

Review Article

“The Good, the Bad and the Ugly”: Interplay of Innate Immunity and Inflammation

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Innate immunity recognizes microorganisms through certain invariant receptors named pattern recognition receptors (PRRs) by sensing conserved pathogen-associated molecular patterns (PAMPs). Their recognition activates several signaling pathways that lead the transcription of inflammatory mediators, contributing to trigger a very rapid inflammatory cascade aiming to contain the local infection as well as activating and instructing the adaptive immunity in a specific and synchronized immune response according to the microorganism. Inflammation is a coordinated process involving the secretion of cytokines and chemokines by macrophages and neutrophils leading to the migration of other leukocytes along the endothelium into the injured tissue. Sustained inflammatory responses can cause deleterious effects by promoting the development of autoimmune disorders, allergies, cancer, and other immune pathologies, while weak signals could exacerbate the severity of the disease. Therefore, PRR-mediated signal transduction must be tightly regulated to maintain host immune homeostasis. Innate immunity deficiencies and strategies deployed by microbes to avoid inflammatory responses lead to an altered immune response that allows the pathogen to proliferate causing death or uncontrolled inflammation. This review analyzes the complexity of the immune response at the beginning of the disease focusing on COVID-19 disease and the importance of unraveling its mechanisms to be considered when treating diseases and designing vaccines.

1. Introduction

In 1908, Mechnikoff and Ehrlich received the Nobel Prize in Medicine for the discovery of innate immunity and acquired immunity, respectively. Although research on acquired immunity subsequently made remarkable progress, innate immunity was, until recently, regarded as an ancient, nonspecific immunity that functions in the lower animal kingdom. Although innate immunity evolutionarily precedes acquired immunity, vertebrates use both types of response in coordination. Innate immunity recognizes the invader through certain invariant receptors named pattern recognition receptors (PRRs), which have broad specificity for conserved features of microorganisms named pathogen-associated molecular patterns (PAMPs) [1]. Cells of innate immunity are dendritic cells, macrophages, neutrophils, NK cells, eosinophils, basophils, and mast cells, among

others. All of them contribute in some extent to trigger a very rapid inflammatory cascade which helps fight the infection and also activates and instructs the adaptive immunity [2]. Adaptive immunity exerts two fine-tuning mechanisms consisting in a cellular-mediated cytotoxicity removing infected cells and the antibody-mediated neutralization of extracellular microorganisms [3]. Here is an overview of those events that occur at the beginning of the immune response where the complex interaction between innate immunity, pathogen, and inflammation could be decisive to the resolution or progression of the disease. These possible scenarios seem to reproduce the movie “The Good, the Bad and the Ugly” (1966) where the “Good” represents the beneficial innate immune response, the pathogens play the role of the “Bad”, while the “Ugly” depicts the uncontrolled inflammation when the innate immune response is delayed.

2. The Good

2.1. Innate Immunity. PRRs play a crucial role in the induction of early signals that establish the inflammatory frame [2]. PRRs have the ability to discriminate between self and nonself since PAMPs, that are not present in the host, are highly conserved among microorganisms of a given class [4]. Among PRRs, Toll-like receptors (TLRs) are evolutionarily conserved between insects and vertebrates recognizing bacterial products and viral nucleic acids [5]. Mannan-binding lectin (MBL) and C-reactive protein (CRP) are soluble PRRs which also act as opsonins [6]. Intracellular microbial sensors include NOD-like receptors which recognize structurally distinct peptidoglycan fragments [7, 8] and the RNA helicase family proteins retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) [9] which recognize single-stranded RNA containing 5' triphosphate and double-stranded RNA, respectively [10] that are absent from cellular RNAs; thus, these distinguish between viral and self-RNAs and inducing an antiviral immunity [11]. Moreover, NOD-like receptors form the "inflammasome," a multiprotein complex involved in activating caspase-1, a protease that processes pro-IL-1 into a mature active and released form [12]. Another well-characterized PRR is dectin-1, a C-type lectin receptor widely expressed among leukocytes [13], which binds β -1,3 and β -1,6 glucans on the fungal cell walls [14], inducing immune responses that are essential in antifungal immunity [15] but also participate in the recognition of mycobacteria [16–18] and inducing radical oxygen species (ROS) in macrophages [19], neutrophils [20], and dendritic cells [21]. Recognition of PAMPs activates innate immune cells to produce tumor necrosis factor (TNF) and interleukin-1 β (IL-1 β) leading to local vasodilation and increasing the permeability of the blood vessel, allowing the recruitment of proteins and leukocytes to the site of infection which in turn activate complement improving opsonin-mediated phagocytosis and engagement of adaptive immunity [22, 23] Figure 1.

