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IMMUNE RESPONSE TO INFECTION
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Biography

Desa Lilic is a Consultant Clinical Immunologist and Honorary Clinical Senior Lecturer at University Hospital Durham and Newcastle University. She qualified in Belgrade, former Yugoslavia (now Serbia) and moved to the UK in 1992. She runs a busy Clinical Immunology Department in Durham and has a research group in Newcastle, investigating immune defects underlying selective susceptibility to infections with the yeast Candida in patients with Chronic Mucocutaneous Candidiasis, where she has also set up specialist clinics for diagnosis and management of these patients.

Learning objectives

At the end of the article, you should be able to understand the following

• The integrated structure of the innate and adaptive immune system
• How pattern recognition receptors of the innate immune system select and guide immune responses to particular pathogens
• How the nature of the immune defect predisposes to particular kinds of infections in primary immune deficiencies

Abstract

The immune system in mammals has two facets – the innate and adaptive immune system - which function as a complex, interdependent entity. This has only recently been fully appreciated when it was realised that the innate immune system has the ability to “sample” micro-organisms via its pattern recognition receptors (PRRs) that recognise pathogen associated molecular patters (PAMPs) – structures present on pathogens but not on mammalian cells. Once activated, PRRs such as Toll-like receptors (TLRs), C-type lectins
and others activate signalling pathways and gene transcription programmes that lead to production of appropriate chemical messengers (cytokines, chemokines etc) that activate the most appropriate immune responses for protection against a particular microorganism. The adaptive immune system mounts cell-mediated responses to deal with intracellular microorganisms (e.g. mycobacteria, viruses etc) and/or humoral (antibody) responses to combat extracellular microorganisms (Streptococci, Haemophilus etc). Primary immune deficiencies predispose to different infections, depending on the nature of the underlying immune defect (e.g. combined immune deficiency, antibody deficiency, autoinflammatory syndromes). Recent recognition of how subtle immune defects predispose to infections with only selected, weak pathogens (“non-classical primary immune deficiencies”) have enhanced our understanding of immunity to infection. Understanding mechanisms underlying the immune response to infection will improve diagnosis and treatment.

Word count 200

Key words

Infection, immunity, innate, adaptive, pattern recognition receptors, Toll-like receptors, non-classical primary immune deficiencies

Manuscript

Structure of the immune system

The immune system has evolved to protect the individual organism from “non-self”, which in natural circumstances mostly pertains to invading microorganisms (bacteria, viruses, fungi, parasites etc). Initially, the evolutionarily older, innate immune system was formed and remains the only protection in species up to primitive fish (colostoma). It consists of an array
of biologically active molecules (such as complement, cytokines, chemokines etc) and phagocytic cells (such as macrophages, neutrophils etc) that are able to identify and destroy harmful intruders. The innate immune system is very quick, reacting in minutes rather than hours, and induces a highly efficient inflammatory response. However, it lacks specificity and memory, because of which responses are not fine-tuned and subsequent responses to the same intruder will not be improved (quicker and more efficient). The innate immune system in this form has been retained in species that have gone on to evolve a more sophisticated, adaptive immune system, which includes antigen-presenting cells (such as dendritic cells - DCs) and lymphocytes - T cells, B cells and Natural-Killer cells. T lymphocytes have well characterised subsets, including T-helper, T-cytotoxic and T-regulatory cells. The adaptive immune system recognises (mostly) protein targets coined antigens and boasts exceptional specificity, distinguishing structural differences encoded even by only one amino acid. It also boasts memory, enabling it to improve specificity and speed of response when it encounters the same antigen on a subsequent occasion [1] [2].

**Role of the innate immune response in infection**

In response to infection, the innate immune system mounts an inflammatory response by triggering cells to produce biologically active chemical mediators such as cytokines (also known as interleukins) and chemokines, which enable cell-cell communication / co-ordination as well as directly mediating biological effects such as cell activation, chemotaxis, vasodilatation etc. The adaptive immune system on the other hand, has evolved two distinct strategies to deal with infection: cell-mediated responses (delivered by effector T-cytotoxic and T-helper cells that recruit phagocytes) which target intracellular microorganisms and humoral responses (delivered by antibodies produced by B lymphocytes), which target extracellular microorganisms [2].
**Pattern recognition receptors**

