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# Innate Immunity and Autoimmune Diseases

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## Abstract

The innate immune response is responsible for the initial defense against invading pathogens and signs of damage; in turn, it activates the adaptive immune response to result in highly specific and lasting immunity, mediated by the clonal expansion of antigen-specific B and T lymphocytes. Inflammation is the acute response to infection and tissue damage to limit aggression to the body. It is a complex reaction of vascularized tissues to infection, toxin exposure or cell injury that includes extravasation of plasma proteins and leukocytes. Paradoxically, uncontrolled and prolonged inflammation can result in secondary damage and the development of immune pathology in the host. The components of the innate immune system have recently been studied as responsible mechanisms in various chronic diseases such as diabetes mellitus, atherosclerosis, asthma and allergies, among others. Autoimmune disease is an attack on auto tissues by the adaptation of the immune system. In general, such diseases are characterized by autoantibodies and/or autoreactive lymphocytes directed at antigens against themselves. The innate immune system is often considered an effector of self-reactive lymphocytes, but also provides protection. Studies in mice with specific gene-directed mutations show that defects in innate immune system proteins may predispose to the development of a systemic lupus erythematosus-like syndrome (lupus) characterized by autoantibodies against double-stranded DNA (ds DNA) or nuclear components. This seems to be due to a failure in the removal of apoptotic cells or nuclear waste. These observations imply that the innate immune system has a general protective role against autoimmune disease. For example, in systemic diseases such as lupus, innate immunity is important in the elimination of nuclear antigens and, therefore, in the improvement of tolerance to B lymphocytes. Alternatively, in specific organ disorders such as type diabetes 1 o Crohn's disease, the innate immune system can be protective by eliminating pathogens that trigger or exacerbate the disease or regulate the presentation of antigens for T lymphocytes. Discuss various disease models in which the innate immune system could provide a protective role, deficiencies in the regulation of B lymphocyte signaling through the antigen/receptor or in the clearance of lupus antigens, (dsDNA and nuclear proteins), can lead to a disease similar to lupus. The repertoire of B cells seems to be very biased toward self-activity, as, possibly, that of the T-cell. This tendency toward self-activity is not surprising because B and T cells are positively selected against highly conserved autoantigens.

**Keywords:** toll, antigens, dendritic cells, lymphocytes, lupus, PAMP, DAMP tolerance, autoimmunity

## **1. Introduction**

The human immune system has two major divisions: innate and acquired. We will talk about innate immunity. Innate immunity can be defined as the first line of defense against pathogens, which represents a great machinery to create an adequate and definitive systemic response to prevent infections and maintain homeostasis of the organism. The elements of innate immunity include external physical barriers, humoral and cellular effector mechanisms. This type of immunity recognizes pathogens such as bacteria and viruses. This works thanks to the phagocytosis of the pathogens with the consequent induction of inflammatory reactions. It also has a critical role in the activation and regulation of adaptive immunity. This immunity has the ability to develop an induced response during primoinfection. This response is specific due to the expression of cell surface pattern recognition (PRR) receptors, which are capable of recognizing complex polysaccharides, glycolipids, lipoproteins, and nucleic acids. We know that pathogens contain in their structure various components that act as substances strange (antigens) and this in turn will induce an innate immune response that will subsequently activate the adaptive response. It is imperative to recognize that the important exploration of these innate mechanisms is essential for the understanding of the complex events involved in human innate immunity and is also crucial for the discovery of new antimicrobials, antitumor drugs, and immunomodulators with therapeutic applications [1]. Innate immunity, which is considered a simple immune system, is essential for the onset of acquired immunity and has been found to play an important role in the pathogenesis of the disease age [2]. Among them, it recognizes nucleic acids derived from pathogens. The innate immune pattern recognition (PRR) receptor recognizes self-derived nucleic acids. Innate pattern recognition receptors regulate antigens for the presentation and subsequent responses of B cells and T cells, for example, physiological management of autoantigens, induction of immature dendritic cells to detect tolerant signals to T cells. The activation of toll-like receptors (TLR), NOD type receptors (NLR) or Helicases similar to RIG (RLH) by molecular agents associated with pathogens where the patterns will induce dendritic cell maturation, costimulation.