2.2. Inflammation. Inflammation begins with recognition of microbes, inducing cell recruitment to the site of infection for microbe clearance and finally returning to homeostasis. However, if the inflammation is not controlled, it could lead to destruction of host tissues and ultimately organ failure and death [24, 25]. Lengthy inflammatory responses can cause deleterious effects by promoting the development of autoimmune disorders, allergies, cancer, and other immunopathologies [26]; nevertheless, weak or ineffective signals could exacerbate the severity of the disease. Therefore, PRR-mediated signal transduction must be tightly regulated to maintain host immune homeostasis [27], and to that, there is a balance in the production of cytokines that can be proinflammatory or anti-inflammatory depending on whether it activates or attenuates the host response. Proinflammatory cytokines (TNF- α , IL-6, and IL-1 family) induce vasodilation and permeability, favoring extravasation of immune cells through the endothelium, whereas anti-inflammatory cytokines (IL-10 and transforming growth factor (TGF- β)) control the collateral damage to sur-

rounding cells [28]. Besides, the microbicide mechanisms displayed by neutrophils (that include the release of proteolytic enzymes, antimicrobial peptides, and the rapid production of ROS) would also be regulated [29, 30] since the excessive neutrophil activation might cause severe tissue damage and inflammatory diseases. In this context, programmed cell death, or apoptosis, constrains the release of inflammatory mediators through the recognition and phagocytosis of the pathogen [31, 32], while in turn, ROS would play a positive role in the processing and antigen presentation by dendritic cells, improving the adaptive immune response [33].

3. The Bad

3.1. The Bad's Strategies. Pathogen virulence factors help to invade the host, cause disease, and evade host defenses; after all, their role is to adapt and to promote transmission to another host. In fact, pathogens must overcome host defense mechanisms, which begin from the first moment of its encounter with innate cells. Enveloped viruses display a variety of host-derived proteins that could be immunoregulators, complement inhibitors, signaling ligands, or adhesion molecules [34]. One of the best studied examples is the gp120 env glycoprotein of HIV, which mediates virus binding and entry to the cell [35]. In addition, RNA viruses have effectively adopted a strategy named antigenic variation which involves different molecular mechanisms [36]. Antigenic variation arises convergent in pathogens across different phyla and is frequently found in obligate pathogens where long-term infection increases the probability of transmission achieving antigen diversification through high rates of point mutation and short generation times. Hepatitis C and HIV have evolved an antigenic variation rate that it effectively outpaces the development of both an effective immune response and efficient prophylactic vaccines [37, 38]. Besides, certain viral proteins could be secreted or expressed by the host cell membranes and exhibit immunomodulatory properties. Those proteins include superantigens, immune cell ligands, receptor mimics, complement inhibitors, binding proteins that sequester cytokines, and regulators of leukocyte activation [39, 40]. On the other hand, for bacteria, the ability to avoid internalization and killing plays a central role in their virulence strategy. Bacteria express a carbohydrate capsule that prevents the deposition of antibodies and complement, thus avoiding opsonization and phagocytosis or modifying lipid A to alter TLR4 responses [41]. For instance, *Yersinia* species, including the causative agent of plague (*Y. pestis*), can neutralize phagocytic activity [42]. Once internalized, microorganisms could elude intracellular killing by escaping from the phagosome, blocking phagosome-lysosome fusion, or by simply surviving in phagolysosomes [43]. Such is the case of *Mycobacterium tuberculosis* which has many surface glycolipids and carbohydrates that prevent phagosome acidification and alter phagosomes [44], making these bacteria so successful. Even more, viruses [45] and bacteria [46] can disrupt cytokine production as well as adaptive immunity since they can interfere

