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The innate immune perspective of autoimmune and autoinflammatory conditions

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Abstract

Innate immunity is one of two immune defence system arms. It is present at birth and does not require 'learning' through exposure to foreign organisms. It activates various mechanisms collectively to eliminate pathogens and hold an infection until the adaptive response are mounted. The innate immune system consists of four elements: the epithelial barrier, cells (e.g. macrophages, NK cells), plasma proteins (e.g. complement) and cytokines. These components act in concert to induce complex processes, as well as recruitment, activation and differentiation of adaptive responses. The innate response is more than just the 'first line of defence', as it essentially withholds the vast majority of any intruder, has a complex interplay with the adaptive arm and is crucial for survival of the host. Finally, yet importantly, a myriad of diseases has been linked with innate immune dysregulation. In this mini-review we will shed some light on these conditions, particularly regarding autoinflammatory ones.

Key words: innate immunity, macrophages, IL-1, autoinflammatory, NK

SUPPLEMENT

Rheumatology key messages

- Innate immune responses are essential for maintaining host defence as well as self-tolerance.
- Abnormalities of the innate immune system, whether inherited or acquired, may not be present clinically until adulthood.
- Targeted therapies at innate immune dysfunctions may become game changers in clinical practice.

Introduction

The human immune responses are divided into two main branches: the innate and adaptive systems. The former is an evolutionarily conserved system acting as the first-line of defence against invading microbial pathogens and other potential threats to the host [1]. Although it was once thought that the innate immune system is important mainly for the recruitment of the adaptive immune responses, it is now known that innate immunity has distinctive and unique features. Moreover, current knowledge emphasizes its crucial roles in host defence and survival, and innate responses are in fact not only the gate keepers of the host defence, but also the pivotal mangers of most immune interactions.

The innate immune functions can be split into four distinct categories, namely: recognition, capture and elimination of pathogens and infected cells, and fourthly recruiting of the adaptive system for creating a wider inflammatory response. For all of these purposes, the various components of the immune system work in concert. The innate immune system can also be divided to four major components: the epithelial barrier, the cellular component (cells and receptors), plasma proteins (e.g. complement system) and cytokines [2]. Once a pathogen invades, the first step of initiation of an inflammatory response is recognition. The innate immune system recognizes molecular structures produced by most microbial pathogens, i.e. pathogen-associated molecular patterns, such as viral RNA or bacterial lipopolysaccharide [3]. It also recognizes endogenous molecules produced or released from damaged cells (i.e. damage-associated molecular patterns, such as heat shock proteins) [3]. These molecules are recognized by relatively non-specific

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pattern recognition receptors, such as Toll-like receptors (TLRs) [4]. These are highly conserved germline-encoded receptors with limited diversity that are found on many cell types [5, 6]. Binding to TLRs induces an immune cascade that causes the release of inflammatory cytokines and promotes cellular migration into the infected area, resulting in capture (e.g. phagocytosis) and elimination of the pathogen and/or infected cells (e.g. apoptosis), as well as recruitment of an adaptive response [2].

There are several critical differences between the innate and adaptive arms of the immune system. The innate one is less specific and identifies a limited number of structures shared by classes of microbes (e.g. pathogen-associated molecular patterns) utilizing few receptors, while the adaptive arm identifies numerous specific antigens [7]. However, the innate patterns of recognition are immediate and do not require previous exposures. By contrast, the adaptive immune system has an exceptionally diverse repertoire of receptors that allow pinpointing a large scale of antigens, and requires time to initiate a specific response. Moreover, adaptive responses improve following recurrent exposures (i.e. immune memory), while the innate response remains constant during recurrent exposures in terms of its magnitude [8].

Each part of the innate immune process has a cardinal role in the battle against pathogens. Defects in each aspect may cause on one hand immunodeficiency and on the other autoinflammatory or autoimmune disease. Although a mandatory definition for autoimmunity is loss of self-tolerance, which is typically caused by adaptive system malfunctions, the innate immune system takes a leading role in the initiation and maintenance of autoimmunity and autoinflammatory, as will be elaborated in the following sections. Hence, in this review while briefly describing the four components of the immune system, we focus on some abnormalities that have been related to inflammatory disorders.

