The immunology of infection

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Abstract

The human immune system is composed of a collection of specialized cells and secreted proteins that allows the identification and removal of an invading pathogen, and, in doing so, limits host injury or death. This system is composed of innate and adaptive branches. It is important to recognize that although the innate and adaptive branches of the immune system differ fundamentally in their mechanisms of pathogen recognition, neither branch functions in isolation. Here, we address how the innate and adaptive immune systems sense the presence of a pathogen, how the immune system then coordinates anti-pathogen effector functions to remove the pathogen, and how immunological memory functions to protect the host against subsequent exposure to the same pathogen. We outline how dysregulated anti-pathogen immune responses can be deleterious. Finally, we consider how vaccines harness the immune system to induce protective immunity against infection and how controlled human infection models can inform our understanding of the immunology of infection.

Keywords Adaptive immunity; B cells; dendritic cells; immunological memory; infection models; innate immunity; macrophages; pandemic; T cells; vaccines

Introduction

Recent experience of the coronavirus disease 2019 (COVID-19) pandemic has served as a powerful reminder that throughout human history pandemics have been among the strongest selective forces driving human evolution.

The co-evolution of vertebrates alongside their pathogens has directed the emergence and development of the vertebrate immune system. In vertebrates, two complementary branches of the immune system emerged: first, an evolutionarily ancient system of innate immunity, followed, second, by the more recent emergence of adaptive immunity.

Our understanding of immunity to infection in humans has been particularly informed by genetic studies of rare individuals with primary immunodeficiencies[1] and population-based studies of infection susceptibility,[2] for example genome-wide association studies.

Key points

- Pathogen recognition mediated by the innate immune system uses germline-encoded pathogen receptors, facilitating rapid immune responses during primary infectious exposure
- Pathogen recognition mediated by the adaptive immune system uses receptors generated by random somatic gene rearrangement and mutation. Recognition of a pathogen by adaptive receptors during a primary infection allows the selection and retention of those receptors for use during a secondary infection, i.e. immunological memory
- Immune effector responses are highly specific to a given pathogen class. The linkage of an appropriate effector response to a pathogen is a key feature of effective immune control; similarly, dysregulated effector responses are an important contributor to poor outcomes from infection
- The innate and adaptive immune systems operate in a highly cooperative manner. Effective immune responses to infection or vaccination engage both the innate and adaptive immune systems
- Vaccination serves to prime the adaptive immune system against specific pathogens, inducing immunological memory and enabling a rapid recruitment of pathogen-specific effector responses in the face of infection

Pathogen recognition

Innate pathogen recognition

Innate pathogen sensors are germline encoded, so their specificities are invariant throughout a person's life. Innate immune recognition of an invading pathogen proceeds by two broad mechanisms: detection of evolutionarily conserved molecular structures displayed by microbes, and surveillance for altered distributions of self-antigens, acting as alarm signals indicating infection and tissue damage.

The first mechanism employs pattern-recognition receptors (PRRs), which bind microbial structures collectively termed pathogen-associated molecular patterns (PAMPs). Toll-like receptors (TLRs) are examples of these. The structural diversity of PRRs allows the detection of a broad range of bacteria, viruses and fungi. In addition to PRRs, a network of plasma proteins (complement) act as innate pathogen sensors (Figure 1).