T cell activation and production of antibodies by B cells. Therefore, recognition of innate patterns is now being considered as a central element of immunity modulation. There are at least 80 different autoimmune diseases discovered so far, which in the US alone, affect 20 million people [3]. These pathologies are established systemically or in a specific organ, but require for their expression certain conditions that are the result of multifactorial processes that involve a deregulation of the innate immune system and therefore adaptive that lead the body to erroneous responses with the subsequent attack itself of their own tissues. The innate immune system as discussed above is the first line of immediate defense against invading microorganisms that links to the adaptive response. Specific cells of the innate immune system, which are dendritic cells (DC) (antigen presenting), which are cells with an important and critical role in promoting the responses of B and T cells. This type of immunity is critical to maintain homeostasis and prevent microbial invasion, eliminating a wide variety of pathogens and contributing to the activation of the adaptive immune response.

## **2. The entrance door: PAMP/DAMP**

It is the control point. A dendritic type receptor that bears the title of “access gate” for innate cellular immunity: this basically consists of a type of toll-like receptor. It has been found that it plays a fundamental role as a sensor in the recognition of pathogens in the innate immune system [4].

### 3. Let's talk about PAMP

This pattern recognition receptor acts on bacteria and viruses (PAMP) [5]. The innate immune response in immunological terms controls the infection and prevents its spread. And more recently it is known that to induce this series of reactions against pathogens, in addition to the existence of antigens, another series of molecules in the pathogens is required. These molecules are known as pathogen-associated molecular patterns (PAMPs). PAMPs play and interact with a series of receptors that are mainly present in phagocytic cells (macrophages), and these “gate” receptors have been called recognition patterns to pathogen-associated molecular patterns (PRRs). These receptors contain other subfamilies where we can find toll type receptors (TLRs), NOD type receptors (NLRs), RIG-1 type receptors (RLRs), and lectin C type (CLRs). This molecular pattern related to the associated damage known as DAMP comes to behave as a type of alert that recognizes signals and most importantly this does not involve pathogen detection. The main molecular recognition patterns (PRRs) include TLR and NLR receptors, also known as nucleotide binding oligomerization domains. TLR is the homologous receptor that has already been identified in the *Drosophila* genetic code, and that to date some TLRs have been found in humans mainly in the cell surface, membrane, and lipids [6]. Types 1, 2, 4, 5, and 6 are those that recognize proteins, nucleic acids located in the endoplasmic reticulum and those that are found in the endosomal membranes. 3, 7, 8, and 9 detect lipopolysaccharides in the outer membrane of gram-negative bacteria (endotoxins). The TLR4 type, which transmits inflammatory signals, is the best known in general and the most studied of the TLR. This receptor responds to MyD88, which becomes a station at the central point of the inflammation signal, and corresponds to the first phase of activation of the transcription factor NF- $\kappa$ B pathway (nuclear factor-kappa B), which in turn, production begins and a kind of “chain reaction” of inflammatory cytokines to eliminate pathogens [7]. Meanwhile, these TLR receptors are incorporated into PAMPs, which by recognizing nucleic acids act as an inflammatory cytokine. Receptors that mediate innate immune responses, such as toll-like receptors (TLR) and specific C-type lectin receptors (CLR) that recognize associated molecular patterns (PAMP), have been implicated in autoimmune disease mechanisms, both directly through self-recognition ligands and indirectly through the regulation of immune homeostasis [8, 9].

### 4. DAMPs: (the antigenic gift of cells)

In intracellular infections, in addition to antigens and PAMPs, the participation of another series of molecules that participate in the activation of the immune response is necessary. Recently, some studies have shown that cells can die from a type of immunogenic “apoptosis” and thus expose their nuclear or cytoplasmic molecules to their membrane. These have a way of stimulating the immune response, thanks to their activity. They are also released during the process of necrosis and have been given the name of molecular patterns associated with damage or warning signs, the famous DAMPs. The NLR receptor is present in the cytoplasm. It has the particularity of recognizing not only PAMP but also several DAMP among them [uric acid, cholesterol, sterols crystals, extracellular ATP (adenosine triphosphate), silica] or even recognizing exogenous DAMP such as asbestos, origin of aseptic inflammation, such as gout, arteriosclerosis, and silicosis [10]. It is clear that it is a cause and attracts attention. The abnormalities in the immune system that are the basis and fertilizer for autoimmune diseases are mainly caused by an



abnormal acquired immunity [11]. In recent years, in contrast to the concept that autoimmune or auto-inflammatory diseases are mainly due to abnormal innate immunity, it is attracting more attention.

