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Interplays between inflammasomes and viruses, bacteria (pathogenic and probiotic), yeasts and parasites

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ABSTRACT

In recent years, scientists studying the molecular mechanisms of inflammation have discovered an amazing phenomenon – the inflammasome – a component of the innate immune system that can regulate the functional activity of effector cells during inflammation. At present, it is known that inflammasomes are multimolecular complexes (cytosolic multiprotein oligomers of the innate immune system) that contain many copies of receptors recognizing the molecular structures of cell-damaging factors and pathogenic agents. Inflammasomes are mainly formed in myeloid cells, and their main function is participation in the cleavage of the pro-IL-1β and pro-IL-18 cytokines into their biologically active forms (IL-1β, IL-18). Each type of microorganism influences particular inflammasome activation, and long-term exposure of the organism to viruses, bacteria, yeasts or parasites, among others, can induce uncontrolled inflammation and autoinflammatory diseases. Therefore, this review aims to present the most current scientific data on the molecular interplay between inflammasomes and particular microorganisms. Knowledge about the mechanisms responsible for the interaction between the host and certain types of microorganisms could contribute to the individuation of innovative strategies for the treatment of uncontrolled inflammation targeting a specific type of inflammasome activated by a specific type of pathogen.

1. Introduction

Although the mechanism and function of inflammation in organisms have been known for many years, the topic is still of central importance. Inflammation is a protective immune response evolved by the innate immune system in response to harmful stimuli, including pathogens, trauma, chemicals, dead cells, and toxins, among others. In recent years, scientists, studying the molecular mechanisms of inflammation, discovered an amazing phenomenon – inflammasomes - components of the innate immune system that can regulate the functional activity of effector cells during inflammation [1]. At present, it is known that inflammasomes are multimolecular complexes (cytosolic multiprotein oligomers of the innate immune system) containing many copies of receptors that recognize the molecular structures of cell-damaging factors and pathogenic agents. Inflammasomes are mainly formed in myeloid cells (macrophages, neutrophils, monocytes, and microglia) and typically participate in the cleavage of the pro-IL-1β and pro-IL-18 cytokines into their biologically active forms (IL-1β, IL-18), inducing inflammation. Active canonical inflammasomes initiate activation caspase-1, which causes the transformation of pro-IL-1β and pro-IL-18 cytokines into IL-1 β and IL-18, respectively [2]. Caspase-1 can also cleave gasdermin D protein (gasdermin D), initiating cell death termed as pyroptosis (the form of programmed necrotic and inflammatory caspase 1-dependent cell death leading to the elimination of the microbial pathogen). It should be noted, that some bacterial toxins eg. lipopolysaccharide (LPS), leads to the assembly of non-canonical inflammasomes. The non-canonical inflammasome initiate activation caspase-11 in mice and caspase- 4/5 in humans, rather than caspase-1 [3].

Several types of inflammasomes have been described, namely, NLR-subset inflammasomes (NLRP1, NLRP3, NAIP/NLRC4, NLRP6, NLRP7, NLRP9b, NLRP10, NLRP12, adaptor ASC), the family of inflammasomes containing AIM2 (absent in melanoma 2) protein, IFI16, and pyrin [2,4]. The composition of a particular inflammasome depends on the activator triggering its formation. Generally, inflammasomes contain three major components: NLR protein (NOD-like receptors (NLRs), which recognizes pathogen-associated molecular patterns (PAMPs) and host-derived danger-associated molecular patterns (DAMPs)); ASC (an apoptosis-associated speck-like protein containing a caspase recruitment domain); and caspase effector (caspase-1). In addition to NLR, inflammasomes can also contain another type of receptor - AIM2 protein

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(absent in melanoma 2). AIM2 belongs to the PYHIN family and can recognize cytoplasmic double-stranded DNA (dsDNA) [2,4].

