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The Immune System: Basis of so much Health and Disease: 1. Overview of Immunity and the Immune System

Abstract: The immune system is the body's primary defence mechanism against infections, and disturbances in the system can cause disease if the system fails in defence functions (in immunocompromised people), or if the activity is detrimental to the host (as in auto-immune and auto-inflammatory states). A healthy immune system is also essential to normal health of dental and oral tissues. This series presents the basics for the understanding of the immune system, this article covering an overview of immunity and the immune system.
Clinical Relevance: Modern dental clinicians need a basic understanding of the immune system as it underlies health and disease.
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We inhabit a world dominated by microbes and toxins, many of which can cause harm to humans (ie they are pathogens). Some pathogens are exogenous but others, such as some bacteria, viruses, and fungi, share their lives with us (ie they are commensals or endogenous), often usually in harmony though, under certain conditions, some may become opportunistic pathogens. Humans are colonized, for example, by over 1,000 different types of micro-organisms. Immunity is the state of having sufficient biological defences to avoid infections (Figure 1).

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The immune system – the body's primary defence mechanism against diseases caused by pathogens – is made up of various interacting cells (sometimes termed immunocytes), soluble substances, and proteins designed to identify and destroy pathogens.

Immune organs and tissues

The main primary organs of the immune system are lymphoid – the *thymus* and *bone marrow* (Figure 2) and secondary tissues such as *spleen*, *tonsils*, *lymph* vessels, *lymph nodes, adenoids, skin* and *liver* ('lymphoreticular system') (Figure 3).

Immune cells (immunocytes)

All cells of the immune system are bone marrow-derived white blood cells (myeloid and lymphoid leukocytes) which are specialized to perform variable functions (Figure 4), for example:

- Macrophages and some polymorphonuclear leukocytes ('polymorphs') are phagocytic cells able to, non-specifically, ingest and destroy the main invading microbes (ie phagocytosis) (Figure 5);
- B-lymphocytes are involved in recognizing foreign proteins (termed antigens);
- Differentiated B-lymphocytes (plasma cells) secrete antibodies (immunoglobulins) – proteins that specifically bind and eliminate extracellular pathogens (eg bacteria) (Figure 6);
- T-lymphocytes recognize and bind to antigens (foreign proteins) presented on the surface of antigen presenting cells (APCs); a heterogeneous group of cells including macrophages, Langerhans and dendritic cells that function primarily to process and present antigens for T-lymphocytes (Figure 7);
- T-lymphocytes eliminate intracellular pathogens (eg viruses) that are out of reach of antibodies;
- T-cytotoxic lymphocytes, a subset of T-lymphocytes that express the CD8 cell surface receptor (they are CD8+), destroy damaged cells including virally infected cells and cancer cells through direct cellular interactions and the release of various cytotoxic substances such as perforin,

granzymes and tumour necrosis factor (TNF);
- T-helper lymphocytes, a subset of T-lymphocytes that express the CD4 cell surface receptor (CD4+), produce a wide range of cytokines that enhance B-cell antibody production and $CD8^+$ T-cells and macrophage cytotoxic function (Figure 8);
- Natural killer (NK) cells are a distinct type of lymphocyte capable of producing proteins termed 'cytokines' and causing direct lysis of infected or damaged cells;
- Other cells of the immune system include neutrophils, eosinophils, basophils, and mast cells – all characterized by variable shapes of their nuclei (hence the name polymorphonuclear leukocytes) and the presence of granules in their cytoplasm (ie they are also termed granulocytes); the granules contain various mediators that are involved in functions such as inflammation, hypersensitivity reactions, and response to parasitic infections.

Immune proteins

In addition to cells, the immune system employs various proteins and soluble molecules, for example:
- Cytokines are a heterogeneous group of small proteins secreted by various cells (mainly immune cells) and function as signalling molecules to facilitate cell-to-cell communication in various biological processes such as inflammation, cellular differentiation, activation and proliferation, and cell death. The cytokines family includes the interleukins (ILs), interferons (IFNs), tumour necrosis factor (TNF), chemokines, and colony stimulating factors (CSFs);
- Complement proteins, another important group of proteins utilized by the immune system, are a set of plasma proteins activated as a proteolytic cascade that functions to coat the surface of pathogens, thereby stimulating their lysis or phagocytosis by immune cells. Complement activation also precipitates inflammation – which recruits blood and immune cells to the area.