## **5. Innate immunity cells: “soldiers of the first line of defense”**

Dendritic cells, macrophages, and other myeloid cells also play an important role in the innate immune response, both as antigen presenting cells as effector cells that mediate the tissue damage [12–14]. Therefore, they are fundamental and will be as in conflicts, “the first line of defense” in the face of a bacterial or other stimulus. We will also take them into account in relation to autoimmune diseases, because of their responsiveness and because they are important mediators of innate immunity, an interest has arisen in this potential to contribute to the pathology of these diseases. Proinflammatory cytokines: mainly TNF $\alpha$  (tumor necrosis factor alpha), induce the activation of endothelial cells, resulting in an increase in the expression of different adhesion molecules (CD62E, CD62P, ICAM-1, and VCAM-1). This causes the leukocytes to roll over them, and during this bearing, they are activated by the intracellular signals that are generated through their adhesion molecules and different chemokine receptors, which interact with the ligands found on the surface of the cells endothelial. Subsequently, these activated leukocytes adhere firmly to the endothelium, change their morphology (cell polarization) and carry out their transendothelial migration, and then migrate to the inflammatory focus, guided by the gradient of chemotactic substances that are released. Macrophages are multifunctional antigen presenting cells, with an important role in innate immunity and, therefore, in the inflammation process [15]. Macrophages are found in almost all organs, and recent studies have demonstrated their multifunctionality and heterogeneous capacities established by their numerous subpopulations, adaptation in specific tissue microenvironments and different stages of maturation. For example, during a bacterial infection, classically activated macrophages show inflammatory functions (type 1 or M1 macrophages), while with alternative activation (by Th2 type cytokines, such as IL-4 or IL-13), macrophages acquire anti-inflammatory functions (type 2 macrophages or M2). In addition to depletion or inhibition of macrophage function, reprogramming of M2 has also been explored. Recently, it has been shown that paracoccin, a protein contained in a fungal human pathogen, induces the repolarization of M1 macrophages through interaction with toll as a receptor (TLR) 4, being a new possible immunotherapeutic agent for pathologies related to M2 macrophages. Macrophage-related therapies have been proposed for various autoimmune and inflammatory pathologies. In the case of PPAR $\gamma$  and PPAR $\delta$ , which are nuclear receptors that control different genes associated with M2 macrophages, and their agonists have been proposed as a therapy directed at macrophages to induce M2 pathways. In addition, the demonstration that TLR9 receptor signaling can reverse the aberrant M2 macrophage phenotype.

Dendritic cells (DC) are professional antigen presenting cells (APC), often referred to as “orchestra directors of the innate immune response” due to their ability to capture, process, and present antigens to T cells. Depending on the nature of the antigen may exhibit an immunogenic or tolerogenic effect, which will be defined by cytokine secretion. They are often considered tolerogenic, because they have autoantigens in the absence of costimulation and, together with anti-inflammatory stimuli, (TGF- $\beta$ ), can promote the induction of regulatory T cells and/or induce anergy of T cells [16]. After activation by proinflammatory stimuli, they mature and generate an expression of costimulatory molecules and the major histocompatibility complex (HCM) class II, which causes a potent response of

specific T cells to the antigens. Therefore, they play a fundamental role in maintaining self-tolerance, and on the other hand, they initiate the response against foreign antigens for their subsequent elimination by effector immune cells. In a state of aberrant hyperreactivity, they could contribute to perpetuating immune responses, backed by evidence of a high frequency of immunogenic infiltration [17]. Due to their ability to modulate the cellular response, they have been considered a powerful target for immune modulation. Strategies such as pharmacological modulation to affect their maturation status and genetic engineering to improve their tolerance or immunogenic properties for the treatment of autoimmune diseases have been studied. In several murine models, they were transduced to express IL-4 and were able to prevent disease in 12-week NOD mice. In a murine model of collagen-induced arthritis (CIA), it was shown that the injection of dendritic cells with tolerogenic activity improves the clinical and the outcome of the disease. Although the treatment was found to be safe and feasible, other studies are needed to evaluate the efficacy of cellular treatment in autoimmunity.