Because NLRP3 can be activated not only by pathogenic agents but also by chemical irritants, UV-B light, amyloid-β, and crystal particles (asbestos, alum, silicic acid, uric acid), it is the most intensively studied inflammasome. This inflammasome consists of NLRP3 protein, ASC adapter, and caspase-1 (Fig. 1). For NLRP3 inflammasome formation, two signals are needed (Fig. 2). The sources of the first signal are microbial components (PAMPs) and endogenous cytokines (DAMPs). Here, the ligands of the Toll-like receptor (e.g., LPS), TNFα or the ligands of the NLR receptor (e.g., muramyl dipeptide (MDP)) activate NFκB, leading to the expression of NLRP3 protein and upregulation of pro-IL-1β and pro-IL-18 synthesis. The second signal is transmitted by extracellular ATP molecules, pore-forming toxins, microbial RNA, mitochondrial dysfunction, reactive oxygen species (ROS) generation, lysosomal damage, calcium pyrophosphate, and cholesterol, among others. These agents activate the NLRP3 expression to first causing NLRP3 protein oligomerization and then ASC oligomerization, leading to the formation of the NLRP3 inflammasome. Inside the formed NLRP3 inflammasome, autoproteolysis of pro-caspase-1 leads to the creation of an active caspase-1, which in turn cleaves pro-IL-1β and pro-IL-18 into potent inflammatory mediators - active IL-1β and IL-18 [5].

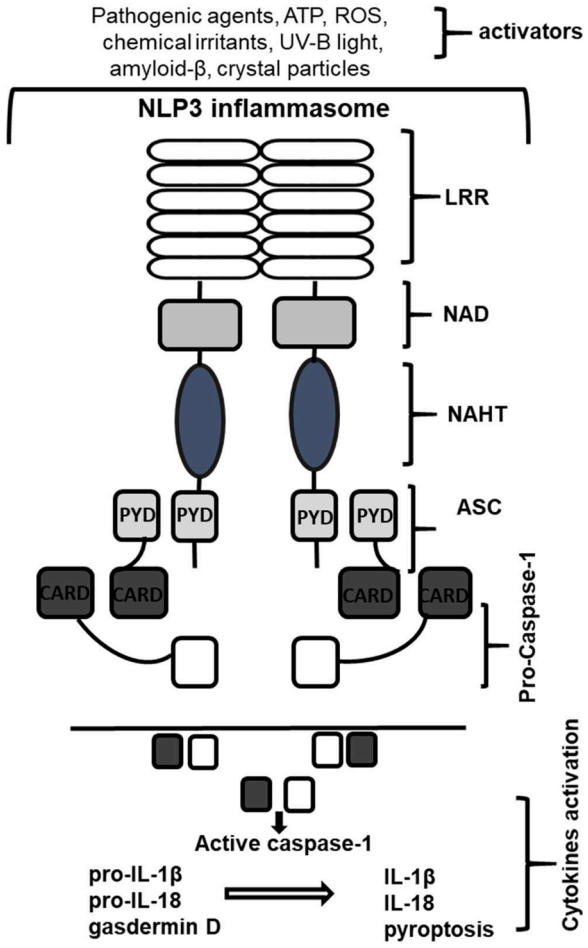

Fig. 1. NLRP3 inflammasome composition. The NLRP3 inflammasome contains the following domains: LRR (leucine-rich repeat domain), NAD (binding domain), NACHT(nucleotide-binding and oligomerization domain); PYD (pyrin domain), CARD (caspase recruitment domain). Pathogenic components and endogenous cytokines trigger NLRP3 inflammasome activation. Active NLRP3 inflammasome initiate activation caspase-1, which causes the transformation of pro-IL-1β and pro-IL-18 cytokines into IL-1 β and IL-18. Caspase-1 can also cleave gasdermin D protein, initiating cell death termed as pyroptosis.

Additionally, activation of the AIM2-inflammasome is often observed in the fight against pathogens (e.g DNA viruses) (Fig. 3). During AIM2 inflammasome activation, the AIM2 protein functions as an initiating component that recognizes the cytoplasmically located dsDNA (DNA-binding HIN-200 domain), whereas the ASC protein functions as the pro-caspase-1 activator and caspase-1 as an effector component. ASC oligomerization is involved in pro-caspase-1 processing and leads to the formation of ASC pyroptosomes and the induction of pyroptosis [4].