Epithelial barriers of the innate immune system

The epithelial barriers are the initial blockade between the host and the hostile external environment. These include the skin, and respiratory, gut and genitourinary mucosa. Apart from being a physical line of defence, barrier cells also produce potent antimicrobial peptides such as defensins and cathelicidins. Furthermore, among barrier cells lie intraepithelial T cells, which are different from the adaptive immune system T cells. Most of the former have a $\gamma\delta$ TCR (as opposed to and $\alpha\beta$ TCR). These receptors recognize both peptide and non-peptide antigens and are present in limited diversity. The intraepithelial T cells mainly function by secreting cytokines, activating phagocytes and killing infected cells. Epithelial barrier dysfunction mainly causes infections, but may also be involved in immune-mediated diseases. A remarkable example of this is atopic dermatitis (AD), an inflammatory skin disease that affects $\sim$20% of children and 1–3% of adults [9]. AD is characterized by intense pruritus, atopy and a chronic relapsing course [10–12]. Damaged epithelial barrier was found to be crucial in the process of AD evolvement, and restoration of this barrier is one of the cornerstones of AD treatment [13]. Epithelial barrier dysfunction is present in most patients with significant AD, and in a minority of patients, a genetic mutation in an epidermal skin barrier protein (Filagrin) can be detected [14–16]. Noteworthy, the role of the gut and the respiratory barriers has taken central stage in recent years as the key locations of the host microbiome. The role of dysbiosis in initiating and perpetuating inflammatory disorders has been suggested, while dysfunctions of the innate system may affect the host microbiome. An interesting example of such interaction is the NOD-like receptor family pyrin domain-containing 6 (NLRP6), a nucleotide-binding domain, leucine-rich innate immune receptor, that participates not only in the formation of the inflammasome but also in the regulation and facilitation of gastrointestinal antiviral functions such as mucus secretion and antimicrobial peptide production. Hence NLRP6 may impact microbial colonization of the gut and thereby be linked to microbiome-related infectious, autoinflammatory and other diseases [17, 18].

Cellular components of the innate immune system

Once the barrier is breached, cellular inflammation is initiated and cell-derived cytokine production is enhanced, enabling capture and elimination of pathogens.

Phagocytes (i.e. macrophages and neutrophils) are a group of cells characterized by their ability to ingest other cells. Most abnormalities of phagocytosis, such as severe neutropenia, result in increased infections but also in autoinflammation and/or autoimmunity. For example, chronic granulomatous disease (CGD) results from an inherited defect in neutrophil oxidation, one of the main methods by which neutrophils eliminate pathogens [19]. CGD is linked with recurrent infections, but also with the inflammatory process of granuloma formation, severe colitis, defects in autophagy and increased release of the cytokine IL-1β [20]. In animal model as well as in humans, blocking IL-1 with an IL-1 receptor (IL-1R) antagonist (anakinra) decreases neutrophil recruitment and Th17 responses, and protects CGD mice from colitis [21]. Another example for the role of neutrophils in immune-mediated pathologies is SLE. This autoimmune disease is demarcated by loss of self-tolerance and overproduction of auto-antibodies, some of which are against extracellular DNA that is released during apoptosis. The pathogenesis of SLE was originally related solely to adaptive dysregulations, but cumulative data suggest a significant role also for innate immune dysfunctions, particularly of the phagocyte lineage and defective clearance of apoptotic cells [22, 23]. In 2006 Denny *et al.* [24] suggested that an innate immunity defect in SLE causes accelerated macrophage apoptosis that is ineffectively processed, and eventually induces autoantibody formation and organ damage. Other studies have documented