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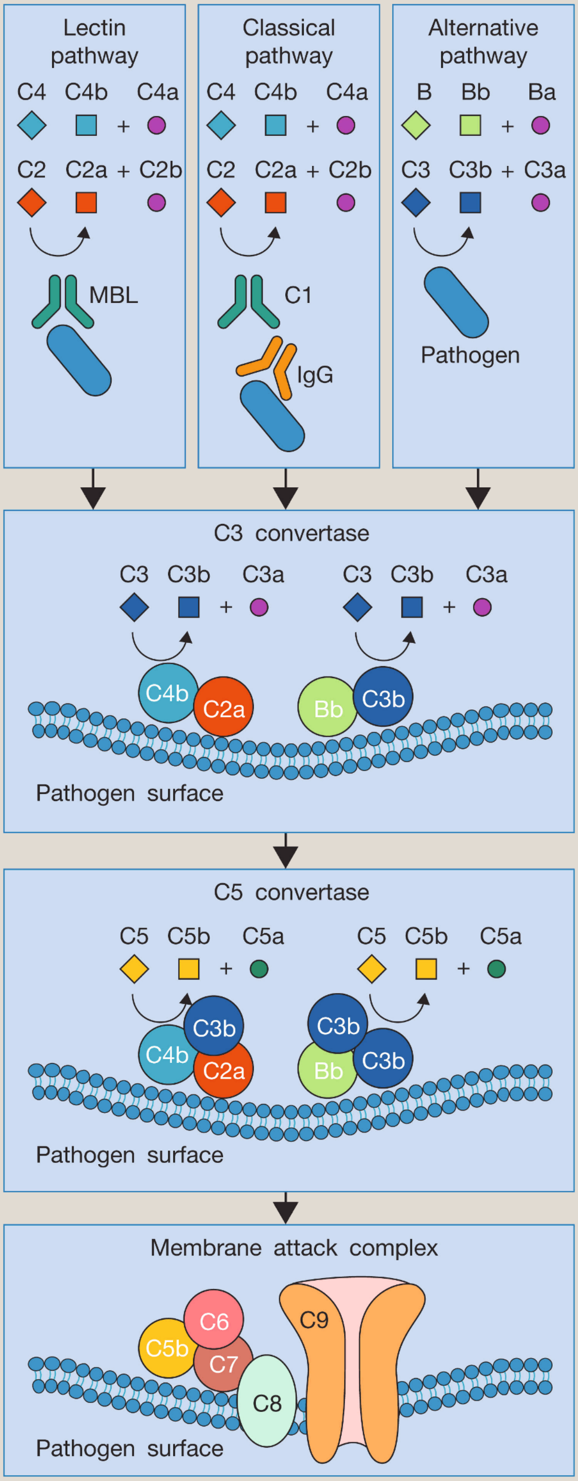
The complement cascade



Complement proteins identify extracellular pathogens via one of three pathways, the lectin, classical and alternative pathways.

- The lectin pathway uses secreted pattern-recognition receptors (PRRs), e.g. mannose-binding lectin (MBL), to directly ligate carbohydrate pathogen-associated molecular patterns (PAMPs) on pathogen surfaces.
- The classical pathway uses the C1 protein complex to bind pathogen surfaces opsonized by other serum proteins, e.g. antibody or C-reactive protein (CRP – binds phosphocholine of lipopolysaccharide).
- Alternative complement pathway components are constantly deposited on cell surfaces. On host cell surfaces, these activated alternative pathway complement components are rapidly removed by surface-expressed host cell enzymes (e.g. decay-accelerating factors), but microbial surfaces, lacking these enzymes are identified and marked for removal by immune effectors.

Complement activation results in formation of a proteolytic enzyme complex – the C3 convertase, which cleaves C3 into C3a and C3b.

- The lectin and classical pathway C3 convertases are composed of C4b and C2a.
- The alternative pathway C3 convertase is composed of C3b and Bb.
- C3a is not retained on the pathogen surface, and functions as a signalling molecule via endothelial and mast cells, supporting local inflammation by increasing vascular permeability facilitating immune cell recruitment to the site of infection.

Addition of the C3b to the C3 convertase results in formation of a second proteolytic enzyme complex – the C5 convertase, which cleaves C5 into C5a and C5b.

- C3b on pathogen surfaces acts as an opsonin for pathogen uptake by phagocytes, e.g. macrophages.
- In common with C3a, C5a is released from the pathogen surface, resulting in immune cell recruitment.

C5b deposition on a pathogen surface triggers recruitment of the terminal complement components, C6, C7, C8 and C9.

- Polymerization of C9 on the pathogen surface results in the formation of membrane-spanning pore structures: the membrane attack complex.
- Membrane attack complex disrupts the integrity of the pathogen outer membrane, resulting in direct pathogen destruction.

Figure 1 The complement cascade functions to identify the surfaces of extracellular pathogens. On identification of a pathogen surface, the sequential formation of proteolytic multiprotein complexes directs the production of activated complement components. Activated complement components function to recruit immune cells to the site of infection, opsonize pathogens for phagocytosis and form multiprotein membrane-spanning pores to directly damage pathogens.

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Natural killer (NK) cells are innate lymphoid cells expressing germline-encoded receptors that monitor host cells for abnormalities, especially downregulation of major histocompatibility complex (MHC) class I (a common consequence of viral infection). Killer cell immunoglobulin-like receptors on NK cells transmit inhibitory signals when they engage normal levels of MHC I on healthy cells.

Virus-infected cells often lose MHC I, reducing NK cell inhibition. Conversely, infected or stressed cells can upregulate ligands for NK-activating receptors. This equilibrium of inhibitory and activating signals allows NK cells to distinguish healthy and diseased cells, and thus initiate the killing of infected/stressed host cells (see below).