Several scientific studies have reported that inflammation is a protective response of the organism against harmful stimuli such as pathogens, damaged cells, or irritants, and dysregulation of this process may lead to delayed wound healing, increasing susceptibility to infections, the appearance of allergies and autoimmune diseases. The leading role of inflammasomes is to activate pro-inflammatory cytokine synthesis and pyroptosis to remove harmful stimuli from the organism. Despite the beneficial effects of inflammation, this process should be tightly regulated due to excessive activation of inflammasomes leading to overproduction of inflammatory cytokines and the appearance of the unregulated inflammatory process that can cause chronic inflammation and autoinflammatory diseases (e.g., familial Mediterranean fever (FMF), hyperimmunoglobulin D syndrome, Crohn's disease, osteoporosis, pulmonary manifestations, etc.) [6–8]. It should be underscored that during autoinflammatory disease, the main role is played by native immunity and not adaptive immunity, as observed in autoimmune diseases. Recent scientific data show that pharmacological inhibition of inflammasome expression in some diseases may lead to an immunosuppressive reaction and thus prevent tissue destruction [9].

Each type of microorganism differentially influences inflammasome activation, and the duration of exposure to viruses, bacteria, yeasts, or parasites could induce uncontrolled inflammation. Therefore, this review aims to present the most current scientific data concerning the molecular interplay between inflammasomes and particular microorganisms. Knowledge of the mechanisms responsible for interactions between the host and pathogen could contribute to the individuation of innovative strategies for the treatment of uncontrolled inflammation and autoinflammatory diseases targeting a specific type of pathogen.

2. Interplays between inflammasomes and viruses

Multiple scientific reports have demonstrated that viruses entering the body activate an innate immune response in which inflammasomes play a crucial role in pathogen destruction [10–12]. To control infection, the immune system detects pathogens in multiple ways. There are two systems of first-line of defense against viruses: the production of Type I interferons and the production of the cytokines IL-1β and IL-18 by inflammasomes. Type I interferons promote an antiviral state in the infected host, whereas cytokines have antiviral effects by inducing inflammatory processes and modulating adaptive immune responses in the organism [13].

The ***influenza A virus (IAV)*** belongs to the Orthomyxoviridae family, which contains negative-sense RNA as its genome. This virus infects and replicates in epithelial cells of the respiratory tract, and the disease severity is regulated by both virus-encoded and host factors and is associated with a high level of morbidity and mortality. The significant factors modulating the pathogenesis of IAV are epithelial damage and lung inflammation [14]. Several intracellular signaling cascades regulate inflammation and cell death in IAV infection [15]. For example, Ichinohe et al. [16] infected bone marrow-derived macrophages (BMM) with influenza A and B virus *in vitro* discovered that influenza viruses activate signal 1 through stimulation of macrophages and DCs via TLR7, resulting in the synthesis of pro-IL-1β and pro-IL-18. Upon infection, virally encoded M2 is expressed in the secretory compartment, including TGN.

Additionally, the ion channel activity of M2 enables H^+ export from acidified Golgi and thereby is a trigger for signal 2 required for the