Immune recognition

With so many powerful, often potentially destructive, immune processes the body needs mechanisms to protect against inappropriate harm from immune reactions. The immune system identifies self from non-self/foreign structures through recognition molecules or receptors found on the surface of immune cells (Figure 9). The immune system uses various types of recognition molecules to identify unwanted incursions including:

1. The pattern recognition receptors (PRRs) which, non-specifically, recognize molecular structures such as certain proteins and carbohydrates on the surface of pathogens;
2. The T-cell and B-cell antigen receptors which, specifically, recognize antigens and bind to small areas of their molecular structures, known as epitopes; and
3. The major histocompatibility complex (MHC) molecules which bind to antigens and display them on the cell surface for recognition by T-lymphocytes.

The immune system is able to cope with the great diversity in non-self structures by 'anticipating' different structures of antigens and creating a diverse repertoire of antigen recognition molecules through various genetic mechanisms, such as gene rearrangement, hypermutation and genetic polymorphism.

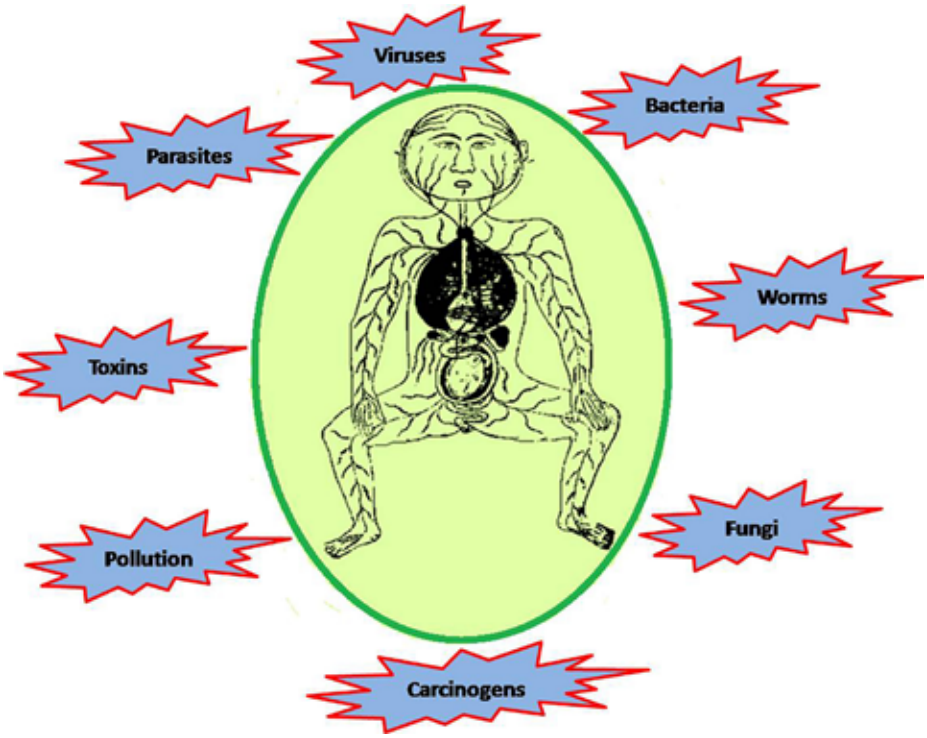

Figure 1. The immune system protects the human body against diseases caused by pathogens.

Figure 2. Primary immune organs where lymphocytes develop and mature. Bone marrow is the site for B-cell maturation while Thymus is the site for T-cell maturation.

