-22	Extracellular bacterial/fungal defense; mucosal barrier integrity	Excess $\rightarrow$ autoimmune and chronic inflammatory disease (strongly implicated in several veterinary and human autoimmune conditions)
Treg	FoxP3	IL-10, TGF- β	Peripheral tolerance; suppression of autoreactive responses	Deficiency/dysfunction $\rightarrow$ autoimmunity, loss of tolerance
CD8 + CTLs	—	Perforin, granzymes, IFN- γ	Direct cytotoxic killing of infected/neoplastic cells	Excess/misdirected activity $\rightarrow$ tissue destruction in autoimmune and some infectious contexts

Conceptual emphasis: The **Th1/Th2/Th17/Treg balance** is arguably the single most important organizing framework. Nearly every immune-mediated disease we will discuss can be framed as a polarization imbalance or tolerance failure within this network.

6. Cytokines and Chemokines

Cytokines as the signaling language of the immune system; chemokines as the directional/positional signaling subset.

- **Cytokines:** small signaling proteins mediating autocrine, paracrine, and (less commonly) endocrine communication between immune cells
 - Pro-inflammatory: IL-1, IL-6, TNF- α
 - Anti-inflammatory/regulatory: IL-10, TGF- β
 - Interferons: Type I (IFN- α/β , antiviral), Type II (IFN- γ , macrophage activation)
- **Chemokines:** specialized cytokine family directing leukocyte migration along concentration gradients (chemotaxis)
 - Classified by conserved cysteine motif (CC, CXC, C, CX3C)
 - Determine which cell types are recruited to a site of inflammation and in what sequence — critical for interpreting the cellular composition of a histopathologic lesion

Clinical translation point: "Cytokine storm" — a state of dysregulated, self-amplifying cytokine release — will be discussed explicitly under infectious disease immunopathology (e.g., in the context of certain viral diseases).

7. Complement System Complement contributes to: Pathogen elimination, Opsonization, Chemotaxis, Inflammation, **and** Membrane attack complex formation

However, uncontrolled complement activation can damage host tissue.

The sequence can be summarized as:

Complement activation ↓ **C3a/C5a generation** ↓ **Inflammatory-cell recruitment and activation** ↓ **Endothelial and tissue injury**

Three activation pathways converging on a common effector cascade, and the dual role of complement in defense and in pathology.

- **Three activation pathways**
 - **Classical pathway:** antibody (IgM/IgG)–antigen complex triggers C1q binding
 - **Alternative pathway:** spontaneous C3 hydrolysis + pathogen surface factors; antibody-independent
 - **Lectin pathway:** mannose-binding lectin (MBL) recognizes microbial carbohydrate patterns
- **Convergence and effector functions**
 - All pathways converge at **C3 cleavage** → C3b (opsonization) and downstream formation of **C5 convertase**
 - **Membrane Attack Complex (MAC, C5b-9):** forms pores in target cell membranes → lysis

- **Anaphylatoxins (C3a, C5a):** recruit and activate inflammatory cells, increase vascular permeability
- **Regulation:** complement regulatory proteins (e.g., CD55, CD59) prevent host cell damage under normal conditions — loss of regulation is directly relevant to some hemolytic and immune-mediated diseases

Immunopathology relevance: Complement is a double-edged mechanism — essential for pathogen clearance and immune complex handling, but a direct mediator of tissue injury in Type II and Type III hypersensitivity reactions .

Immunopathology is the study of **tissue and organ damage caused by abnormal, excessive, misdirected, or persistent immune responses.**

The immune system normally protects the host against: Infectious microorganisms, Foreign antigens , Toxins , and Abnormal or transformed cells

However, the same mechanisms that provide protection can produce disease when they are: **excessive, inappropriate, prolonged, or directed against self-tissues.**

Therefore: **Immunity → protection** but under inappropriate conditions:

Immune response → inflammation → tissue injury → disease

A general model of immune-mediated disease

We should remember the following framework:

Initiating event Infection / injury / allergen / self-antigen / tumor

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Recognition **PRRs / BCR / TCR / antibodies**

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Immune activation **Innate + adaptive immunity**

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Mediator release **Cytokines / chemokines / complement / antibodies**

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Cellular recruitment **Neutrophils / monocytes / macrophages / lymphocytes**

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Tissue effects **Inflammation / endothelial activation / cellular injury**

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Outcome **Resolution → repair** or **Persistent inflammation → chronic tissue damage → disease**