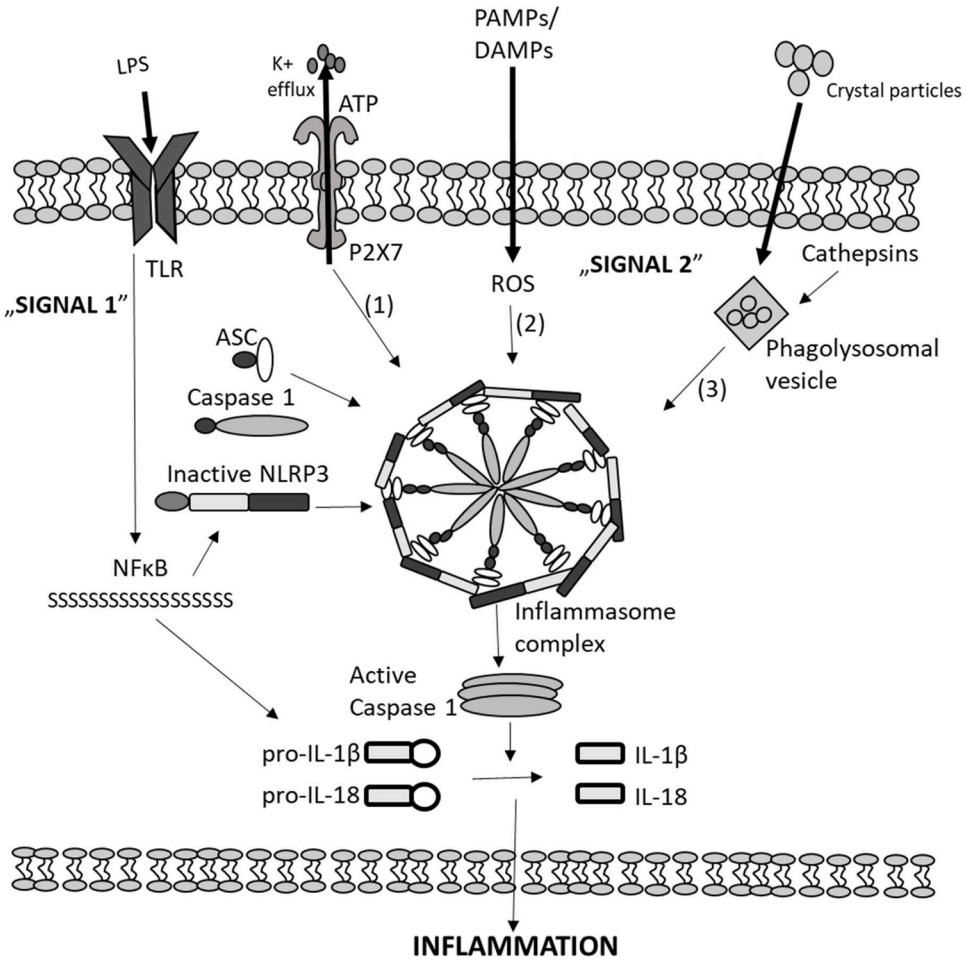

Fig. 2. The scheme of NLRP3 inflammasome activation. For NLRP3 inflammasome formation, two signals are needed. The sources of the first signal are microbial components and endogenous cytokines (PAMPs or DAMPs). Here, the ligands of the Toll-like receptor (e.g., LPS) activates NFκB, leading to the expression of NLRP3 protein and upregulation of pro-IL-1β and pro-IL-18 synthesis. The second signal is transmitted, for example, by extracellular ATP molecules (1), reactive oxygen species (ROS) generation (2) or environmental irritants form intracellular crystalline (3). These agents activate the NLRP3 expression to first cause NLRP3 protein oligomerization and then ASC oligomerization, leading to the formation of the NLRP3 inflammasome. Inside the formed NLRP3 inflammasome, autoproteolysis of procaspase-1 leads to the creation of an active caspase-1, which in turn cleaves pro-IL-1β and pro-IL-18 into active IL-1β and IL-18.

formation of the NLRP3 inflammasome complex. The authors also underscored that the M2-His37Gly mutant, which is capable of transporting Na^+ and K^+, may induce elevated amounts of inflammasome activation, and imbalances in the concentrations of other cations which may signal the activation of inflammasomes [16]. Next, McAuley et al. [17] demonstrated that an IAV component, protein PB1-F2, could activate signal 2 of the NLRP3 inflammasome and thereby mediate the activation of the NLRP3-inflammasome [17]. In contrast, Chung et al. [18] examined the role of the IAV non-structural protein 1 (NS1) in the activation of NLRP3 inflammasome. They found that NS1 proteins derived from low and highly pathogenic strains decreased the secretion of IL-1β and IL-18 from human leukemia monocytic cells (THP-1 cells) treated with lipopolysaccharides (LPS), leading to a decrease in the levels of inflammatory cytokines as a viral immune avoidance strategy [18]. In addition to NLRP3, AIM-2 can also induce ASC-dependent inflammasome activation after becoming activated by the presence of dsDNA fragments in dying infected cells [18].