Immunity

The immune system is organized into two interconnected and overlapping components; innate (natural) immunity and adaptive (acquired) immunity (Table 1). Innate immunity is the first line of defence for the

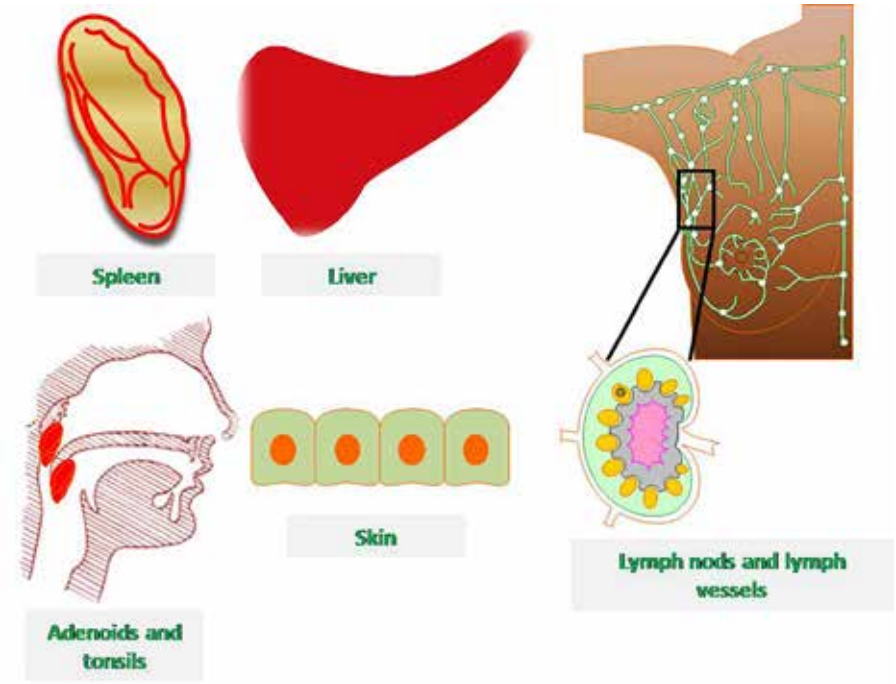

Figure 3. Secondary immune organs where mature lymphocytes get exposed to antigens.

body. Innate immunity is responsible mainly for protecting the surfaces of the body (skin, oral, respiratory, gastro-intestinal and urogenital mucosae) which are readily open to colonization by pathogens. It employs natural barriers (eg intact mucosal surfaces), body secretions (eg saliva and tears), and non-specific cells (eg macrophages, natural killers and granulocytes), molecules (eg acids, complement components and interferons) and processes (eg inflammation) to attempt to eliminate invading micro-organisms (Figure 10). Interestingly, some commensal bacterial microbiota on mucosal surfaces can also afford some protection against exogenous pathogens. Loss of these 'friendly' surface bacteria – for example after antibiotic therapy – can, in the mouth and other mucosae, give rise to candidosis if Candida fungi proliferate, or in the gut, if *Clostridium difficile* (C. diff) proliferates, pseudomembranous colitis can arise. Aspects of the innate immune response are quickly mobilized (in seconds to

