# 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. In this article, 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 finally how immunological memory functions to better protect its host against subsequent exposure to the same pathogen.

**Keywords** Adaptive immunity; B cells; dendritic cells; immunological memory; innate immunity; macrophages; MRCP; neutrophils; NK cells; T cells

## Key points

- Pathogen recognition mediated by the innate immune system utilizes germline-encoded pathogen receptors, facilitating rapid immune responses during primary infectious exposure
- Pathogen recognition mediated by the adaptive immune system utilizes 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 receptor is a key feature of both the innate immune system and immunological memory in the adaptive immune system
- 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

## Introduction

Infection-associated morbidity and mortality, in particular mortality before reproductive maturity, have made infectious agents among the strongest selective forces driving human evolution.[1] 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 by 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[2] and population-based studies of infection susceptibility,[3] for example genome-wide association studies (Table 1).

## Pathogen recognition

### Innate pathogen recognition

Innate pathogen sensors are germline-encoded, and as such their specificities are invariant throughout a person's lifespan. Innate immune recognition of an invading pathogen proceeds by two broad mechanisms: through the identification of evolutionarily conserved molecular structures displayed by microbes, or by 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 detection of a broad range of bacteria, viruses and fungi (Table 2). In addition to PRRs detailed in Table 2, a network of plasma proteins (complement) act as innate pathogen sensors (Figure 1).

Natural killer (NK) cells are innate lymphoid cells expressing germline-encoded receptors facilitating the identification of infected, especially virus-infected, cells. The best-characterized family of NK cell-expressed innate receptors are killer cell immunoglobulin-like receptors (KIRs).

Depending on the associated intracellular signalling domain, KIRs can act as inhibitory or activating receptors. Inhibitory KIRs bind surface-expressed major histocompatibility complex (MHC) class I molecules monitoring total MHC expression. Viral infection of a cell results in down-regulation of MHC class I expression, which results in loss of NK cell KIR inhibitory signals. By contrast, activating KIRs bind surface-expressed ligands on infected cells, which are expressed as markers of cellular stress that increase in concentration in infected cells.

Thus, there is an equilibrium between activating and inhibitory KIR signals when an NK cell interacts with a cell. This determines whether the NK cell identifies that cell as being infected and kills it (see below).

### Adaptive pathogen recognition

In contrast to innate immune receptors, adaptive immune receptors are generated by random somatic gene rearrangements and mutations. This allows the generation of a highly diverse

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## Genetic susceptibility to infectious diseases in individuals and populations

| | Primary immunodeficiencies | | | Genetic susceptibility in populations | | |
|---|---|---|---|---|---|---|
| **Immune pathway** | **Gene(s)** | **Disease** | **Infection susceptibility** | **Gene(s)** | **Infection susceptibility** | **Autoimmune disease susceptibility** |
| Innate cytosolic pathogen sensing | | | | *NOD2* | Leprosy | Crohn's disease |
| Complement | *C1QA*, *C1QB*, *C1QC*, *C1QR*, *C1QS*, *C2*, *C4A*, *C5*, *C6*, *C7*, *C8A*, *C9*, *CFD*, *CFP* | Complement deficiencies | Encapsulated bacteria, especially pathogenic *Neisseria* | *CFH*, *CFHR3*, *C4A* | Meningococcal disease | SLE |
| TLR-mediated NF-κB activation | *IRAK4*, *MYD88* | IRAK4/MYD88 deficiency | Pneumococcal disease | *TLR1* | Leprosy | |
| TLR-mediated IRF activation | *UNC93B1*, *TLR3*, *TRAF3* | UNC93B1/TLR3/TRAF3 deficiency | HSV encephalitis | | | |
| Oxidative burst | *CYBA*, *CYBB*, *NCF1*, *NCF2*, *NCF4* | Chronic granulomatous disease | Catalase-positive microbes, e.g. *Staphylococcus aureus*, *Aspergillus* | *NCF2* | | SLE |
| Th1 responses | *IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB1*, *NEMO*, *CYBB*, *IRF8*, *TYK2*, *ISG15* | Mendelian susceptibility to mycobacterial disease | Non-tuberculous mycobacteria, non-typhoidal *Salmonella* | *IL12B*, *STAT1*, *IFNGR2*, *TK2* | | IBD, SLE, MS |
| Th17 responses | *CARD9*, *IL17RC*, *IL17F*, *STAT1* | Familial chronic mucocutaneous candidiasis | *Candida albicans* | *IL23R* | Leprosy | IBD, psoriasis, MS |
| Antibody production/ function | *BTK* | X-linked agamma-globulinaemia | Sinopulmonary infection and encapsulated bacteria | *IGH* | Rheumatic heart disease | |
| MHC class I antigen presentation | *TAP1*, *TAP2*, *TAPBP* | Bare lymphocyte syndrome type I | Respiratory tract infections | *HLA-A/B/C* | HIV | Psoriasis, ankylosing spondylitis |
| MHC class II antigen presentation | *RFX5*, *RFXAP*, *RFXANK*, *CIITA* | Bare lymphocyte syndrome type II | Disseminated viral and fungal infections, *Pneumocystis* | *HLA-DP/DQ/ DR* | HBV, HCV, typhoid, leprosy, leishmaniasis, tuberculosis | Rheumatoid arthritis, IBD, type 1 diabetes mellitus, MS, SLE |

Examples of human primary immunodeficiencies and genetic susceptibility to infectious and autoimmune diseases in populations (as identified by genome-wide association studies). These studies highlight the overlapping genetic factors underlying infectious disease susceptibility and autoimmune disease susceptibility, implicating selection pressure imposed by infectious agents in the evolution of autoimmune diseases. The studies also highlight the pathogen-specificity of genetic risk factors for infection susceptibility, an observation that has greatly facilitated our understanding of the roles of distinct responses of the human immune system in anti-pathogen defence.
HBV, hepatitis B virus; HCV, hepatitis C virus, IBD, inflammatory bowel disease; MS, multiple sclerosis; SLE, systemic lupus erythematosus, For other abbreviations, see text.

**Table 1**

receptor repertoire, further shaped by pathogens encountered during an individual's lifespan.

T and B lymphocytes of the adaptive immune system express two classes of pathogen recognition molecule. B cells express immunoglobulin molecules, as membrane-bound B cell receptors (BCRs) on naive B cells, and secreted immunoglobulin/antibody molecules from effector B cells (Figure 2). T cells express the membrane-bound T cell receptor (TCR), which allows the detection of pathogen-derived peptide presented on cell surfaces associated with MHC molecules (Figure 3).

Each naive B cell and T cell has a unique antigenic specificity defined by the sequence of its receptor (BCR, TCR). The human antibody repertoire (i.e. the number of potential antigenic specificities) is estimated to be of the order of 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 and coupled with clonal expansion of antigen-specific cells on encountering a receptor's cognate antigen.