The ***human immunodeficiency virus (HIV)*** is a retrovirus of the lentivirus genus that infects immune system CD4 + T cells, comprising mainly T-helpers, macrophages, monocytes, microglial cells, Langerhans cells, and dendritic cells. As a result, the immune system is depressed, leading to the development of acquired immune deficiency syndrome (AIDS) when the organism loses its ability to defend itself against infections and tumors [19]. The literature data show that in human monocytes and macrophages (main cell target of HIV), the HIV-1 virus efficiently induces the expression of pro-IL-1β via TLR8-mediated mechanisms and activates caspase-1 through the NLRP3 inflammasome to cleave pro-IL-1β into IL-1β. The HIV-1 induced production of reactive oxygen species and lysosomal protease cathepsin B play a crucial role in HIV-induced inflammasome activation and IL-1β production [19]. Using human primary monocyte-derived macrophages (MDMs) obtained from healthy donors Hernandez et al. [10] discovered, that HIV-1 could activate the 'priming' signal for NLRP3 inflammasome activation through NF-κB signaling, leading to IL-1β secretion in the presence of specific NLRP3 inflammasome activators such as ATP, nigericin, silica, alum, and MSU. In that experiment, the authors noticed that when HIV-1 was used as the priming and second signal, the MDMs were unable to secret IL-1β and concluded that early phases of HIV-1 infection were unable to induce the second signal for NLRP3 inflammasome activation [10]. In another study were reported that HIV could activate the inflammasome in monocytes and macrophages in an infection-independent process requiring clathrin-mediated endocytosis and viral recognition by distinct endosomal TLRs. It was also discovered that HIV is not required for inflammasome activation of TLR7 [20]. Moreover, peripheral blood $CD14^{++}CD16^{-}$ monocytes of HIV-1-infected persons release large intracellular protein aggregates of the inflammasome adaptor ASC (PYCARD)) into the bloodstream, which can contribute to inflammasome activation [21].

Furthermore, inflammasomes play a significant role in HIV-associated neuroinflammation. For example, in *in vitro* experiments on human primary neurons (HPNs) and microglial cells (HFMG) collected from healthy patients, it was discovered that treatment of the cells with HIV ssRNA40 (specific GU-rich single-stranded RNA from the HIV long terminal repeat region) activates the NLRP3 inflammasome and increases the expression and extracellular secretion of pro-inflammatory cytokines (IL-1β, IL-18) and neurotoxic cytokines (TNF-α, IL-1α, C1q). HIV ssRNA40 causes a blockade of autophagy/mitophagy-mediated negative regulation of NLRP3 inflammasome activity with the release

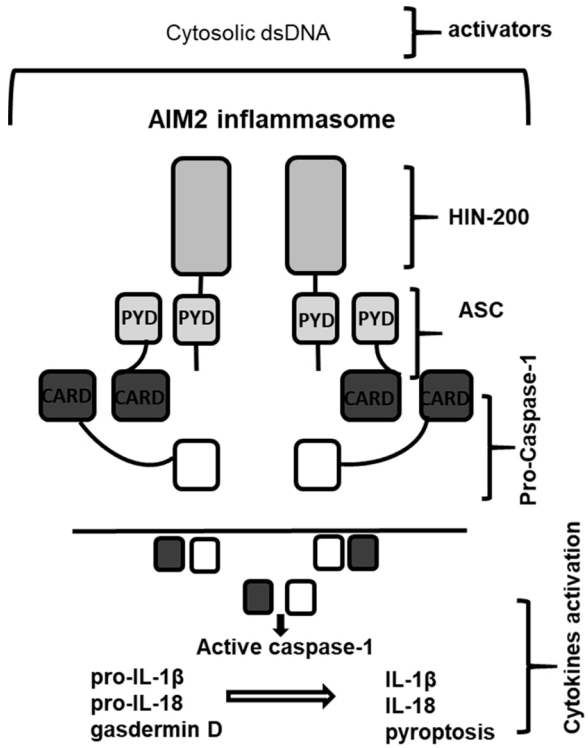

Fig. 3. AIM2 inflammasome composition. The AIM2 inflammasome contains the following domains: HIN-200 domain; PYD (pyrin domain), CARD (caspase recruitment domain). During AIM2 inflammasome activation, the AIM2 protein functions as an initiating component that recognizes the cytoplasmically located dsDNA (DNA-binding HIN-200 domain), whereas the ASC protein functions as the pro-caspase-1 activator and caspase-1 as an effector component. Active AIM2 inflammasome initiate activation caspase-1, which causes the transformation of pro-IL-1β and pro-IL-18 cytokines into IL-1 β and IL-18 and induction of pyroptosis.

of inflammatory cytokines, caspase-1 activation, and pyroptotic microglial cell death [22]. Another report has shown that HIV-1 induces the expression of NLRP3 inflammasome and IL-1β secretion in dendritic cells from healthy individuals but not HIV-1-infected patients, suggesting that inflammasome activation contributes to disease progression [23]. There is also evidence that since the HIV-1 genome contains two RNA molecules that in turn are reverse-transcribed into a cDNA molecule, the NLRP3 inflammasome may be activated in response to both RNA and DNA [11].