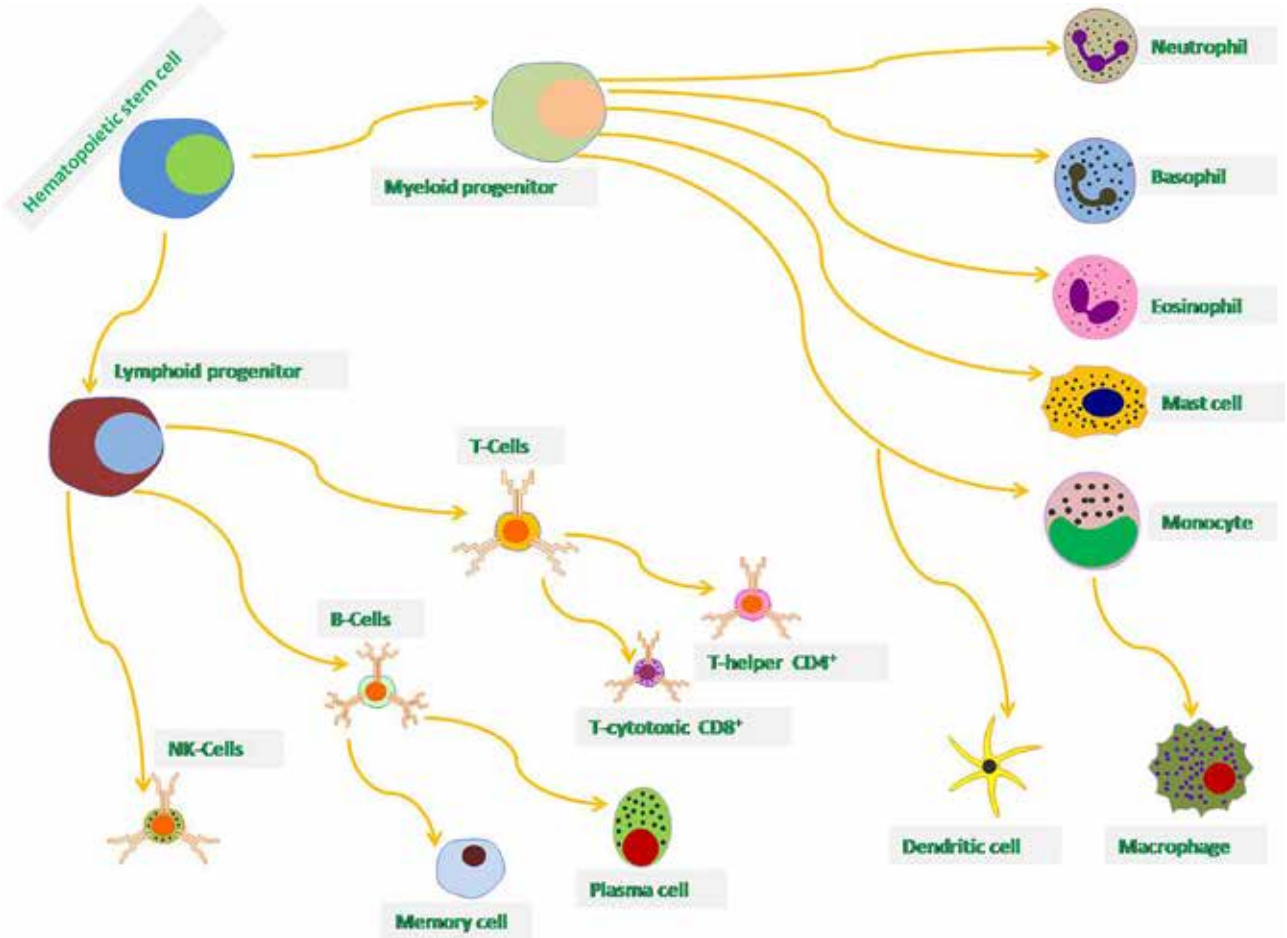

Figure 4. Origin of cells of the immune system.

minutes) in response to foreign invaders. The innate immune response utilizes the pattern recognition receptors (PRRs) to recognize foreign invaders. Pathogens' molecules that are recognized by PRRs are called pathogen associated molecular patterns (PAMPs) and include carbohydrates, nucleic acids, peptides and lipoproteins. PRRs have little ability to discriminate between various foreign invaders and, therefore, the innate immune system is characterized by a lack of specificity (ie response is the same regardless of the trigger) and lack of memory (ie response to a second exposure to the same agent is of the same type and degree as that to the first exposure). As shown later, in contrast, adaptive (specific) immunity has specificity and memory.

Adaptive immunity

If, despite effective surface immunity, a pathogen does manage to pass an external surface and enters the tissues (eg via a needlestick injury), the immune system reacts in a complex defensive way, by launching the adaptive immune response. The adaptive immune response utilizes specific cells (eg B- and T-lymphocytes), molecules (eg antibodies), and processes (eg clonal selection) to eliminate invading pathogens. The adaptive immune response is:

- Slow to develop (days); and
- In contrast to innate immunity, it can distinguish one specific pathogen from another and develop memory for subsequent exposure to the same organism.

The adaptive immune response recognizes antigens using the B-cell receptors, T-cell receptors, and the major histocompatability complex molecules (also known as human leukocyte antigens, HLA). These antigen recognition molecules can recognize unique areas on the molecular structures of antigens (ie epitopes) and discriminate between different antigens.

There are two types of the adaptive immune response:

1. Humoral immunity; and
2. Cell-mediated immunity.

Humoral immunity deals with extracellular pathogens (ie most bacteria), is mediated by B-lymphocytes and involves the production and release of antibodies (immunoglobulins) that bind and destroy target antigens (Figure 11).