It has only recently been recognised that the innate and adaptive immune system are very closely functionally linked and that it is the “primitive” innate immune system that actually guides and instructs how the adaptive immune system will respond to a particular type of microorganism. This is achieved by the innate immune’s ability to “sample” microorganisms via pattern-recognition receptors (PRRs) on mammalian cells which recognise pathogen-associated molecular patterns (PAMPs) – vital structures specific to microorganisms but alien to mammals, that cannot be readily modified or mutated without consequence [3]. Different PRRs trigger distinct signalling pathways, leading to production of selected panels of cytokines and chemokines which then lead to activation of appropriate mechanisms of the adaptive immune response, ensuring that the strategy employed is the appropriate one for eradicating that particular microorganism. If efficient protection requires cell-mediated immunity i.e. recruitment of T-cytotoxic and phagocytic cells, the innate immune system will recruit T-helper 1 (Th1) cells that produce cytokines such as interferon gamma (IFNγ), interleukin (IL)-12 and tumour necrosis factor alpha (TNFα) which activate monocytes and macrophages. If antibodies are required, the innate immune system will secrete cytokines such as IL-4, IL-5, IL-13 and IL-10, inducing a Th2 type response ensuring activation of B cells and antibody production [1].

PRRs can be divided into several categories depending on localisation and function. Soluble PRRs include mannan binding lectin (MBL) and C-reactive protein (CRP) which act as opsonins to neutralise and clear pathogens through activation of complement [4]. Intracellular PRRs such as NOD-like receptors (NLRs) are composed of more than 20 proteins which together form the “inflammasome” that is activated by bacterial products [5]. To date, the most studied PRRs are the transmembrane, cell-surface receptors which include
Toll-like receptors (TLRs) 1-10 and C-type lectin receptors (CLRs) such as the mannose receptor (MR), Dectin-1, Dectin-2 etc. TLRs and CTLs are signalling receptors where ligand recognition activates signalling cascades that leads to gene expression programs with differential activation of cytokine and chemokine production. All TLRs (except TLR3) share the adaptor MyD88 leading to activation of nuclear factor (NF)-κB, mitogen-activated protein (MAP)-kinases and interferon-releasing factor 3 (IRF3), stimulating Th1 responses through production of IL-12, IFNγ, tumour necrosis factor (TNFα) and type 1 IFNs [6]. TLR 1, 2, 4 and 5 are present on the plasma membrane and recognise bacterial components, while the anti-viral TLR 3, 7, 8 and 9 are expressed in intracellular compartments [4] [7]. TLR 1, 2 and 6 recognise lipopeptides, TLR4 lipopolysaccharide (LPS), TLR5 flaggelin, TLR7 and 8 single-stranded RNA and TLR9 unmethylated CpG. TRL3 double-stranded RNA. TLR 1, 2, 4 and 5 are present on the plasma membrane and recognise bacterial components, while the anti-viral TLR 3, 7, 8 and 9 are expressed in intracellular compartments [4] and Fig 1 (http://www.nature.com/nri/focus/tlr/nri1397.html).

**Infections due to deficiencies of the innate immune system**

The importance of the innate immune response in human infection has long been assumed, although evidence has only recently accumulated through reports of specific genetic defects and ensuing pathology. Patients with defects of cytokines or cytokine receptors for IL-12 and IFNγ are susceptible to infections with intracellular microorganisms such as mycobacteria and *Salmonella*; disorders of the complement pathway predisposes to *Neisseria* infections; disorders of TLR3 and UNC-93B-IFN-α/β pathway confers selective predisposition to herpes simplex virus (HSV) encephalitis [8]. The importance of TLRs in protection against infection has been recently confirmed in patients with MyD88 deficiency, who suffer with recurrent pyogenic bacterial infections [9]; deficiencies of the NLR
inflammasome components lead to a range of auto-inflammatory syndromes, that have only recently been elucidated [5] as the cause of diseases such as Familial Mediterranean Fever, Cold Familial auto-inflammatory syndrome etc, while defects in the Dectin-1 pathway have only recently been shown to predispose to chronic *Candida* infections [10].

**Role of the adaptive immune response in infection**

As mentioned above, the innate immune system initiates the inflammatory process triggered by invading microorganisms, which is both protective and leads to appropriate activation of the adaptive immune system toward a Th1 or Th2 type response, resulting in cell-mediated or antibody-mediated immunity. T cells express antigen-specific cell-surface receptors that recognise only processed (not free) antigen, presented in the context of major-histocompatibility (MHC) molecules (HLA in humans – Human Leucocyte Antigen) on antigen-presenting cells (APCs) such as dendritic cells (DCs). CD4 T lymphocytes recognise antigen in the context of MHC-class II alleles, expressed only on APCs, while CD8 T lymphocytes recognise antigen in the context of MHC-class I alleles, expressed on all nucleated cells.