The ***hepatitis C virus (HCV)*** is an enveloped, single-stranded RNA-containing virus with a virion size of 30−60 nm belonging to the *Flaviviridae* family that causes chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. In infected hepatocytes, hepatitis C virus blocks viral poly-U/UC PAMP/RIG-I-mediated production of type 1 and 3 interferons through the action of the viral NS3/4A protease, which targets and cleaves the innate immune adaptor molecules mitochondrial antiviral signalling protein (MAVS) to destroy the intracellular antiviral defense system [24]. Multiple scientific reports have shown that in patients infected with HCV, inflammasomes not only participate in virus eradication but cause chronic inflammation and liver fibrosis and can participate in hepatocellular carcinoma (HCC) [12]. A study on THP-1 cells (model of hepatic macrophages) showed that TNF-α serves as a priming factor in hepatic macrophages, leading to NFκB activation and pro- IL-1β production; mainly the HCV core protein can activate the NLRP3 inflammasome. Viral core protein directs intracellular calcium mobilization to impart NLRP3 inflammasome assembly through activation and signalling of phospholipase-C, leading to the synthesis of bioactive IL-1β from macrophages, thus establishing the hepatic inflammatory environment [24]. These data show that the NLRP3 inflammasome and IL-1β induce liver inflammation and may be used as a target for treating liver disease induced by HCV. It should also be noted that in patients suffering from HCC, inflammasomes suppress HCC cell proliferation and differentiation, indicative of positive roles of inflammasomes against HCC [12].

The ***Enterovirus 71 (EV71*** or **EV-A71**) is a single-stranded RNA (ssRNA) virus of the genus Enterovirus in the *Picornaviridae* family. EV71 usually infects children under the age of 5 years. EV71 mainly causes hand-foot-and-mouth disease, and it can also cause brain stem encephalitis, aseptic meningitis, and other nervous system disorders [25]. Scientific reports have shown that in the early phase of infection, EV71 activates the NLRP3 inflammasome in infected mice and the human monocytic cell line THP-1, and it causes an increase in IL-1β, IFN-γ, TNF-α, and IL-6 secretion supporting the protective role of the NLRP3 inflammasome against EV71 infection. In the later phase of THP-1 cell infection, in contrast, the toxic EV71 viral proteases 2A and 3C could antagonize inflammasome activation by cleavage of NLRP3 protein at the G493-L494 or Q225-G226 junction, thereby inhibiting inflammasome activation [26]. Additionally, EV-A71 3D protein, an RNA-dependent RNA polymerase (RdRp), interacts with the leucine-rich repeat domain (LRR) of NLRP3 to facilitate assembly of the inflammasome complex [27]. In addition to the NLRP3 inflammasome, the AIM2 inflammasome also plays an important role in limiting EV-A71 replication in encephalomyelitis patients. In the neuroblastoma cell line SK-N-SH, cells transfected with EV-A71 RNA showed increased AIM2 gene expression. In contrast, silencing of AIM2 in SK-N-SH cells resulted in decreased activation of IL-1 and increased viral replication upon EV-A71 infection [28].

Human gammaherpesvirus 4 (Epstein−Barr virus (EBV) is a DNA virus of the Herpesvirus (HHV) family. EBV can replicate in B-lymphocytes, epithelial cells, or dendric cells and is associated with a variety of tumors, including Burkitt lymphoma, immunocompromise-associated lymphomas, and nasopharyngeal cell carcinoma [29]. EBV-positive endemic BL cell line HH514-16 and peripheral blood mononuclear cells (PBMC) isolated from the blood of patients with NOMID syndrome had heterozygous germline mutations in their NLRP3 gene which showed assembly of the TXNIP−NLRP3 inflammasome and activation of procaspase-1 and active caspase-1 during lytic growth. Inflammasome-activated caspase-1 then led to a partial loss of KAP1/-TRIM28 to turn on the expression of the viral replication switch protein within a subpopulation of cells [30]. EBV may also infect primary human monocytes, and in *in vitro* experiments on the THP-1 cell line and primary human monocytes discovered that EBV could induce caspase-1-dependent IL-1β production mainly to activate the AIM2 inflammasome [31].