## **6. Innate lymphoid cells (ILC): “the element of surprise”**

They are a growing family of immune cells that reflect the phenotypes and functions of T cells. Natural killer cells (NK) can be considered innate homologs of cytotoxic CD8 + T cells, while ILC1, ILC2, and ILC3 correspond to innate homologs of T cells CD4 + (TH1), TH2, and TH17. However, in contrast to T cells, they do not express antigen receptors or undergo clonal selection and expansion when stimulated [4]. The ILCs react and respond to the signs of tissue damage and produce a series of cytokines, which direct the immune response and this adapts to contain the lesion. Therefore, these cells can control or unleash the immune response. As with B cells and T cells, these also originate from the common lymphoid lineage but the specific transcription factors of these suppress and modify their development until the generation of the different types of ILC. The precursors of these can migrate from their primary production site in infected and injured tissues, where they complete their maturation, in a process very similar to the differentiation of virgin T cells into TH effectors. The cytokines produced by local cells, as well as some trauma and stress response ligands as well as bacterial and dietary compounds regulate the maturation and activation of ILC in effectors that play an important role in early immune responses to pathogens in particular has been found relationship with symbionts, helminths, and allergens. The cytokines they produce induce innate responses in stromal, epithelial, and myeloid cells that in turn will regulate the activity of dendritic cells and will also play a central role in the transfer of information between ILC and T cells. ILCs by activating DC found in tissues to migrate to the lymph nodes, where they cause specific T-type cellular responses. ILCs also regulate T cells directly through the presentation of peptide antigens through CMH type II. However, ILCs are also involved in autoimmunity, because their cytokine production can exacerbate and exaggerate the inflammatory process.

## **7. The eye of the hurricane: autoimmunity and innate immune system. How can an autoimmune disease use machinery of innate immunity?**

Recent research has revealed new knowledge about the respective roles of these cells in relation to cellular and humoral immunity as well as the extension to adaptive immunity [18]. There is talk of a recent study in which a genetically modified mouse prototype model was developed with an autoimmune disease similar to lupus

that does not require to express the adaptive immune system machinery, but is triggered directly by the innate immune response [19]. For many autoimmune diseases, we largely know the roles that key cells (T cells and B cells) play and for example are evident in the success of existing therapies (anti-CD3 and anti-CD20). Then knowing this, each of the functions of myeloid cells, and in general of the innate immune response cells, can “autoimmune” disease occur in the absence of adaptive immunity and these cells act as effectors in disease progression? The answer to this could be yes [20]. The most recent example is the study of mice eaten by moths that have been genetically modified to have deficiencies in hematopoietic cells, and to express an autoimmune disease characterized by alopecia (giving a “peeled or eaten by moths”) and edema in their legs. These were also accompanied by high antibody titers, with renal and pulmonary functions being compromised due to immune complex deposits [21, 22]. However, in another study, mice with deficiency in hematopoietic cell phosphatase were crossed with mice that lack the recombina-1 activator gene (RAG-1) that caused a subsequent deficiency in the production of T and B cells and found that the disease autoimmune had progressed normally in the absence of an adaptive immune response [22, 23] even though these mice lacked high antibody titers and immune complex deposits, and they exhibited all other symptoms of the disease. Subsequently, although the onset and progression of the disease could not be defined, it was concluded that the autoimmune disease of this type of mice was mediated by an aggressive response of macrophages and other myeloid cells. Now, a study with murine models is also described, with mice with a genetic alteration associated with the deficiency in the enzyme  $\alpha$ -mannosidase type II ( $\alpha$ M-II) where there is premature aging with the clinical expression and the characteristic symptoms of SLE and Lupus nephritis (high titers of anti-DNA antibodies, glomerulonephritis, and renal compromise due to deposition of immunoglobulins in the kidney) that seems to be driven by a mechanism that also seems to involve the innate immune system [12, 24, 25]. In the case of the murine model, evidence was provided that the abnormal presence of hybrid glycoprotein structures acts as a trigger for the induction of an innate immune response mediated by members of the C-type lectin family that is specific for mannose. Serum mannose-binding lectins (MBL-A and MBL-B) are soluble lectins that mediate innate immunity to pathogenic bacteria and fungi that express glucans (mannose). It is also believed that the macrophage of the mannose receptor cell surface (MMR) participates in innate immune responses, and its expression has been documented in mesangial renal cells [26, 27]. In mice with  $\alpha$ M-II deficiency, MBL lectins are deposited in renal glomeruli which, when they express high levels of mannose glucans in mesangial cells, also express higher levels of MMR, which can bind mannose ligands in the serum. Monocyte chemoattractant protein 1 (MCP-1) levels, produced by activated mesangial cells, represent the entry of activated macrophages. By aberrantly expressing mannose-containing glucans in mice with  $\alpha$ MII deficiency, they act as triggers for an innate immune response mediated by mannose-specific C-type lectins programmed to recognize mannose glucans as PAMP.