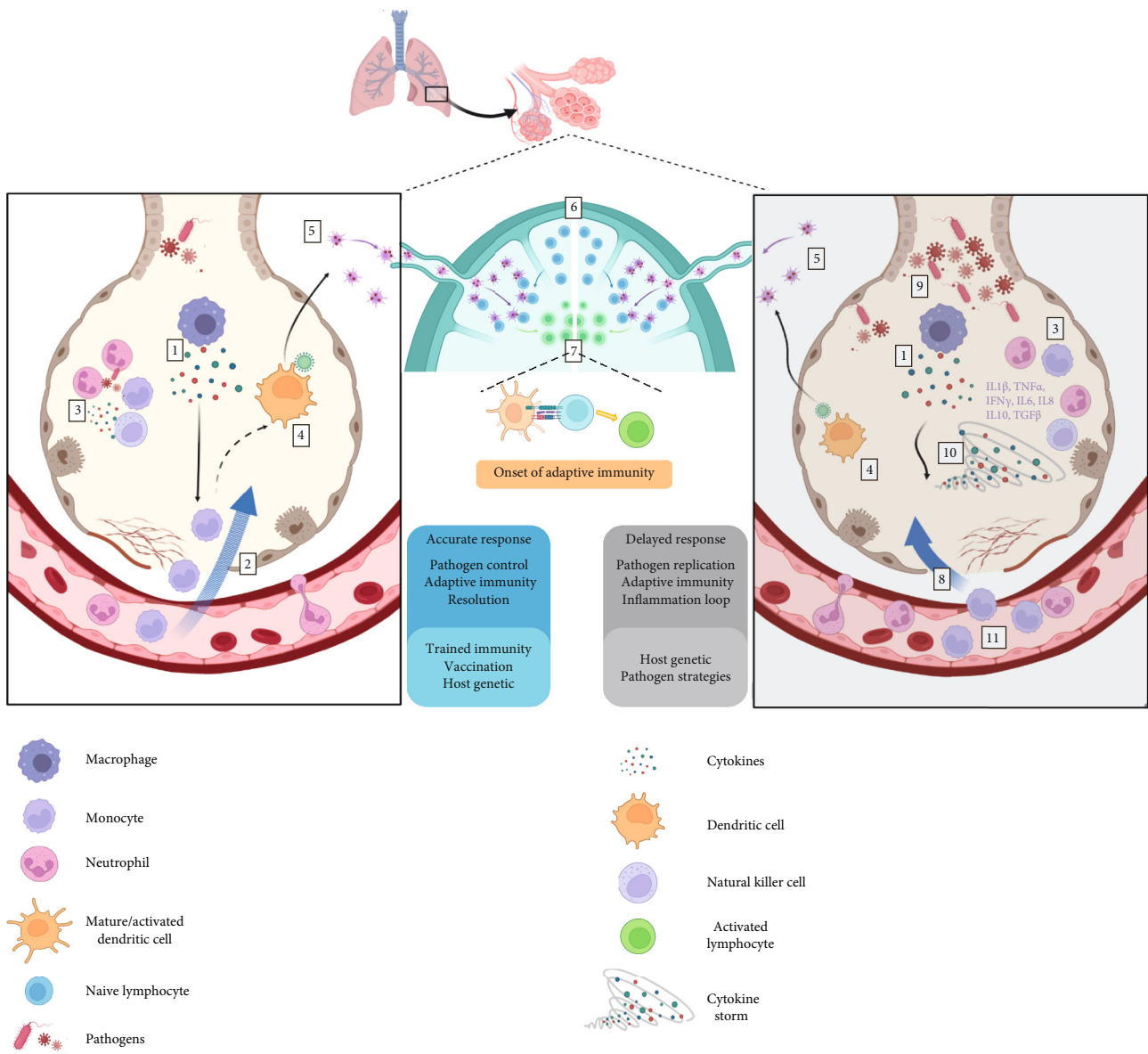


FIGURE 1: Innate immunity and inflammation. Resident macrophages secrete cytokines in response to infection (1), triggering the recruitment of innate cells to the infected tissue (2) (The Good). Neutrophils phagocytose and destroy pathogens (The Bad), contributing to the control of infection (3), whereas monocytes differentiate into dendritic cells (DCs) (4). DCs take up the pathogen, become activated (5), and migrate to draining lymph nodes (6) where they present processed antigens to naive T cells, initiating the adaptive immunity (7). Whether the innate immune response is delayed (8), the pathogen becomes uncontrolled (9) and the adaptive response is also delayed. An inflammatory loop is then generated that converges in a cytokine storm (10) (The Ugly) and the constant recruitment of inflammatory cells (11) leading to tissue damage.

with dendritic cells either disrupting their differentiation or inhibiting effector functions [47, 48].

3.2. The Bad's Opportunities. Sometimes, the state of the host's immune system determines the degree of pathogen colonization and tissue damage. Pathogens might harness certain weakness in the host; for instance, individuals with defects in cytokine production or cytokine receptors (e.g., L-12 and IFN- γ) are susceptible to infections with intracellular microorganisms such as mycobacteria and Salmonella [49]. In addition, disorders of the complement pathway pre-