Adaptive pathogen recognition

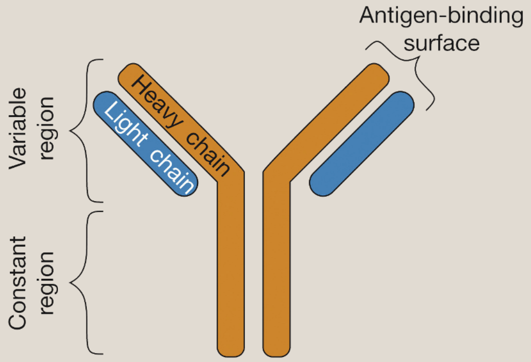
In contrast to innate immune receptors, adaptive immune receptors are generated by random somatic gene rearrangements and mutations. This process generates a highly diverse receptor repertoire, further shaped by pathogens encountered during an individual's lifespan.

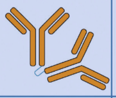
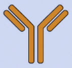
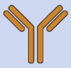
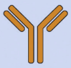
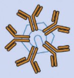
The lymphocytes of the adaptive immune system, B cells and T cells, each express a unique antigen receptor. Naive B cells have immunoglobulin molecules as their B cell receptors (BCRs), which can also be secreted as antibodies from effector B cells, known as plasma cells (Figure 2). T cells have T cell receptors (TCRs) that recognize peptide antigens displayed on MHC molecules on cell surfaces (Figure 3).

Each naive B cell and T cell has a unique antigenic specificity defined by the sequence of its receptor (BCR, TCR). The potential diversity of these receptors is estimated to be at least 10^{11}. To generate that degree of receptor diversity, both B and T cells employ random somatic rearrangement of immunoglobulin- and TCR-encoding gene segments. This is accompanied by somatic mutation on encountering a receptor's cognate antigen.

Both BCR (and antibodies) and TCR chains are germline-encoded by gene segments that require rearrangement to produce a gene that can be transcribed in a lymphocyte. The variable regions in TCR and immunoglobulin chains are encoded by the V and J segments, with an additional D segment in TCR-β chains and immunoglobulin heavy chains. Receptor diversity is

The structure and function of antibody



Class	Structure	Subclass	Major functions
IgA	Dimeric 		Neutralizing antibody at epithelial surfaces
IgD	Monomeric 		Unclear
IgE	Monomeric 		Mast cell and basophil sensitization
IgG	Monomeric 	IgG1	Neutralization Opsonization NK cell sensitization Complement activation Placental transfer
		IgG2	Neutralization
		IgG3	Neutralization Opsonization NK cell sensitization Complement activation Placental transfer
		IgG4	Neutralization
IgM	Pentameric 		Complement activation

Antibodies (in their monomeric form) are composed of two heavy and two light chains, each comprising immunoglobulin protein domains (two in the case of light chains, four for heavy chains). Each chain's amino terminus contributes to two variable regions of the antibody molecule, which forms the antigen-binding surface. The carboxy terminus of each chain contributes to the constant (non-variable) regions of the antibody molecule, which determines interaction of the pathogen-bound antibody with cells and molecules of the immune systems, thus determining its effector functions. The first secreted antibody response from a B cell after priming is IgM. Depending on the invading pathogen and the appropriate immune response, this can be subsequently changed to another antibody class in a process termed class-switching. The structure and function of the major antibody classes are depicted in the table.

Figure 2

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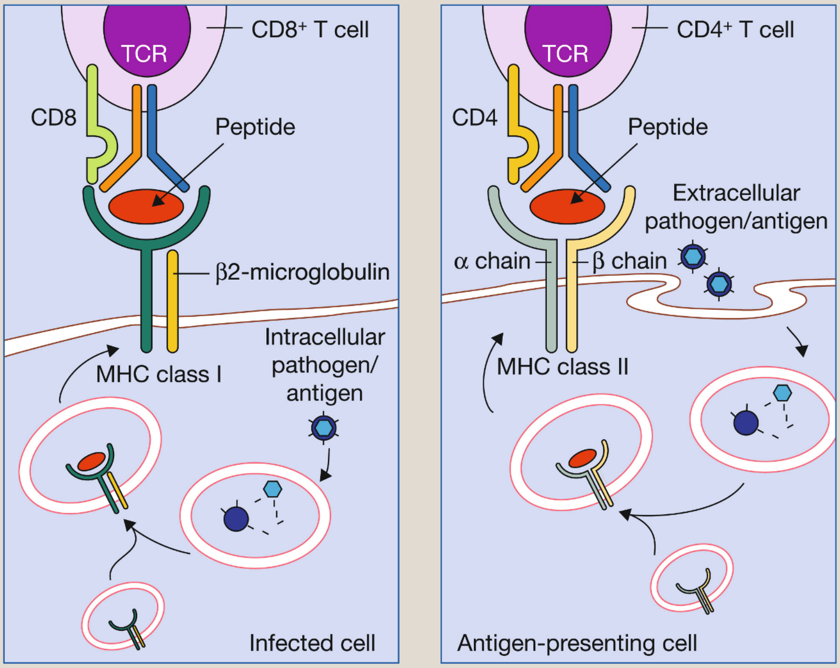
TCR antigen recognition



TCRs ligate pathogen-derived peptide presented by MHC molecules expressed on host cell surfaces.