Feature	Protective immunity	Immunopathology
Immune activation	Controlled	Excessive or inappropriate
Target	Pathogen/foreign antigen	Pathogen, allergen or self
Duration	Usually limited	Persistent/prolonged
Inflammation	Beneficial	Tissue damaging
Cytokines	Regulated	Dysregulated
Immune regulation	Intact	Insufficient or excessive
Tissue outcome	Protection/repair	Injury/dysfunction
Clinical consequence	Health	Disease

Immune checkpoints are regulatory pathways that fine-tune the amplitude and duration of immune responses — essentially molecular "brakes" that prevent

excessive or misdirected immune activation. They're a critical extension of the peripheral tolerance mechanisms we just covered, and they've become one of the most clinically important areas of immunology in the last decade because of cancer immunotherapy. For this course, checkpoints matter both as a tolerance mechanism *and* as a lens for understanding immunopathology when they fail or are therapeutically manipulated.

Checkpoints operate mainly at the **T cell activation synapse**, balancing costimulatory (activating) and coinhibitory (braking) signals delivered alongside TCR–MHC engagement. Without adequate coinhibitory signaling, T cell activation runs unchecked — a major route to autoimmune and chronic inflammatory tissue damage.

Major Checkpoint Molecules

CTLA-4 (CD152)

- Expressed on activated T cells and constitutively on Tregs
- Competes with CD28 for binding to CD80/CD86 on APCs, with much higher affinity — effectively outcompeting the costimulatory signal
- Also can strip CD80/86 from the APC surface via trans-endocytosis
- Acts primarily to dampen T cell priming in **lymph nodes**, early in the response
- Global CTLA-4 knockout in mice is lethal — massive lymphoproliferation and multi-organ lymphocytic infiltration within weeks, underscoring how essential this single checkpoint is for tolerance

PD-1 (CD279) / PD-L1, PD-L2

- PD-1 expressed on activated T cells, B cells, and NK cells; upregulated further with chronic antigen exposure
- PD-L1 broadly inducible on many tissue types (including epithelial cells) in response to inflammatory cytokines (especially IFN- γ) — this is a key **peripheral tissue-level tolerance mechanism**, distinct from CTLA-4's lymph-node-level action
- PD-1 engagement inhibits TCR signaling and promotes a state of **T cell exhaustion** — functionally hyporesponsive T cells that persist but don't kill effectively
- Physiologically important for limiting collateral tissue damage during prolonged immune responses (e.g., chronic viral infection) and for maternal-fetal tolerance

LAG-3, TIM-3, TIGIT (additional/newer checkpoints)

- Each engages distinct ligands and reinforces the exhausted T cell phenotype, often co-expressed with PD-1 on chronically stimulated T cells
- Increasingly relevant in both cancer immunology and chronic infection immunopathology as combinatorial targets

Checkpoint Failure and Immunopathology — Two Directions

This is the key conceptual pivot for the course: checkpoint dysregulation causes disease in **opposite directions** depending on whether the brake is too weak or too strong.

1. Checkpoint deficiency/loss → Autoimmunity and hyperinflammation

- Genetic CTLA-4 haploinsufficiency in humans causes a syndrome of lymphoproliferation, autoimmune cytopenias, and organ-infiltrative disease
- More broadly relevant to this course: **checkpoint inhibitor drugs** (anti-CTLA-4, anti-PD-1/PD-L1), now widely used in human and increasingly veterinary oncology, cause a well-documented class of **immune-related adverse events (irAEs)** — essentially iatrogenic autoimmune/inflammatory disease (colitis, hepatitis, dermatitis, endocrinopathies, pneumonitis) resulting directly from releasing the brakes that normally maintain peripheral tolerance. This is a clean, mechanistically explicit example of "checkpoint failure = immunopathology" that's excellent for seminar discussion.

2. Checkpoint overactivity → Immune evasion and failure to clear pathology

- Chronic infections (many persistent viral infections in veterinary and human medicine) drive sustained PD-1/PD-L1 upregulation, pushing antigen-specific T cells into **exhaustion** — the immune system fails to clear the pathogen because its own regulatory machinery is suppressing the effector response
- **Tumors exploit this directly:** many cancers upregulate PD-L1 to co-opt the checkpoint system and evade immune surveillance — this is the entire rationale behind checkpoint inhibitor cancer immunotherapy (blocking the brake to restore antitumor T cell activity)

M1/M2, Cross-presentation, Inflammasome/caspase-1 pathway