Cell-mediated immunity deals with intracellular pathogens (ie viruses and some

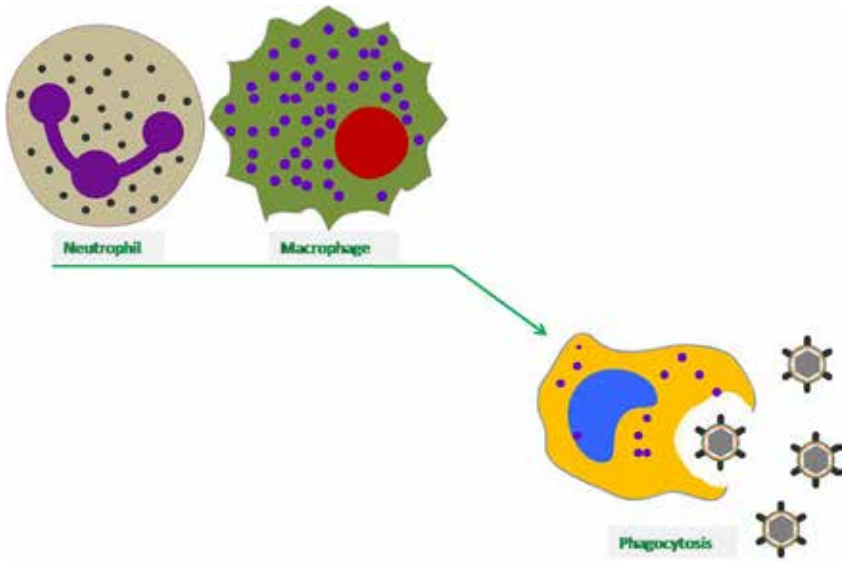

Figure 5. Macrophages and neutrophils can engulf and destroy invading pathogens; a process called phagocytosis.

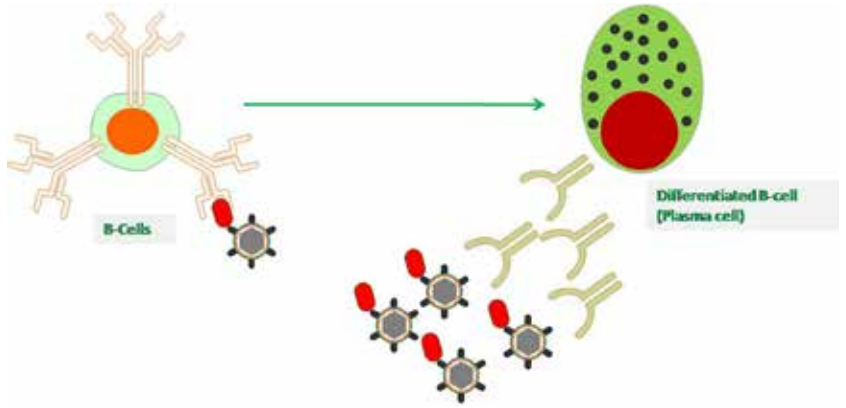

Figure 6. B-cells recognize antigens on the surface of extracellular pathogens and differentiate into plasma cells that release antibodies to destroy the invading pathogen.

Innate	Acquired or Adaptive
Response has little discrimination	Response is highly discriminatory
Response is immediate or very soon after infection	Response takes time to develop
Response to a second exposure to the same agent is of the same type and degree as that to the first exposure	Response to a second exposure to the same agent is qualitatively (faster) and quantitatively (larger) different from that in the first (initial) immune response
Recognition repertoire is limited	Response can anticipate all possible variants of the original stimulus
Involves myeloid leukocytes (such as phagocytes and NK [natural killer] cells), as well as mediators and receptors	Involves lymphoid leukocytes (such as T- and B-lymphocytes)

Table 1. The two elements of immunity.