The second point in importance is the role of antibodies in stimulating the innate immune response. How can this be to the production of autoantibodies in autoimmune diseases, such as our old friend, lupus? Systemic lupus erythematosus (SLE) is an autoimmune disease that translates inflammation and exaggerated immune responses and thus with a large generalized associated tissue damage. We are clear that innate immunity plays a great role in its development and sequentially its clinical expression, and it has been shown that defects found in any of the immune recognition pathways will promote autoimmunity. First, dendritic cells and macrophages activated by TLR receptors can regulate the differentiation of self-reactive B cells through the expression of CD40 and the action of IL-6. Second, by



nucleic acids. These can activate and in a powerful and disorderly way certain TLR and RLH receptors; therefore, these are normally protected from immune recognition by multiple mechanisms (epigenetic modifications, nuclear compartmentalization, and the rapid elimination of cells that have entered apoptosis and extracellular compartments by a type of DNase and RNase enzymes). These immune complexes containing chromatin or circulating RNA particles can avoid being “digested” by these enzymes in the extracellular space and facilitate the uptake of the complex in intracellular compartments through Fc receptor-mediated endocytosis (FcR) in dendritic cell-mediated uptake or by B cell receptor (BCR) in B cells. And it has also been confirmed by studies with lupus-prone mice deficient in TLR receptors and their respective signaling molecules. As an exception, mice with TLR-9 deficiency with a predisposition to lupus produce more autoantibodies against it, indicating that TLR-9s have additional functions in the regulation of systemic autoimmunity. Innate pattern recognition (PRR) receptors regulate the production of autoantibodies associated with lupus and self-reactive T cells by modulating the presentation of autoantigens and also contribute directly to the end result that is tissue or organ injury secondary to autoimmunity. In general, it is believed that this “injury” or tissue damage is generated from the deposition of the immune complex, complement activation, and subsequent release of cytokines and chemokines to trigger local inflammation. This concept has been redefined. For example in glomerulonephritis, in the glomerular immune complex, deposits are not always associated with innate and adaptive immune responses. These are traditionally seen as separated from each other, but emerging evidence suggests that they overlap and interact with each other. Recently discovered cell types, particularly innate lymphoid cells and myeloid cell-derived suppressors that are gaining increasing attention. It is a rapidly evolving field with molecular pathways and new types of discovered cells and multiple constantly changing paradigms. In general, it is believed that many autoimmune diseases are triggered by aggressive responses of adaptive immunity by an automatic antigen system, resulting in tissue damage and pathological sequelae.

The third point is undoubtedly the role of infectious agents, which have the potential to trigger an exaggerated immune response, through molecular imitation, polyclonal activation or antigen release. For example, there are certain diseases that respond to certain infectious autoantigen peptides. This is the case of multiple sclerosis, where T cells are activated by Epstein-Barr virus peptides, type A flu, and human papilloma and that react with the myelin autoantigen peptide [28]. In this case, the viral infection could cause the activation of the lymphocytes, and the autoantigen could maintain this activation, even after the eradication of the infectious agent. Microbial infection can also cause polyclonal activation of lymphocytes, and this is the underlying mechanism in increasing the incidence of autoimmunity in murine models exposed to microbial pathogens [29]. Microbes (viruses or bacteria) that destroy cells also cause an inflammatory response and also the release of antigens that have been previously captured and this could also result in autoimmunity. There is another important point. Inflammation, even in the absence of infection, can trigger polyclonal activation and self-activity. This is that through the activation of anergic cells, by inflammatory mediators or the activation of new self-reactive cells in an inflammatory environment for example in the context of ischemia of any tissue, tissue autoreactivity could be caused and because not at a systematic level [3]. Within non-infectious detonators, we have those of the hormonal type that in many autoimmune diseases are more common in women than in men. Drugs can also alter the immune repertoire. One of the most common and studied procainamide induces antinuclear antibodies and sometimes induces a lupus-like syndrome. And even some substances produced by the same cells can act as haptens and make autoantigens immunogenic, for example, CD1 T



cells, with receptors (gamma/delta), CD4+, CD25+, and cytokine-producing agents that monitor activity, reduce, and control self-reactive cells, and they can become pathogenic. As some must complete their maturation in the thymus, and others the activation of autoantigens in the periphery, in these processes alterations in the number and function of regulatory cells that can contribute to autoimmunization can be generated.

