The immune system

Malcolm Howell

Malcolm Shepherd

Abstract

This article intends to provide an up-to-date overview of the relevant physiology required to pass the FRCA. The immune system is our defence against pathogens. This includes the recognition of non-self organisms, and protection through a variety of non-specific and highly specific mechanisms. Failure of the immune system leads to immunodeficiency or immunopathology either may be catastrophic for the host.

Keywords Anaphylaxis; innate immunity; pathogen recognition

Royal College of Anaesthetists CPD Matrix: 1A01

Learning objectives

After reading this article, you should understand:

- The principles of immunity are: discrimination between self and non-self; specificity; memory and resolution of tissue damage
- Human immunity has evolved to defend hosts against invading pathogens
- Innate immunity is an active system of sensing and reacting to infection and injury
- Adaptive immunity emerges after initial exposure to selectively protect hosts from re-exposure

Introduction

Defense of the human body against infection by bacteria, viruses, fungi and multi-cellular parasites requires barriers to invasion and a network of cells, chemical mediators and destructive enzymes that can be selectively recruited to destroy invading pathogens. The immune system is the selectable component of this host defence network.

Understanding the basic concepts of immunity informs clinical practice reducing risk to patients, for example in developing safe care bundles for mechanically ventilated patients. Invasive procedures, certain medications and clinical circumstances associated with anaesthesia challenge the integrity of the immune system. Furthermore, understanding the basis of immunology provides insight into pathologies including autoimmunity, immunodeficiency and allergic emergencies such as anaphylaxis.

The interaction between anaesthetic agents and the immune system is not fully understood. The relationship between anaesthetic techniques, the immune system and cancer recurrence is the focus of ongoing research.

Immunity

Structurally, the immune system can be divided into the non-specific innate and the highly specific adaptive immune systems. Functionally, the three essential properties of the immune system are: recognition of and discrimination between self and non-self; activation of pathways that eliminate pathogens, and long lasting memory. The adaptive immune system holds the key to selective recognition and memory for infective pathogens. Alongside defence against infection, the properties of the immune system allow surveillance for host tissue damage and mutation and can protect against the progression of malignancy.

Maintaining health requires orderly interaction between innate and acquired immunity and timely activation of inflammatory pathways. Inflammation is a network of cells and chemical mediators that work alongside immunity during illness to restore normal tissue function after an infection or injury. Disruption to the orderly communication within this protective matrix can lead to disease. Such diseases are broadly classified into two groups – immunodeficiency disorders and immunopathology (hyper-reactivity). Allergy and auto-immunity are examples of immunopathology.

Innate or non-specific immunity

The innate immune system provides the first line of defence against pathogens and includes cellular elements along with physical, physiological and chemical barriers to pathogen entry, replication and survival. These elements are present from birth, and are described as non-specific because the pathogen recognition systems are fixed rather than adaptive to new exposures.

Physical, physiological and chemical barriers

Anatomical barriers are epithelial layers including the skin and mucous membranes, which prevent pathogen entry. Far from offering passive resistance, these structures recognise invading organisms via pathogen recognition receptors (PRRs) that recognise non-mammalian molecular patterns known as, pathogen associated molecular patterns (PAMPs). Binding of PAMPs to PRRs on the surface and within the cytoplasm of host cells activates protective inflammatory cellular responses. PRRs are expressed on inflammatory, immune and epithelial cells and act as first responders to pathogen exposure at surfaces prone to pathogen entry. Table 1 details the main PRRS and their ligands, demonstrating how they are distributed on the surface of lung tissues and inflammatory cells. IN this way they provide first line of defence against airborne pathogens.

Physiologic and chemical barriers include body temperature, acidic pH of gastric fluid, lactic acid and lysozyme. These help prevent spread and replication of pathogens.

Malcolm Howell *MB ChB FRCA is a Specialty Registrar in Anaesthesia at Queen Elizabeth University Hospital, Glasgow, Scotland, UK. Conflicts of interest: none declared.*

Malcolm Shepherd *MRCP PhD is a Consultant Respiratory Physician and Director of the West of Scotland Anaphylaxis Service at Queen Elizabeth University Hospital, Glasgow; and Honorary Associate Clinical Professor at the University of Glasgow, Scotland, UK. Conflicts of interest: none declared.*

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Pattern recognition receptors, pathogen ligands and cellular distribution in human lung

PRR	PAMP	Pathogen	Host cell distribution
Membrane Bound			
TLR 1/2/6	Lipopeptides	Bacteria	Ep, SmMu, MP
TLR 4	Lipopolysaccharide	Bacteria	Ep, SmMu, MP
TLR 5	Flagellin	Bacteria	Ep, SmMu, MP, PlC
CLR	B glucan	Fungi	Ep, MPs
Cytoplasmic			
TLR 3	DS DNA	Virus	Ep, SmMU, MP
TLR 7	SS RNA	Virus	Neu,Ep, Ma,
TLR 9	CPG DNA	Bacteria	Ep, MP
NLRC	Peptidoglycan, Flagellin	Bacteria	

Multiple different receptors are distributed among immune, inflammatory and structural cells in the human lung, demonstrating the intricate network of defense against infection in organs with an external environmental exposure. (PRR: pattern recognition receptor, PAMP: pathogen associated molecular pattern, TLR: toll like receptor, CLR: C-type lectin receptor, NLR: NOD like receptor, DS DNA: double stranded DNA, SS RNA: single stranded RNA, Ep: Epithelium, SmMu: smooth muscle, MP macrophage, PlC: plasma cell, Neu: neurone, Ma: Mast cell).