dispose to Neisseria infection and deficiencies of the NLR lead to a range of autoinflammatory syndromes [7]. The importance of TLRs in protection against infection has been recently confirmed in patients with MyD88 deficiency which has recurrent pyogenic bacterial infections [50]. Similarly, disorders of TLR3 confer predisposition to herpes simplex virus (HSV) encephalitis [49]. Moreover, certain polymorphisms in dectin-1 have been shown to be associated with invasive aspergillosis [51] and predispose to chronic candida infection in hematopoietic transplantation patients [52]. Likewise, specific human genetic polymorphism has been

described to be related to susceptibility and severity of tuberculosis infections such as TLR1, TLR2, IL-6, IL-8, IL-9, TNF- α , IL-1 receptor antagonist (IL-1RA), IL-10, resistance-associated macrophage protein 1 (NRAMP1), vitamin D receptor (VDR), dendritic cell-specific ICAM-3-grabbing nonintegrin (DC-SIGN), monocyte chemoattractant protein-1 (MCP-1), NOD2, IFN- γ , inducible nitric oxide synthase (iNOS), MBL, mannose receptor (MR), and surfactant proteins A (SP-A) [53–55]. Indeed, polymorphisms in genes of the human leukocyte antigen (HLA) system, the human version of MHC, are associated with celiac disease, inflammatory bowel disease, rheumatoid arthritis, psoriasis, type 1 diabetes, and multiple sclerosis. Additional studies have found genetic associations between MHC-I and infectious diseases such as HIV, human hepatitis B virus, and tuberculosis [56].