neutrophil defects in SLE, and particularly in production of the neutrophil extracellular traps (NETs). These NETs are important in the host defence against microbes [25, 26], and in different inflammatory reactions. The process of NETosis (formation of NETs) is defective in SLE, potentially due to anti-NET antibodies, the increased number of a subset of pro-inflammatory neutrophils and the low density of granulocytes that has been demonstrated in several autoimmune and infectious diseases, as well as overproduction of NETs [27, 28] and delayed NETs clearance [29]. Hence, one may suggest that the primary immune defects in SLE are actually within the spectrum of the innate responses as decreased clearance of apoptotic cells and enhanced NETosis, which is later followed by autoantibodies production.

Innate lymphoid cells (ILCs) are cells with lymphocyte morphology and cytokines production similar to those made by adaptive T cells, but lacking TCRs. Three different subsets of ILCs (ILC1, ILC2 and ILC3) were defined mainly according to secretion of different types of cytokines, somewhat similar to $CD4^+$ T cells. NK cells function as cytotoxic effector cells and are somewhat similar to $CD8^+$ T cells [30]. NK cells represent 5–20% of circulating lymphocytes and secrete granules containing proteins that mediate killing of infected cells via apoptosis [31]. By doing so, NK cells manage to contain viral and bacterial infections as primary defence, but also as a second line of security for infected cells that manage to escape the adaptive cytotoxic T cell responses. T cell adaptive responses require TCR recognition, which is MHC dependent. Reducing expression of class I MHC molecules is one way by which infectious agents escape the adaptive immune responses. Similarly, malignant cells also have abnormal class I MHC molecules presentation and may be resistant to T cell cytotoxicity [32], and are thus an important target for NK elimination [31].

Abnormalities in NK cells are associated with immunodeficiency [33], autoimmunity and autoinflammatory diseases. Typical autoinflammatory conditions with NK cell dysfunction are the life-threatening conditions haemophagocytic lymphohistiocytosis and macrophage activating syndrome. Whether familial or acquired, these conditions are the result of highly stimulated, but ineffective, innate immune responses, mainly due to an intrinsic defect that causes an abnormal number and function of NK cells. Haemophagocytic lymphohistiocytosis/macrophage-activating syndrome are characterized by fever, cytopaenias, splenomegaly, metabolic abnormalities and low or absent NK cell activity [34]. NK cells kill their targets (e.g. infected macrophages) and terminate macrophage activation through secretion of cytolytic granules containing perforin and granzyme. Inability of NK cells to secrete their granules may lead to uncontrolled immune activation and production of inflammatory cytokines. In this context hypersecretion of pro-inflammatory cytokines such as IL-1, IL-6, IL-18, IFN-γ, TNFα and M-CSF is typical. Autoimmune disease may also arise from loss of NK tolerance, following either removal of inhibitory signals or stimulation of activating signals. For example, in SLE, the prototype of systemic autoimmune disease, the number of circulating NK cells is moderately low and is linked to a decrease in regulatory T cells [35–37]. RA [38], SS [39], APS and psoriasis have also been associated with disturbed NK cells [40].

Lymphocytes with limited diversity are cells belonging to the innate immune system, characterized by expressing antigen receptors; similar to those of T and B cells. T lymphocytes with limited diversity include the invariant NK T cells, $\gamma\delta$ T cells, mucosa-associated invariant T cells and intraepithelial T cells with $\alpha\beta$ TCR. Innate lymphocytes and particularly $\gamma\delta$ T cells, which account for $<5\%$ of the peripheral lymphocytes, take part in the regulation of autoimmune diseases (RA, SLE, IBD, autoimmune hepatitis). B cell may also present with limited diversity, specifically the B-1 cells and marginal-zone B cells [41].