- Two classes of MHC present pathogen-derived peptides: MHC classes I and II. Both are composed of two polypeptide chains, are membrane-bound and present peptide at the cell surface in a highly polymorphic binding groove. MHC class I molecules are composed of a polymorphic chain, which makes up the peptide binding groove, and an invariant β2-microglobulin chain. MHC class II molecules, by contrast, are composed of two polymorphic polypeptide chains (α and β), both of which contribute to the peptide-binding groove.
- Peptide presented by MHC class I molecules (left panel) is derived from cytosolic pathogen proteins by the cytosolic proteasome. Pathogen-derived peptides can then be transported to the endoplasmic reticulum, where they are loaded onto MHC class I molecules. MHC class I-associated peptide is recognized by TCRs on CD8+ T cells.
- MHC class II molecules present peptides derived from pathogen antigen in endosomes of antigen-presenting cells (right panel). Extracellular antigen is taken up by antigen-presenting cells either via receptor-mediated endocytosis of opsonized pathogens (e.g. via complement or Fc receptors), or by random sampling of the environment (termed macropinocytosis), before loading onto MHC class II molecules and presentation at the cell surface. MHC class II-associated peptide is recognized by TCRs on CD4+ T cells.

Figure 3

generated by virtue of each gene segment having multiple copies, and these are spliced together randomly.

Through this process, each naive B and T lymphocyte expresses multiple copies of a single receptor of unique antigen specificity. On binding its cognate antigen, a lymphocyte bearing that receptor is then triggered to undergo clonal expansion, allowing highly specific pathogen recognition, and also the capacity for immunological memory.

Adaptive immunity also relies on antigen presentation by MHC molecules. MHC class I molecules (on nearly all nucleated cells) present cytosolic peptides from intracellular pathogens; this flags infected cells for destruction by CD8+ cytotoxic T cells (see below). In contrast, MHC class II molecules are restricted to specialized immune cells (dendritic cells, macrophages, B cells) and present peptides from extracellular pathogens.

Dendritic cells at sites of infection (e.g. skin, mucosae) ingest pathogens and associated antigens and then migrate to lymph nodes, where they present antigen peptides on MHC II to activate naive CD4+ T cells. Activated CD4+ T cells in turn help coordinate immune responses. B cells and macrophages can also present antigen on MHC II, but they primarily interact with activated CD4+ T cells (rather than priming naive T cells). Activated T cells can then provide necessary help for the B cell to proliferate and differentiate (see below).

Similarly, macrophages presenting antigen to activated CD4+ cells receive signals (such as interferon (IFN)-γ) that enhance the

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macrophage's microbicidal mechanisms. This dialogue is especially important for eliminating pathogens (e.g. mycobacteria, *Salmonella*) that can survive inside macrophages.

Effector functions

Innate effector functions

Complement and secreted antimicrobial molecules: effector mechanisms of the complement cascade are outlined in Figure 1.

In addition to complement, many secreted antimicrobial molecules have direct antimicrobial activity. Lysozyme and phospholipase A_2 are secreted at mucosal surfaces (including oral mucosa, conjunctiva and gut) and by phagocytes, acting to disrupt bacterial cell walls. Similarly, antimicrobial peptides, such as defensins, are secreted by phagocytes and epithelial cells at mucosal surfaces, and form membrane-disrupting pores in microbes.

Clearance of extracellular bacteria by phagocytes: when microbes breach tissue barriers, they encounter macrophages. PRR engagement on macrophages triggers phagocytosis and the microbe is engulfed into a phagosome. The phagosome then fuses with lysosomes to form a phagolysosome, where the pathogen is killed by acidic pH, reactive oxygen species (produced by reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase), hydrolytic enzymes and deprivation of nutrients (e.g. sequestration of iron).

Activated macrophages and neutrophils also release chemokines and cytokines to recruit additional leucocytes (neutrophils, monocytes, lymphocytes) to the infection site. Neutrophils can also extrude webs of chromatin and DNA called neutrophil extracellular traps that entangle and kill extracellular pathogens.