4. The Ugly

In addition to developing strategies to avoid immunity, some pathogens are able to delay an appropriate response, causing the pathogen to proliferate and to trigger uncontrolled cytokine production called a “cytokine storm,” which can lead to symptoms such as hypotension, fever, and edema, and ultimately death [57]. Diverse pathogenic viruses (e.g., SARS-CoV, MERS-CoV, SARS-CoV-2, Ebola virus (EBOV), HIV, and bacteria (*Francisella tularensis*)) have been found to induce hypercytokinemia [58, 59]. The H1N1 strain that caused the 1918 pandemic has been shown to induce higher levels of proinflammatory immune cells and cytokines in the lungs than seasonal influenza viruses inducing vasodilation, permeability, complement, and opsonization [60]. Interestingly, infection with *F. tularensis* via the inhalational route causes a delay in the induction of cytokines and chemokines, resulting in a systemic inflammatory response [60]. In addition, phospholipid platelet-activating factor (PAF) binding activates platelet aggregation, coagulation cascades, and proinflammatory cytokine production contributing to the process of pulmonary edema systemic inflammation [61, 62]. The most increased cytokines and chemokines reported are TNF- α , IL-1 β , IL-6, IL-8, MCP-1, IP-10, and IL-17 [63] (Figure 1). Indeed, IL-8 increases 200 times in Ebola fatalities and it was described to be markedly increased in patients with pulmonary infections [64–66] and may be the most significantly induced cytokine in SARS-CoV-2 infection [67]. Several works have shown to date that the outcome of the disease is related to the intensity of the inflammatory phenomena [68–70], and in this regard, many treatments have focused on preventing the excessive effect of these cytokines. The strategy has addressed the neutralization of cytokines as well as the blockage of cytokine receptors with antibodies or antagonists. For instance, anti-IL-6 receptor antibodies, tocilizumab and sarilumab, have been used for the treatment of rheumatoid arthritis [71], and today, clinical trials to assess the benefits of these drugs in COVID-19 treatment are in progress [72].

Interestingly, although not all COVID-19 patients develop severe respiratory illness [73], some cases would progress to a cytokine storm, acute respiratory distress syn-

drome (ARDS), and multiorgan dysfunction [74]. As a matter of fact in fatal cases, inflammatory increased cytokines [75] together with mononuclear infiltrate in the lungs have been observed throughout the time [76]. Moreover, inflammatory CD14+/CD16+ monocytes, which are related to chronic inflammation and autoimmunity [77–79], have been found to be expanded in the peripheral blood of those patients who require hospitalization [80, 81] reinforcing the idea that innate immune cells determine the outcome of cytokine dysregulation. In this way, blockage of CCR2 and/or CCR5—chemokine receptors that regulate monocyte migration—could potentially help to reduce the accumulation of pathological monocytes in inflamed tissues (NCT04343651).

However, it would be the early immunological features which define the prognosis of the disease in these patients. Notably, proinflammatory monocytes were found to be elevated in the circulation at early stages of the disease in deceased patients [75] together with delayed antibody response which correlated with poor clinical outcome of the disease [82]. This late onset in the humoral response is in line with the delay in differentiation of plasma cells in severe [83]. Although the early presence of inflammatory monocytes in the lungs of patients with mild COVID-19 has not been described, to our knowledge, those monocytes are likely to play a positive role at the site of infection mounting an effective cellular immune response [84] while remaining normal in circulation (Figure 1). Although the mechanisms that regulate cell migration remain unclear, it could be speculated that a delay in the migration of innate immune cells to the site of infection would be decisive for the resolution of the disease, by preventing the growth of the pathogen and the consequent uncontrolled release of inflammatory mediators.

5. Innate Immunity Past and Future

Trundle on the knowledge about how innate immunity detects microbes offers a great opportunity for the design and development of a wide variety of adjuvants [85]. In this way, innate immunity is crucial for the successful activation of protective humoral immunity during vaccination and the development of new adjuvants for use in vaccines against COVID-19 and future pandemics. Several COVID-19 vaccines available triggered innate immunity via different pathways: for mRNA vaccine, the endosomal Toll-like receptors (TLR3 and TLR7) bind to single-strand RNA (ssRNA) in the endosome, while MDA5, RIG-1, NOD2, and PKR bind to ssRNA in the inflammasome and double-stranded RNA (dsRNA) in the cytosol [86]. Adenovirus vector vaccine (AdV) contains a vector's hexon protein with adjuvant properties involving Toll-like receptor 3 (TLR3), TLR7/8, and in particular TLR9 to recognize dsDNA, ssRNA, and ssDNA of the viral vector [87]. In this context, it has been recently demonstrated that the innate immune responses after the first dose of ChAdOx1nCoV-19 vaccination correlated with the neutralizing antibody production elicited by the boost, confirming that innate immune activation is crucial for the successful protective humoral immunity [88].

TABLE 1: Pathogen-associated molecules and vaccines with experimental evidence of cross-protection.