Mast cells are present in variety of tissues and when activated by different stimuli, secrete inflammatory cytokines. These myeloid cells contain granules with vasoactive amines (such as histamine), prostaglandins, cytokines (such as TNF) and proteolytic enzymes that can induce death of different pathogens. Their role in protection against helminths is well established and potential effects against bacteria and viruses have been suggested [42]. When considering mast cells dysregulation, the main example is allergic diseases. In other words, an inappropriate response to non-harmful external antigens via activation of the adaptive Th2 skewing response [43, 44]. However, mast cells have also been implicated in inflammation in non-allergic conditions, such as IBD. In Crohn's disease there is an increased expression of many inflammatory cytokines, including IL-16 release from mast cells. Furthermore, mast cells are redistributed and found particularly in the muscle layers of the gut stricture, suggesting a role of mast cells in stricture formation [45]. The hallmark of association between mast cells and autoimmunity is chronic urticaria [46, 47]. This disorder is characterized by spontaneous appearance of cutaneous wheels, pruritus and angioedema. Auto-antibodies against the IgE receptor (FcϵRI) on mast cells induce degranulation of the cells with release of different mediators such as histamine, prostaglandins, platelet-activating factor and others [48]. Mast cells have also been linked with Type 1 diabetes mellitus [49], Guillain–Barré syndrome [50], skin diseases [51], SS [52] and multiple sclerosis [50]. With regard to autoinflammatory disease, comparable to macrophages and monocytes, mast cells also express functional inflammasomes. Moreover, mast cells are a both the source of and the target for IL-1β [53]. The autoinflammatory disease Schnitzler's syndrome is characterized by chronic urticarial rash, monoclonal gammopathy and systemic inflammation. IL-1β is pivotal in the pathophysiology of Schnitzler's syndrome, and IL-1β-positive dermal mast cells are found in biopsies from diseased skin [54].

Dendritic cells (DCs) are the main antigen-presenting cells and are thereby crucial to the fourth innate role: recruiting of adaptive responses [55]. This is due to the fact

that they hold different TLRs and pattern recognition receptors, making them the most sensitive cells for the identification of pathogens. DCs also express antiviral cytokines essential for combating viral infections. In response to identifying a pathogen, DCs secrete inflammatory markers that recruit and activate adaptive cells. In addition, DCs have a major role in determining the nature of the adaptive reaction, and according to the specific pathogen they identify, DCs induce T cell differentiation into different effector cells (e.g. Th1, Th2 or Th17) [56]. On the other hand, DCs can limit an immune response by inducing peripheral tolerance and facilitating the homeostasis of peripheral Tregs [57]. This regulatory role of DCs is thought be involved in preventing graft-*vs*-host disease [58]. Having said that, one can understand also the plausible roles of DCs in the pathogenesis of autoimmunity in which self-tolerance loss is the hallmark [59]. This concept was documented via induction of psoriasis, SLE and Type 1 diabetes in animal models [59, 60] and by decreased regulation in APS [61]. In SLE, mutation in death receptor CD95 (Fas Cell Surface Death Receptor) was sufficient to induce the disease in mice [62]. In Type 1 diabetes mellitus, the disease is induced by β-islet cell-derived antigens that are captured by DCs and presented to autoreactive T cells [63], and similar roles for DCs were recognized in autoimmune myocarditis [64] and multiple sclerosis [65].

Receptors of the innate immune system: TLRs are actually located on most cell types, but mainly on the cells of the innate immune system such as DCs and macrophages. These pattern recognition receptors may be membrane-bound or cytosolic, and recognize damage-associated molecular patterns and pathogen-associated molecular patterns. There are at least 13 different TLRs, each of which induce a signalling cascade upon activation. Some of these signalling patterns contribute to the activation of the adaptive immune system [66]. Therefore, it is understandable that abnormalities of the TLRs pathway are linked to autoinflammation [67] and autoimmunity [68]. Notably, regulation of TLR activation may be used to treat inflammatory conditions. HCQ inhibition of TLR-7 is considered particularly significant for ameliorating SLE disease and anti-RO/SSA antibody-mediated congenital heart block [69], whereas hypersensitivity to TLR-9 was acknowledged in TNF receptor-associated periodic syndrome. This hereditary autoinflammatory disorder is characterized by recurrent episodes of fever and inflammation and autosomal dominant mutations in the *TNFRSF1A* gene [67]. A role for TLR-4 was suggested in the pathogenesis of 'deficiency of IL-36Ra' (DITRA), a systemic autoinflammatory disease that includes generalized pustular psoriatic fever and systemic symptoms [70]