The basis of the adaptive immune response is clonal selection, where a T cell, activated by recognising its specific antigen, proliferates, producing a clone of T cells with the same specificity, thus providing an antigen-specific response. Antigens presented by MHC-class II on APCs are mostly exogenous antigens, taken up by APCs, while antigens presented by MHC-class I are mostly endogenous, although there is evidence of cross-presentation. This ensures that all nucleated cells can present microbial (e.g. viral) endogenous antigens which can be recognised by cytotoxic T cells (mostly CD8) and destroyed in case of infection. T-helper (mostly CD4) lymphocytes are activated either to promote cell-mediated immunity (Th1 cells) which produce inflammatory cytokines (such as
IFNγ) and chemokines that recruit and activate macrophages, neutrophils and other cells to the site of infection or Th2 cells which promote antibody production by B cells. Recently, another type of T-helper cell with a major role in cell-mediated immune responses has been identified, coined Th17, which secretes IL-17 and IL-17 inducing cytokines (IL-21, IL-22 etc) that have a major role in infection as well as in autoimmunity [11]. Cell-mediated Th1 responses are crucial for protection from intracellular microorganisms such as mycobacteria and viruses. IL-17 plays a role in protection against Gram-negative bacteria (*Klebsiella, Psudomonas, E. Colli* etc) and fungal infections [12]. In contrast, Th2 cells promote B cell differentiation by secreting IL-4, IL-5 and IL-13, which leads to production of antibodies IgM, IgG and IgA (and IgE and IgD in certain circumstances) [1]. Most B cell responses are T cell dependent so that optimal antibody production cannot develop in the absence of T lymphocytes. Much attention has recently focused on T regulatory cells (Treg) which have different origins and function and seem to be crucial in ending and limiting the immune response once the pathogen has been cleared [13].

**Infections due to deficiencies of the adaptive immune system**

Defects that undermine the development of the adaptive immune system cause major immune deficiency and susceptibility to infection depending on the nature of the underlying defect. Failure to develop both T and B lymphocytes results in the fatal phenotype of Severe Combined Immune Deficiency (SCID), with profound immune deficiency from the first days of life, usually presenting with defects of cell-mediated immunity and susceptibility to viral and fungal (*Candida* thrush) infections. SCID can be caused by more than 15 known gene mutations, which cause profound immune defects incompatible with life, that can only be treated with life-saving bone-marrow transplantations. Isolated T cell defects are not recognised because of the dependency of an optimal B cell response on T cell help. However,
(more-or-less) isolate humoral i.e. antibody defects are recognised and present with profound susceptibility to infection, with encapsulated, pyogenic bacteria (*Streptococci, Hemophilus*) and certain viruses (Entero viruses) where protection relies on antibody opsonisation for the destruction of the microorganisms. Replacement therapy with intravenous immunoglobulins has hugely improved outcome and quality of life in these patients, although susceptibility to infections and other (autoimmune diseases) remains higher than in healthy individuals, strongly suggesting that there is still a lot we don’t know about the role of B lymphocytes in infection and immunity.

**Non-classical primary immune deficiencies**

Recently, a new and intriguing concept of non-conventional primary immune deficiencies (PIDs) has been put forward [8], defining these as a selective susceptibility to a single weakly pathogenic or opportunistic organism. Surprisingly, in these PIDs, a predisposition to a single type of infection is caused by immune defects affecting pathways central to the immune response. Examples include disorders mentioned above, such as defects of the interleukin (IL)-12/interferon (IFN)γ circuit resulting in selective susceptibility to infections with mycobacteria and *Salmonella*; defects in the TLR3 pathway resulting in selective predisposition to Herpes Simplex Virus (HSV) infection; MyD88 deficiency and susceptibility to pyogenic bacterial infections. The infectious phenotype that the above disorders confer in humans is much narrower than those of corresponding mutant mice, suggesting there is much redundancy in human host defence in nature [8], [9]. Our own work in patients with Chronic Mucocutaneous Candidiasis, who suffer with selective susceptibility to infections with the fungus *Candida* suggests that defects of DC cytokine production, maturation and / or PRR cell signalling pathways may underly this still elusive non-conventional PID [14].
Taken together, we have only recently begun appreciating the complexities of interactions between the innate and adaptive immune system in response to infection and the flexibility our immune system has to allow it to select the most efficient response to a particular pathogen. We are also becoming more aware of subtle immune defects, predisposing to infections with only particular pathogens, persuading us to redefine our understanding of infection and primary immune deficiencies. Understanding mechanisms underlying the immune response to infection will improve diagnosis and treatment of patients in the future.

Word count 1883

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