Inflammatory and antiviral responses: TLR signalling in innate immune cells results in activation of nuclear factor-κB (NF-κB) or IFN regulatory factor transcription factors. NF-κB activation results in the production and secretion of a range of proinflammatory cytokines, including interleukin (IL)-1β, tumour necrosis factor (TNF), IL-6, IL-8 and IL-12. These cytokines direct immune cell recruitment and activation at the infection site. IL-1β, TNF and IL-6 also have systemic effects, supporting the acute-phase response, triggering fever, neutrophil egress from the bone marrow and hepatic production of acute-phase proteins.

A second, independent mechanism of inflammatory cytokine induction by innate immune cells is pyroptosis. Nucleotide-binding oligomerization domain-like receptors, on sensing cytosolic PAMPs, activate the formation of multiprotein scaffolds — inflammasomes — which activate proinflammatory caspases. This triggers pyroptosis (proinflammatory programmed cell death), which includes the production and release of IL-1β and IL-18.

IFN regulatory factor activation is induced by innate sensors of viral PAMPs (e.g. TLRs 3, 7, 8 and 9 and retinoic acid-inducible gene 1 (RIG1)). This results in the production of type 1 IFN (IFN-α, IFN-β), of which plasmacytoid dendritic cells are particularly potent producers. Type 1 IFN induces viral resistance in host cells, activating enzymes that degrade viral RNA and suppressing protein translation (and thus viral replication). Type 1 IFN also upregulates IFN-induced transmembrane proteins that suppress viral membrane fusion with endosomal membranes (thus inhibiting viral invasion), and MHC class I expression.

Natural killer cells trigger infected cells to undergo apoptosis by the release of perforin and granzymes onto the surface of infected cells (see Effector functions of CD8+ T cells, below). Additionally, activated NK cells act as an innate source of IFN-γ, upregulating the antibacterial effector mechanisms of macrophages and enhancing clearance of intracellular pathogens.

Adaptive effector functions

Effector functions of CD8+ T cells: on binding to its cognate MHC class I—peptide pair, a naive CD8+ T cell proliferates and differentiates into a cytotoxic CD8+ T lymphocyte (CTL). Like NK cells, CTLs induce apoptosis in infected host cells via the release of pre-formed granules containing perforin and granzymes onto the surface of infected host cells.

Perforin forms pores in the host cell membrane, allowing granzymes to be delivered into the infected cell cytosol. Granzymes induce apoptosis by directly damaging mitochondria and initiating caspase activation. Notably, CTL-induced cell death is immunologically silent: it does not induce inflammation, minimizing neighbouring tissue damage.

Effector functions of CD4+ T cells: naive CD4+ T cells, on binding to their cognate MHC—peptide pair, proliferate and then differentiate into one of five effector subsets. Effector CD4+ T cells are defined by the profile of cytokines they produce, which determines the immune cells they recruit and activate, and thus the type of infection they are specialized to clear.

The five main effector subsets are designated T helper 1 (Th1), Th2 and Th17 (Figure 4), follicular helper T (Tfh) and regulatory T (Treg) cells. Tfh cells develop in parallel to Th1/Th2/Th17 responses, providing support for the maturation of antibody responses (see below). CD4+ Treg cells, in contrast to the other four effector subsets, are inhibitory and act to limit autoreactivity (and thus autoimmune disease).

Effector functions of B cells: antibody binds to pathogens and pathogen-derived molecules, functioning to neutralize pathogens and toxins (e.g. binding viral particles preventing host cell invasion), and opsonize pathogens for destruction by immune cells and complement. The constant region of the immunoglobulin heavy chain determines the class of that antibody, and thus its function (see Figure 2).

For a naive B cell to differentiate into a mature antibody-secreting plasma cell or memory B cell, it needs to recognize cognate antigen via its surface-bound BCRs and also receive co-stimulatory signals. With a protein antigen, this co-stimulation is provided by Tfh cells. Antigen internalized by the B cell is presented on MHC class II molecules and then recognized by Tfh cells.

Tfh co-stimulation supports B cell proliferation and survival, somatic hypermutation (further rounds of somatic mutation of immunoglobulin variable regions that result in enhanced antigen—antibody affinity) and antibody class-switching. The antibody class to which the B cell switches is a complex and partially understood process determined by engagement of BCRs and TLRs on the B cell surface and the local cytokine environment.