## **8. “War”: mechanisms of tissue damage of innate immunity**

Upon contact with the stimulus, whether microbial or of any substance, the recruitment and activation of macrophages will begin. The macrophages will serve as the primary effector cells that cause tissue damage and loss. And it has been concluded that the vast majority of autoimmune diseases could be explained by an aberrant adaptation as an immune response to the antigens themselves. On the other hand, autoimmunity as a disease contrasts with innate immunity. The first in which the term autoinflammatory was used was the periodic fever syndrome related to the TNF receptor (tumor necrosis factor), whose causative gene is TRAPS 4 and which was directly related to the presence of genetic abnormalities associated with innate immunity autoinflammatory diseases that are generally considered as a group of diseases where we can find an active responsibility for aberrant innate immunity and in which T cells are not detected and include TRAPS, cryopyrine-associated syndrome (secondary to mutations in the NLRP3 gene in children) (CAPS), Familial Mediterranean Fever (FMF), Bechet’s disease, Still’s disease in adults, Crohn’s disease, Gout, Type 2 diabetes, and various metabolic disorders [30]. The mechanism of its many initiation is still unclear, but the symptoms and diseases themselves are caused by the collapse of immune tolerance. Thymus autoreactivity and subsequent and completely abnormal inactivation of receptive and regulatory (Th) T cells suppress the reaction to the foreign antigen. The other part of the aberrant response of the innate immune response is carried out in the recipients of recognition of autoimmune patterns and diseases recognized by nucleic acids (PRR). This recognition is transmembrane due to its location in the cell and is divided into two general and cytoplasmic phases. This receptor is found in the endoplasmic reticulum or endosome and is directly related to autoimmune diseases (SLE = TLR7/9). When comparing the sequence of own nucleic acids and pathogen derivatives by means of the TLR7/9TLR9 receptors, it is noted that it contains unmethylated CpG sequences, and these are derived from pathogens that in turn recognize a type of single stranded DNA. TLR7 on the other hand recognizes single stranded RNA derived from viruses and other types, as well as messenger RNA (mRNA). From this, TLR7/9 is self-sufficient, and this receptor can strictly distinguish between conventional nucleic acids and pathogen derivatives. Stimulates an immune response in response to auto-nucleic acid. In other words, viruses and infected cells are captured by endosomes, and these nucleic acids are recognized by TLR7/9. In the case of SLE, the TLR7/9 receptor, due to the genetic modification secondary to the aberrant response to the own nucleic acids that were released and transferred to the endosome and therefore increases the genetic expression of the type I IFN and is known as the “IFN signature.” This signature of IFN is directly related to SLE, rheumatoid arthritis (RA), and systemic sclerosis (SSc) and its effects, suggesting the importance of type I IFN in autoimmune disease [31]. It also activates and stimulates plasma cells that in turn produce large amounts of type I IFN.

The TLR7/9 receptor also mediates the response of plasmacytoid cells and is considered an IFN type I producing cell, which through the TLR7/9 Fc receptor

activates the signal to induce the production of non-protein IFN type I histone in the core (HMGB1), to subsequently activate DAMP. The balance between TLR7 and TLR9 is also considered important for inflammation and immune response. The other transmembrane PRR receptors TLR3 and TLR8 also recognize double stranded and single stranded RNA. On the other hand, the cytoplasmic PRR receptor, type RIG-I, and MDA-5 normally identifies a specific structure of single stranded RNA. By recognizing double-stranded RNA, the specific proteins of these DAI, IFI16, and DDX41 receptors induce the production of IFN and inflammasome and, in turn, the production of IL-1 $\beta$  and IL-18.

### **Conflict of interest**


“The authors declare no conflict of interest.”

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