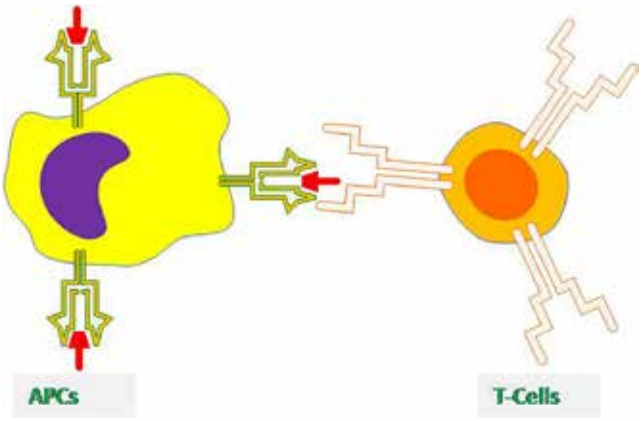

Figure 7. Antigen presenting cells (APCs), such as macrophages and dendritic cells, process and present antigens to T-lymphocytes for recognition.

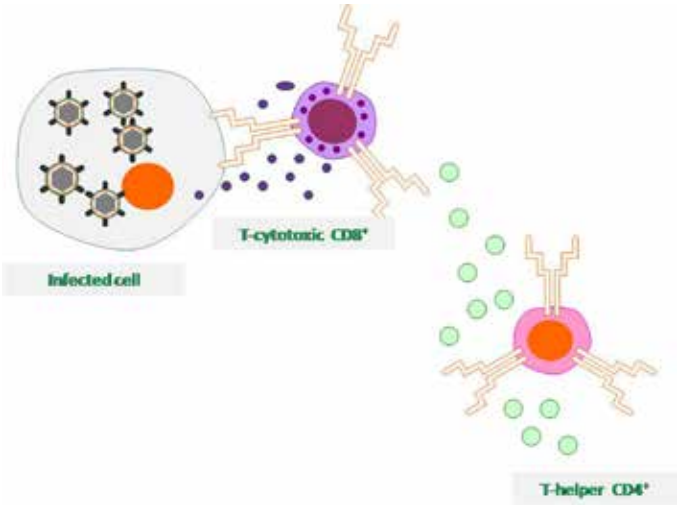

Figure 8. Cytotoxic T-cells destroy infected cells through direct cellular interaction and the release of active substances such as perforin and TNF. Helper T-cells release a wide range of cytokines to enhance the function of cytotoxic T-cells and macrophages.

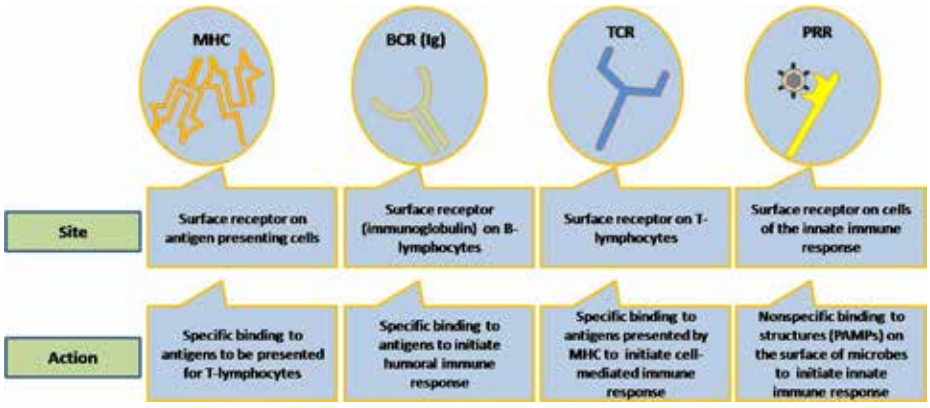

Figure 9. Receptors used by immune system for the recognition of foreign invaders: TCR – T-cell receptor; BCR – B-cell receptor; MHC – Major histocompatability complex; PRR – Pattern recognition receptor.