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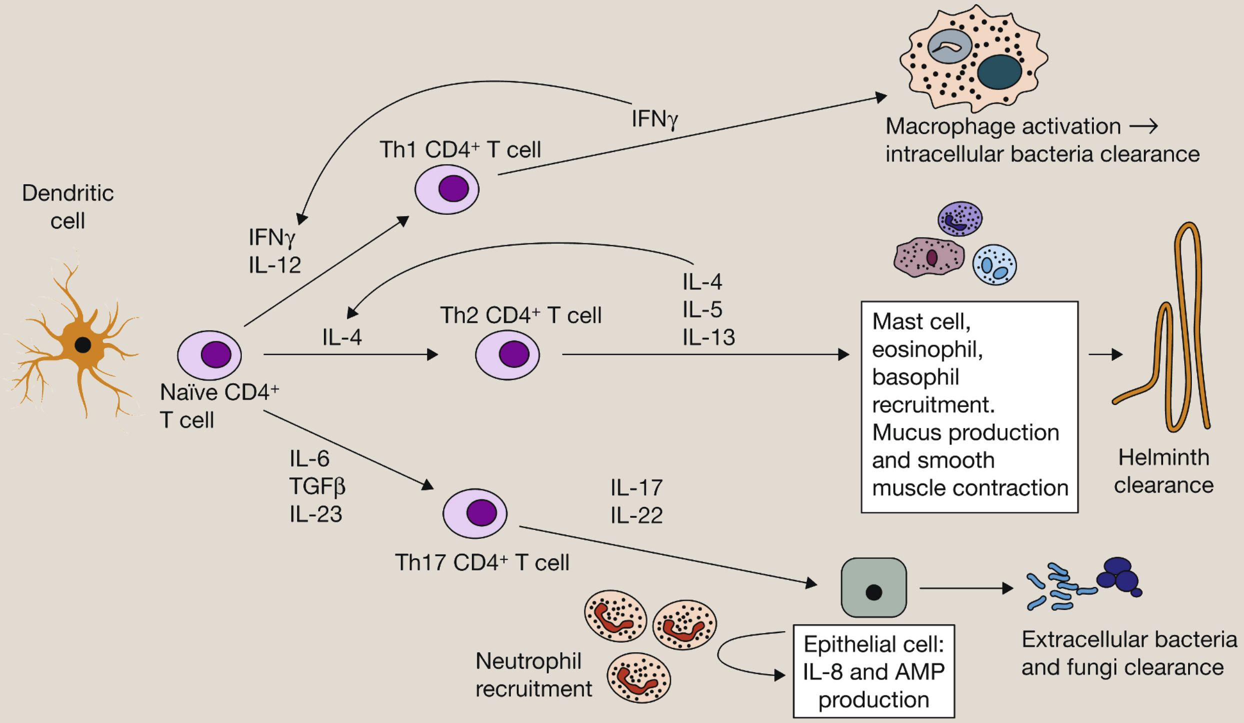
Effector functions of CD4+ Th cells



- Th1 cells produce IFN-γ and support macrophage activation to control intracellular bacteria. Th2 cells produce IL-4, IL-5 and IL-13, recruiting and activating mast cells, eosinophils and basophils, facilitating defence against extracellular parasites. Th17 cells produce IL-17 and IL-22, stimulating epithelial cells to release chemokines, which recruit neutrophils, and antimicrobial peptides facilitating host defence at epithelial surfaces.
- The fate of a naive CD4+ T cell during priming is determined by the local cytokine environment, with IL-12 and IFN-γ supporting Th1 development, IL-4 supporting Th2 development, and IL-6, TGF-β and IL-23 supporting Th17 development. These cytokines are initially provided by innate cells (e.g. NK cells providing an initial IFN-γ source), but the overlap between cytokines determining differentiation and effector cytokines (in the case of Th1 and Th2 cells) mean that differentiated CD4+ T cells support their own differentiation by positive feedback.
- Effector cytokines from Th1, Th2 and Th17 cells inhibit differentiation of naive CD4+ T cells into effector Th cells other than their own.

Figure 4 AMP, antimicrobial peptides; for other abbreviations, see text.

Immunological memory

B cell memory

B cell immunity results in long-lasting, pathogen-specific memory by two principal mechanisms: long-lived plasma cells and memory B-cells.

A proportion of primed B cells (plasmablasts), formed after the primary response to infection, migrate from secondary lymphoid tissue to bone marrow, where they form long-lived plasma cells. These cells are capable of long-term antibody production in the absence of continuing antigenic stimulation. In doing so, they give rise to serological immunity, i.e. steady-state production of antigen-specific antibodies in serum, which are ready to act in a neutralizing capacity at the point of pathogen invasion.