Trained immunity inducers	Cross protect from	Evidenced in	Ref.
Microbial components			
β -Glucan	<i>Staphylococcus aureus</i>	Mice	[109], [110]
	<i>Listeria monocytogenes</i>	Mice	[111]
	<i>Mycobacterium tuberculosis</i>	Human	[112]
Flagellin	<i>Streptococcus pneumoniae</i>	Mice	[113]
	<i>Rotavirus</i>	Mice	[114]
Muramyl dipeptide	<i>Influenza virus</i>	Mice	[115]
	<i>Toxoplasma gondii</i>	Mice	[116]
CpG oligodeoxynucleotides	<i>Escherichia coli</i>	Mice	[117]
Chitin	<i>E. coli</i> , <i>Candida albicans</i> , <i>S. aureus</i>	Mice	[118]
LPS	<i>P. aeruginosa</i>	Mice	[102]
Poly IC:LC	SARS-CoV	Mice	[119]
Live vaccines			
Bacillus Calmette-Guérin (BCG)	Childhood mortality	Human	[95]
	<i>C. albicans</i>	SCID mice	[120]
	Viral infections	Human	[90]
	<i>Yellow fever model</i>	Human	[105]
	Respiratory syncytial virus (RSV)	Human	[121]
	Malaria infection	Human	[122]
	Respiratory infection	Human	[123]
	Respiratory viral infections	Human	[124]
	SARS-CoV-2	Human	[125], [126], [127]
Other live vaccines			
Measles	Childhood mortality	Human	[89]
Polio	Childhood mortality	Human	[128]
Smallpox	HIV-1	Human	[129]
MTBVAC	<i>S. pneumoniae</i>	Mice	[130]
MMR	Respiratory syncytial virus (RSV)	Human	[131]
Nonlive vaccines			
AdHuAg85A	<i>M. tuberculosis</i>	Mice	[132]
<i>F. hepatica</i> extract	Autoimmune encephalomyelitis	Mice	[133]
MV130	Influenza (H1N1)	Mice	[134]
RZV	SARS-CoV-2	Human	[135]
New vaccines			
BPZE1	<i>Bordetella bronchiseptica</i>	Mice	[136]
BNT162b2 mRNA	ND	Human	[137]
MV130	SARS-CoV-2	Human	[138]
CG:CoVac	SARS-CoV-2	Human	[139]
BCG-adjuvanted <i>Mtb</i>	Tuberculosis	Human	[140]
MV-based SARS-CoV-2	SARS-CoV-2	Mice	[141]

Poly IC:LC: synthetic double-stranded polyriboinosinic-polyribocytidylic acid (poly IC) stabilized with poly-L-lysine and carboxymethyl cellulose (LC). Hiltonol®; MMR: live vaccine against measles, mumps, and rubella; RZV: recombinant adjuvanted zoster vaccine; SCID: severe combined immunodeficient; BPZE1: modified live attenuated pertussis vaccine strain; BNT162b2: Pfizer–BioNTech mRNA vaccine; AdHuAg85A: recombinant human serotype 5 Ad-based TB vaccine expressing an immunodominant Ag 85A; MV130: polybacterial mucosal vaccine composed of different proportions of whole heat-inactivated Gram-positive (90%) and Gram-negative (10%) bacteria including *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. *BCG:CoVac: BCG-adjuvanted COVID-19, combination of BCG with a stabilized, trimeric form of SARS-CoV-2 spike antigen. ND: not determined.