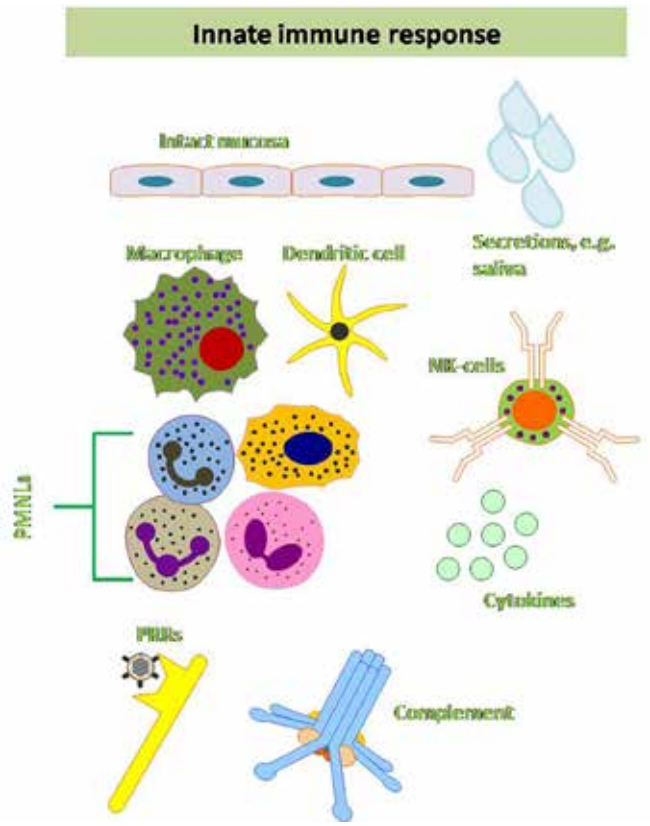

Figure 10. Innate immune response grants non-specific protection against pathogens using natural barriers, cells and proteins.

bacteria). It is mediated by T-lymphocytes (T-helper and T-cytotoxic) and involves direct lysis of infected cells and release of a wide range of cytokines that enhance antibody production by B-lymphocytes and phagocytosis by macrophages and neutrophils (Figure 12).

Conclusion

A healthy immune system is essential to normal health of dental and oral tissues.

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MD, PhD, MDS, FDSRCS, FDSRCPS, FFDRCSI, FDSRCSE, FRCPath, FMedSci, FUCL, DSc, DChD, DMed(HC), Dhc, who has long worked with colleagues in Finland, teaching and publishing mainly in Helsinki and Turku, has now been awarded a **Fellowship of the Finnish Academy of Medical Sciences**.