Memory B cells, after their generation from primed B cells, reside in secondary lymphoid organs in a quiescent state. On re-encountering their cognate antigen during a subsequent infectious challenge, they express large amounts of cell-surface, class-switched immunoglobulin and MHC class II molecules. This facilitates the rapid production of class-switched plasma cells producing antibody of high affinity immediately after a secondary infectious challenge.

In addition, during a secondary infectious challenge, memory B cells can re-enter germinal centres, allowing further rounds of somatic hypermutation and affinity maturation, resulting in the iterative improvement of antibody affinity for a given pathogen after each exposure.

T cell memory

After resolution of a primary infection, a proportion of antigen-specific CD4+ and CD8+ T cells persist as memory T cells. Both CD4+ and CD8+ T cells have three classes of effector memory cell, defined according to the tissues they home to.

Central memory T (T_{CM}) cells circulate in the peripheral blood, homing to secondary lymphoid organs. Effector memory T (T_{EM}) cells also circulate in the peripheral blood, but lack lymphoid homing markers and instead home to peripheral tissue. Finally, tissue-resident memory T (T_{RM}) cells do not circulate in blood, but instead remain *in situ* in peripheral tissues.

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This distribution of memory T cells allows three waves of memory T cell effector functions on re-encountering a pathogen. First, T_{RM} cells act to monitor peripheral tissue for invading pathogens, allowing activation of immediate T cell-mediated immunity on pathogen invasion. Second, peripheral T_{EM} cells are rapidly recruited to sites of inflammation, supplementing the T_{RM} response. Third, T_{CM} cells encountering cognate antigen in secondary lymphoid tissue rapidly generate secondary effector T cells, further supplementing the T_{EM} and T_{RM} responses.

Memory and innate immunity

Whereas immunological memory is largely the preserve of the adaptive immune system, memory-like characteristics are exhibited by innate immune cells.

After a primary infectious or vaccination, innate cells (e.g. NK cells, macrophages) undergo epigenetic modification that results in enhanced effector function in response to a subsequent infectious exposure. These effects, termed ‘trained immunity’, are heterologous, i.e. they can enhance responses to unrelated pathogens, reflecting the fact that innate receptors are invariant and not altered by pathogen exposure.

Interestingly, however, NK cell memory can also function in an antigen-specific manner. This is best characterized in cytomegalovirus (CMV) infection, in which NK cells bearing innate receptors identifying CMV-infected cells expand in response to a primary infection and persist after resolution.

Induction of memory responses by vaccination

By safely inducing immunological memory, vaccination prevents millions of infectious deaths annually and is the most impactful and cost-effective health intervention in the history of medicine.[3] Vaccines can be separated into two broad groups.

The earliest vaccines consisted of whole organisms that were either live and attenuated, with measles, mumps, rubella, rotavirus and BCG (bacillus Calmette—Guérin; for tuberculosis) vaccines as modern examples, or killed, such as present-day whole-cell pertussis, influenza, cholera and rabies vaccines. Attenuation or inactivation by killing allows such vaccines to be administered safely.

The immune response and immunological memory are directed against the whole organism and supported by the full engagement of innate receptors. For some pathogens, this approach works well (e.g. measles), while for others, protective immunity is short-lived (e.g. Ty21a-attenuated whole-cell typhoid vaccine) or excessively reactogenic (e.g. whole-cell killed typhoid vaccines).

Most recent vaccines consist of one or more critical specific portions or ‘subunits’ of a pathogen that are key targets of protective immunity. Examples of such subunit vaccines include toxoid vaccines (e.g. tetanus, diphtheria), recombinant protein vaccines (e.g. hepatitis B), protein—polysaccharide conjugate vaccines targeting the capsules of encapsulated bacteria (e.g. pneumococcal, meningococcal and *Haemophilus influenzae* type B conjugate vaccines) and virus-like particles (e.g. human papillomavirus and malaria vaccines).

Delivery of purified pathogen molecules sometimes requires the co-administration of adjuvants to induce sufficient immunological memory for long-term protection. Adjuvants (e.g. alum, MF59) are not pathogen-specific, and act partly by engaging innate receptors.

The COVID-19 pandemic led to the rapid development of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) deploying novel technologies including mRNA and viral vectors, providing an ever-broadening array of platforms for vaccine development. However, there are key global infectious diseases including HIV and tuberculosis that still lack effective vaccines, partly because of highly polymorphic surface structures and incomplete understanding of the relevant mechanisms of protective immunity.

Sepsis and hyperinflammatory syndromes

Immune-mediated recognition and removal of infectious agents allows humans to survive constant exposure to potential pathogens. However, misdirected or excessive immune responses to pathogens can themselves be deleterious to human health.