Until recently, innate immunity was assumed to lack specificity and memory. However, the innate immunity of mammals also exhibits an immunological memory mediated by epigenetic and metabolic modifications widely known as “trained immunity.” In this context, measles vaccine is strongly associated with better childhood survival in developing countries. Since this effect cannot be explained by the specific prevention of measles, measles vaccination may be associated with a nonspecific beneficial activation of the immune system [89]. Similarly, the tuberculosis vaccine Bacillus Calmette-Guerin (BCG) protects against influenza virus, yellow fever virus, herpes simplex virus, respiratory syncytial virus, and human papilloma virus [90], and was also associated with a decrease in the incidence of sickness during the COVID-19 pandemic helping to reduce hospitalizations [91, 92]. First evidences of nonspecific immunity induced by BCG vaccine dated from 1932, when child mortality unrelated to tuberculosis disease was reduced after BCG vaccination [93]. Nearly 70 years later, it was described a 45% reduction in mortality due to neonatal sepsis and respiratory tract infections by BCG vaccination in West Africa [94, 95]. The existence of innate memory was demonstrated when the BCG vaccine was able to protect against lethal infections in SCID mice [96, 97]. Afterwards, it was shown that β -glucans present in fungi lead to a change in cellular metabolism from oxidative phosphorylation to glucose fermentation [98, 99]. All in all, the protective effects of BCG involve a shift of glucose metabolism to glycolysis, which induces in turn histone modifications and functional changes in innate immune cells such as monocytes [100] and in bone marrow [101].

Trained immunity inducers are mostly microbial-derived products that stimulate innate immune cells through different PRRs. In this context, it has recently been described that TLR4 and TLR3 signaling give rise to trained immunity [102]. In this way, RIG-I and MDA5 that also sense viral dsRNA may also play a role in training [103]. In addition, the binding of β -glucans to dectin-1 initiates a cellular response dependent on monocytes and the long-term epigenetic reprogramming through the noncanonical Raf-1 pathway [99, 104]. Considering the advantages offered by the trained immunity, nowadays, trained immunity-based vaccines (TIbV) are being designed to generate adequate activation of circulating monocytes and signaling for T cell [105]. TIbV provides nonspecific protection against different pathogens [106]—and potentially against cancer [107] and allergies [108]—based on innate immune cells and on their self-adjuvant properties. Pathogen-associated molecules and vaccines with experimental evidence of cross-protection are depicted in Table 1.

6. Conclusions

The inflammatory nature of the innate immune response restricts the growth of pathogens. However, activation of innate receptors by different ligands may determine the appropriate degree of inflammation. This, in turn, may determine the rate of cell migration, although the mechanisms remain undefined. Like the movie, the final scene is

decisive to the infected host: you would die with the bad guy's bullet (the pathogen wins the game), you would die with the ugly guy's bullet (the cytokine storm wins the game), or you would kill the bad guy and control the ugly inflammation. Understanding the mechanisms underlying the early recognition of the pathogen and the consequent inflammatory events is extremely important to propose different strategies in the treatment of diseases and vaccine design. Taking into account that the memory conferred by innate immunity would determine the outcome of the disease by driving the rapid migration of innate immune cells to the site of infection, it is important to consider the design of vaccines that carry epigenetic self-adjuvant beyond their antigenic formulation, providing nonspecific protection against different pathogens.

Abbreviations

ARDS:	Acute respiratory distress syndrome
BCG:	Bacillus Calmette-Guerin
CRP:	C-reactive protein
DC-SIGN:	Dendritic cell-specific ICAM-3-grabbing nonintegrin
HIV:	Human immunodeficiency virus
HSV:	Herpes simplex virus
IL:	Interleukin
IL-1 β :	Interleukin-1beta
iNOS:	Inducible nitric oxide synthase
ITAM:	Immunoreceptor tyrosine-based activation motif
MBL:	Mannan-binding lectin
MCP-1:	Monocyte chemoattractant protein-1
MR:	Mannose receptor
NET:	Neutrophil extracellular traps
NK:	Natural killer cells
NOD:	Nucleotide oligomerization domain
NRAMP1:	Resistance-associated macrophage protein 1
PAMPs:	Pathogen-associated molecular patterns
PRRs:	Pattern recognition receptors
ROS:	Radical oxygen species
SP-A:	Surfactant proteins A
TLRs:	Toll-like receptors
TNF:	Tumor-necrosis factor alpha
VDR:	Vitamin D receptor.

Consent

Consent is not applicable.

Conflicts of Interest

The author declares to have no competing interests.

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