The complement system

Various proteins are utilized by the innate immune system including the complexed complement system. This encompasses a cascade of activated and regulatory proteins that eventually recognize and eliminate pathogens by direct killing of infected cells or initiation of phagocytosis. Deficiency of complement proteins is linked with immune deficiency (e.g. meningococcal infections), autoimmunity and other immune-mediated conditions (e.g. hereditary angioedema) [71]. Notably, the complement system is essential for production of immune complexes and, as such, is activated concomitantly during innate and adaptive responses. Activation of the complement system initiates a proteolytic cascade through one of three pathways: classical, alternative or the lectin pathway. Typical complement activation and consumption in a certain autoimmune disease is mediated by one of the three specific pathways; in this manner differences in the complement pattern of deficiencies may be unique to each disease. Low or absent levels of the classical pathway components are associated with susceptibility to SLE or SLE-like syndromes in humans [72] and in animal models [73]. Abnormal activation of the classical pathway is also linked to cryoglobulinemia vasculitis. This small vessel vasculitis may be monoclonal, mixed or polyclonal, and one of its hallmarks is consumption of C4, C1q and abnormal CH50 [74, 75]. In contrast, ANCA-associated vasculitis involves the alternative pathway [76], with a pivotal role of C5a in stimulation and degranulation of neutrophils. HScP, another vasculitic disease, is related to activation of both the alternative and the lectin pathway [77, 78]; thus in addition to IgA, C3 component is also deposited in the dermal vessels. Similarly, a contributing role for complement dysregulation in autoinflammatory diseases has been suggested, further eluding to the overlap between autoinflammation, autoimmunity and immunodeficiency [79].

Cytokines of innate immunity

Last but not least, are the innate cytokines, the fourth component of this system. These soluble molecules mediate regulation, initiation and seizing of immune responses. The long list of such cytokines includes TNF, IFN, interleukins IL-1β, IL-4, IL-6, IL-10, IL-12 and IL-18, Chemokine (C-C motif) ligand 4/regulated on activation, normal T cell expressed and secreted and TGFβ [80–83]. Although all take part in the innate responses, some are more prominent then others in autoinflammatory processes, such as IL-1, IL-6, TNF and IFN.

IL-1, was once considered mainly a haematopoietic factor post-bone marrow transplantation [84], is currently acknowledged as one of the dominant mediators of inflammation [85]. IL-1 signalling involves binding of IL-1 to several specific receptors (i.e. IL-1R1, IL-1R2, IL-1Ra) on the surface of target cells, and this is already exploited to treat inflammatory disorders. The IL-1 family of ligands and receptors is mostly secreted by activated mononuclear phagocytes, neutrophils, epithelial and endothelial cells, and includes 10 structurally related members, and the distantly related soluble protein IL-18BP [84].

Secretion of IL-1 is mediated by activation of TLRs-dependent cascade of innate receptors termed the inflammasomes. In this context, the more intense the activation of TLRs, as documented during severe infections, or the

higher or uncontrolled activation of the inflammasome due to other causes, the more robust is the activation of pro-IL-1β into active IL-1. The latter has two forms: IL-1α and IL-1β. These forms are non-homologous in structure, although they share target receptors, and prompt similar activities. IL-1β is the central form in response to infections. The IL-1R is membrane-bound on a variety of cells (e.g. leukocytes, endothelial and epithelial cells), and its activation induces downstream signalling and gene transcription [1, 85]. Therapeutic blocking of the IL-1 pathway was first appreciated as a partially successful intervention during sepsis [86], while nowadays it is mainly utilized to control non-infections inflammatory conditions. Several biological drugs can block the IL-1 pathway, namely: anakinra (an IL-1R antagonist), rilonacept (IL-1 inhibitor) and canakinumab (anti IL-1β antibody). These drugs have been used in a variety of familial and acquired autoinflammatory diseases: FMF [87], Behçet disease [88], Cryopyrin-associated autoinflammatory syndromes [89, 90] JIA [91], adult Still's disease [92] and macrophage-activating syndrome [93].