This is most notable in individuals with sepsis, whereby infection results in dysregulated immune responses characterized by hyperinflammation, endothelial injury and organ damage early in the disease, followed by post-sepsis immunosuppression. The need to control excessive immune responses in uncontrolled infection was exemplified by the use of tocilizumab (an anti-IL-6 monoclonal antibody) to improve survival in severe COVID-19 disease.

Haemophagocytic lymphohistiocytosis (HLH) provides an extreme example of how unchecked immune responses, often triggered by infection, drive tissue injury and death. In HLH, excessive T cell and macrophage activation results in a fulminant cytokine storm with severe systemic inflammation, bone marrow failure and multiorgan dysfunction.

HLH has been classically considered to be primary (genetic), resulting from inherited defects in immune signalling pathways, or secondary, caused by immunological triggers such as infection, malignancy, autoimmune disease or drugs. There is, however, a growing appreciation that even where HLH occurs with a defined trigger, inherited factors play a critical role in the likelihood of it developing.

Regardless, an ineffective cytotoxic function of effector cells permits macrophage overactivation by T cell cytokines (e.g. IFN-γ),[4] creating a self-perpetuating inflammatory cycle, which needs immunosuppressive drugs (e.g. corticosteroids, anti-IL1 agents) to abort it.

Controlled human infection models

Our understanding of the immunology of infection has to date largely relied on clinical observation and immunological analysis of samples from individuals with naturally acquired infections, and from animal models. The former approach suffers from a lack of understanding of the subject’s premorbid state and background immunity, while the latter is limited by inherent differences between human and animal immunology.

Controlled human infection models, where volunteers are artificially infected with a known dose of a pathogen and where the course of infection is carefully monitored, are increasingly used to accelerate our understanding of the immunology of infection.[5] Such studies are conducted under tightly controlled conditions to ensure participant safety, and provide valuable insights into the pathogenesis of infection and mechanisms of protective immunity.

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By comparing the background immunity of participants who do and do not develop clinical disease after an infectious challenge, it is possible to establish which immunological parameters correlate with protection, i.e. the immunological correlates of protection. Such information is valuable for informing the design and development of new vaccines. Controlled infection studies also provide an early understanding of the protective efficacy of new candidate. Current examples of controlled human infection models include those for influenza, malaria, typhoid, cholera and *Shigella*.

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To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 30-year-old man presented for review. He had undergone an allogeneic hematopoietic stem cell transplant for acute leukaemia 1 year previously and was in remission and off all immunosuppressants. He had completed all the standard childhood immunizations before the transplant.

What advice should be given about repeat immunization?

A. Advise that no re-vaccination is necessary because his pre-transplant immunity is retained
B. Administer a full schedule of routine vaccinations to rebuild his immunity
C. Defer all immunizations until at least 5 years after transplantation to allow full immune recovery
D. Perform antibody titre testing for vaccine-preventable diseases and only vaccinate if titres are low
E. Provide only annual influenza vaccination and pneumococcal vaccine

Question 2

A 35-year-old man presented with a 4-month history of fever, night sweats and weight loss, accompanied by a productive, persistent cough. He had Crohn's disease, which was treated with an anti-tumour necrosis factor agent (adalimumab). He had been born in Pakistan and had moved to the UK at the age of 15 years.

Investigation

- Sputum microscopy showed acid- and alcohol-fast bacilli

What T cell effector function is likely to have facilitated control of his latent infection before his presentation?

A. CD4+ T helper (Th) 17 cell secretion of IL-17, leading to neutrophil recruitment and activation
B. CD4+ Th2 secretion of interleukin (IL)-5 leading to eosinophil recruitment and activation
C. CD8+ T cell cytotoxicity of infected host cells
D. CD4+ follicular Th cell support of anti-pathogen neutralizing antibody
E. CD4+ Th1 cell secretion of IFN-γ, leading to macrophage activation

Question 3

A group of researchers developed a controlled human infection model for *Neisseria gonorrhoeae*, enrolling healthy adult male volunteers under strict ethical supervision. Participants were given a urogenital inoculum of the pathogen with close monitoring and prompt antibiotic treatment upon confirmation of infection or clinical signs of urethritis. The primary aim was to assess immune responses in asymptomatic individuals compared with those who developed urethritis.

What is the most valuable immunological outcome that such a study is likely to provide?

A. Identification of antimicrobial resistance mechanisms in *Neisseria gonorrhoeae*
B. Identification of possible immunological correlates of protection
C. Insights into genetic susceptibility factors for gonorrhoea
D. Long-term evaluation of vaccine-induced herd immunity
E. Pharmacokinetics of antibiotic treatment

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