Table 1

Inflammatory mediators and cellular components of innate immunity

Cellular components include polymorphonuclear cells (neutrophils, eosinophils, basophils, mast cells), phagocytic cells (monocytes, macrophages, dendritic cells) and natural killer (NK) cells. These recognize PAMPs on non-host species leading to: internalization and destruction (phagocytes); apoptosis and cell lysis (NK cells); and presentation of foreign antigens on cell surfaces (dendritic cells and phagocytes – the antigen-presenting cells). Antigen presentation in the context of major histocompatibility complex proteins (MHC) initiates the specific molecular pathways that lead the adaptive immune system to develop highly specific pathogen recognition receptors, immunoglobulins and T-cell receptors.

The final response of innate immunity to pathogen recognition is the generation of inflammatory mediators by epithelial and inflammatory cells. These molecules are involved in direct responses against pathogens and control the activity of cellular defences. Direct responses against non-self cells include lysis of pathogens by complement and cell wall destruction by lysozyme. Chemokines attract inflammatory and immune cells to sites of infection while prostaglandins and leukotrienes increase vasodilatation and vascular permeability, allowing access of these cells to damaged or infected tissue sites. Other cytokines activate specific pathways in immune cells directing their behavior and selecting an appropriate 'flavour' of immune response depending on the nature of the invading pathogen.

PRRs have further adapted to recognize host tissue damage by recognizing damage associated molecular patterns (DAMPS). In this way the mechanisms utilized to protect against infection are used to identify harm and initiate repair pathways. These also are the first line in recognition of cellular mutation and tumour progression.[1]

Adaptive or specific immunity

The adaptive immune system develops highly targeted responses to foreign antigens and is known as specific immunity. It is distinct from innate immunity in that it undergoes a process of selectivity based on exposure to foreign material and 'adapts' by developing ever more specific molecular recognition motifs as receptors for invading pathogens.

Following pathogen exposure, cells and inflammatory mediators from sites of infection, travel to local lymph nodes. Here non-host antigens on the surface of antigen-presenting cells (APCs) are recognized by host B- and T-lymphocyte receptors. A complex process of clonal deletion and expansion of lymphocytes leads to a population (clone) of highly selective cells capable of targeting the original pathogen. This process is known as clonal selection.

The primary response of adaptive immunity is slower than innate immunity; however, immune memory provides a mechanism for accelerated expansion that delivers a more rapid and substantial response to subsequent exposure to the same pathogenic antigen. This has been utilized clinically in immunisation with vaccines.

The specific immune system consists of humoral and cellular components.

Humoral immunity

Humoral immunity describes the B-lymphocyte response. Binding a non-host antigen of an invading pathogen to the B cell antigen receptor, a membrane bound antibody associated with a cellular signaling complex, engages a molecular signaling cascade that drives B-cell activation. Activated B cells differentiate into plasma cells or become memory B cells. Plasma cells synthesize and secrete antibodies, which target and bind to the pathogen. Memory B cells lie inactive until a secondary antigen exposure, when they will recognise this particular pathogen more quickly. They can also function as antigen-presenting cells.

Antibodies are immunoglobulin (Ig) proteins constructed from two heavy and two light polypeptide chains bound by disulphide bridges. The antigen binding domain, termed fragment antigen binding (Fab), is the adaptive variable region, while the domain, termed fragment crystalline (Fc), is invariable and binds cell surface receptors. The Fc region determines which of the five immunoglobulin isotypes or class an antibody belongs to. This, in turn, determines the subsequent immune response. Thus activation of complement and cell lysis is triggered by IgM and IgG; bacterial toxin neutralisation is achieved by IgG, IgM and IgA, antiviral activity by IgG, IgA, and mast cell and basophil degranulation follows IgE activation. These are termed class-specific functions.

Cellular immunity

Cellular immunity describes the T-cell response. T cells arise in the bone marrow and fetal liver, before migrating to the thymus for maturation and development of their T-cell receptor (TCR). These receptors can discriminate between self and non-self, by recognizing differences in MHC molecules on the cell surface. Clones of T cells possessing TCR motifs that recognize self-antigens (auto-reactive T cells) are recognized and eliminated

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