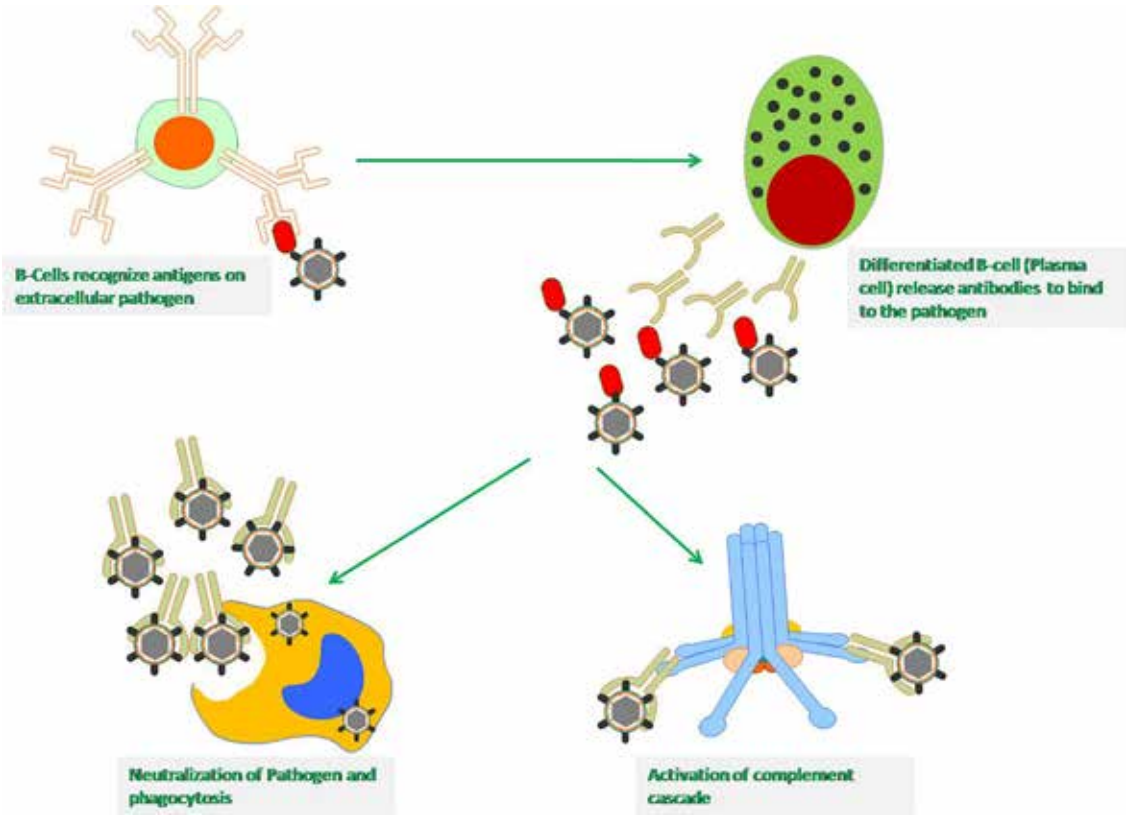

Figure 11. Humoral immunity grants specific protection against extracellular pathogens. This is mediated primarily by B-lymphocytes.

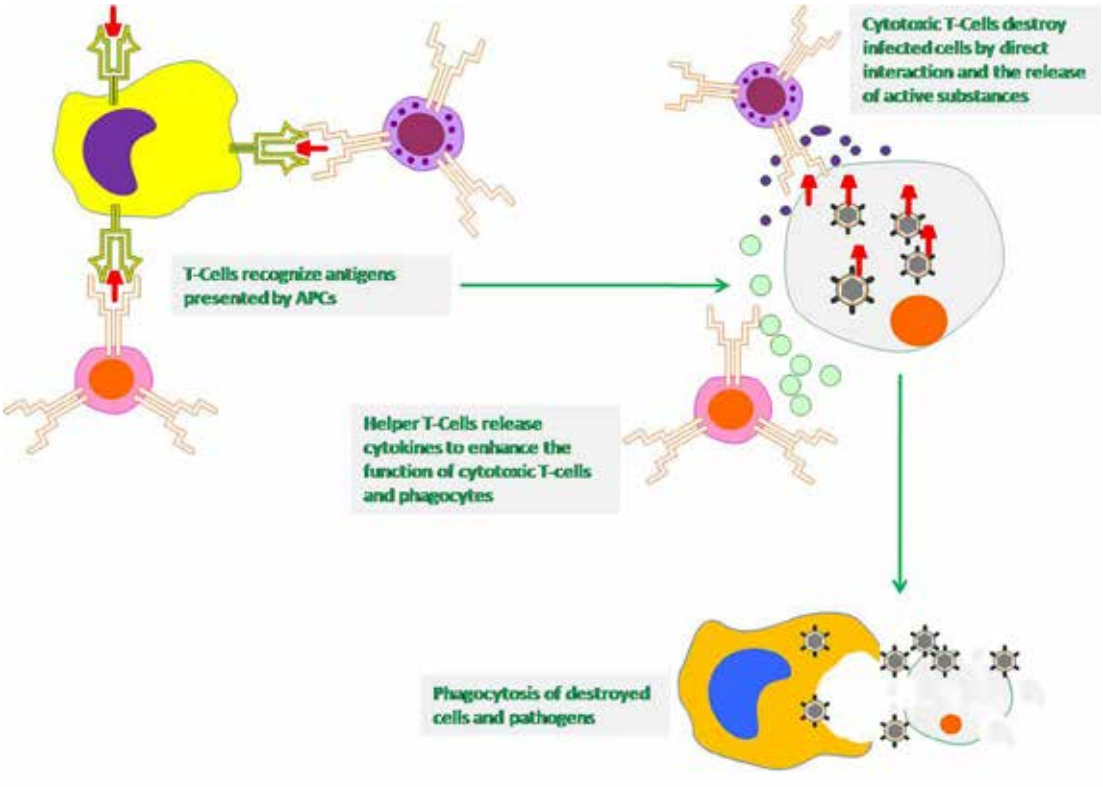

Figure 12. Cell-mediated immunity grants specific protection against intracellular pathogens. This is mediated primarily by T-lymphocytes.