IL-6 is another cardinal player in acute inflammatory responses. It is produced by mononuclear phagocytes, DCs, vascular endothelial cells, fibroblasts and others. IL-6 induces synthesis of acute-phase reactants by the liver, stimulates neutrophil production and promotes the differentiation of IL-17 Th cells. As with blocking IL-1, blocking the IL-6 pathway has been investigated in different inflammatory diseases (i.e. JIA [91] and RA [94]). In 2010 tocilizumab, an IL-6 receptor antagonist, was approved by the Food and Drug Administration and is currently in use for various autoimmune and autoinflammatory conditions. Recently, other inhibitors have been developed, of which sarilumab has been approved for treating RA [95], and sirukumab and olokizumab are under investigation [96].

TNFα mediates granuloma formation, as seen in normal response to infection with *Mycobacterium tuberculosis* [96], and several inflammatory diseases such as sarcoidosis [97, 98] and CGD [20]. TNF is also a key cytokine in many autoimmune and immune mediated conditions (e.g. JIA, RA, IBD and PsA). In these diseases the use of anti-TNF inhibitors (e.g. infliximab, adalimumab, etanercept, etc.) has become common practice [99–101].

The IFN signature is part of the innate immune response and a key cytokine in several inflammatory and autoimmune conditions [102]. There are three major types of the IFN protein family [102, 103] and various genetically measurable changes define the IFN signature. The latter was first implicated in describing an increased expression of type I IFN-inducible genes in peripheral blood cells. Due to the fact that there is a significant overlap between the genes induced by IFN types I and II (IFN-γ), several studies have demonstrated that IFN-γ also plays a pivotal role in the development and severity of autoimmune diseases [104]. Defective regulation of type I IFN response and IFN signature is remarkable in SLE, JIA, diabetes mellitus and others [102]. In addition, a primary disorder of IFN was proposed in 2011 by Crow [105], who argued that upregulation of IFN-1 may be clustered in a Mendelian way of inheritance. Today, the entity of type I interferonopathies are classified as a clinically heterogenic group of Mendelian diseases in which activation of the IFN-1 pathway causes severe and early onset of rheumatic manifestations [106]. Similar to other key cytokines, specific mAbs that inhibit IFN activation and signalling are under investigation.

Conclusion

Our understanding of the complex and intriguing innate immune system has greatly evolved in recent decades. Though much is yet to be revealed, many old misconceptions have been erased. The innate immune system is nowadays regarded as a multicomponent system essential for maintaining immediate defence against pathogens, as well as for recruitment of the adaptive immune system and maintaining self-tolerance. In other words, the innate immunity is not just the opening act for the adaptive responses, but in fact a leading player by itself and a constant co-player to the adaptive immune system. For years dysregulated innate immune responses were considered lethal very early in life, and thus innate-related therapies were thought irrelevant for diseases that appear during childhood and adulthood. It is now known that many diseases, either inherited or acquired, are tightly linked with malfunctions of innate immunity. Moreover, diseases that are mainly induced by innate dysfunctions, such as the autoinflammatory diseases, have been defined. Last, but not least, the vast knowledge accumulated throughout the years has enabled the development of targeted therapies, many of which have become 'game changers' in clinical practice (e.g. IL-1 inhibitors for autoinflammatory diseases). Increasing our index of suspicion and understanding of the specific immune mechanisms related to each disease may enable early diagnosis, and improve our ability to target, intervene in and treat these conditions.

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