Coronaviruses (CoVs) are an enveloped, positive-sense single-stranded RNA-containing (+ssRNA) viruses with a virion size of 80−220 nm belonging to the *Coronaviridae* family *Orthocoronavirinae* subfamily [32]. Coronaviruses are combined into two subfamilies that infect humans and animals. Human coronaviruses generally infect the epithelial cells of the respiratory tract, while animal coronaviruses infect the epithelial cells of the digestive tract. Coronaviruses have one of the largest among RNA viruses genome size. Their genome size is from approximately 26–32 kilobases. The genome encodes a non-structural replicase polyprotein and structural proteins, including spike (S) (essential for viral entry into host cells), envelope (E) (necessary for viral virulence and is involved in several signalling mechanisms which induce inflammation during infection), membrane (M) and nucleocapsid (N) proteins [32]. Currently, worldwide among human population circulate four coronaviruses (Human coronavirus: HCoV-OC43, HCoV-HKU1, HCoV-NL63, HCoV-229E), which induce the mild symptoms of the common cold, and three novel coronaviruses (SARS-CoV, MERS-CoV, SARS-CoV-2) which infect the lungs epithelial cells and causes respiratory diseases in humans ranging from common colds to fatal pneumonia. As first, at the end of 2002, appeared severe acute respiratory syndrome coronavirus (SARS-CoV) - the causative agent of the severe acute

respiratory syndrome (SARS). In 2012 appeared middle east respiratory syndrome-related coronavirus (MERS-CoV)- the causative agent of the middle east respiratory syndrome (MERS), whereas at the end of 2019 appeared pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 (Coronavirus disease 2019) [33]. The genetic sequence of SARS-CoV-2 shows close sequence homology to the SARS-CoV (approximately 76 % amino acid sequence identity) [34]. It is known, that MERS-CoV enters into human cells using the dipeptidyl peptidase 4 (DPP4 or CD26) receptor which is broadly expressed on alveolar, intestinal, renal, hepatic and prostate cells as well as on activated leukocytes [35]. In the case of SARS-CoV, S proteins bind to the angiotensin-converting enzyme 2 (ACE2) which is present on nonimmune cells (endothelial, respiratory and intestinal epithelial cells, alveolar monocytes/macrophages, cerebral neurons, kidney cells) [36].

It should be noted that the binding affinity of SARS-CoV-2 with ACE2 seems stronger than SARS-CoV and down-regulation of ACE2 function causes lung damage during SARS-related pneumonia [37]. Therefore, an increasing ACE2 level in respiratory epithelial cells is seriously considered as a novel promising therapeutic in SARS treatment. Furthermore, SARS-CoV-2 for S-protein priming and facilitating cell entry following receptor binding has evolved to utilize a wide array of host proteases including transmembrane protease serine 2 (TMPRSS2), elastase, furin, trypsin, factor X, cathepsin L and cathepsin B [38,39]. When SARS-CoV-2 enters into healthy cells decreases the amount of ACE2, which leads to an increase of angiotensin II level in the blood. It was found out that angiotensin II triggers the inflammatory pathway of NF-κB and IL-6-STAT3 in endothelial and epithelial cells, but not in immune cells what leads to the development of a cytokine storm (hyperproduction of cytokines) that ultimately result in the acute respiratory distress syndrome (ARDS) [37,39]. Moreover, patients occur a secondary reaction - immunodeficiency, which contributes to the development of opportunistic bacterial and mycotic infections and septic shock, which then may lead to multiple organ dysfunction syndrome (MODS) [39]. Clinical reports show that both mild and severe forms in SARS-CoV, MERS-CoV, and SARS-CoV-2 infections cause the activation of myeloid and lymphocyte subsets in the blood that leading to the cytokine storm. During cytokine storm changes in cytokines secretion are observed, particularly IL-6, IL-1β, IL-10, TNF, IFN-γ, GM-CSF, IP-10 (IFN-γ -induced protein 10), IL-17, MCP-3, and IL-1ra. It was noted, that the serum SARS-CoV-2 viral load is closely associated with IL-6 levels in critical patients and this cytokine may contribute to the development of ARDS in COVID-19 patients. Also, in both SARS and MERS patients, activation of CCR4+ CCR6+ Th17 cells takes part in a cytokine storm [40]. Additionally, inflammasomes play an essential role in cytokine release. It is known, that innate immune system and optimal activation of inflammasomes play an important role in antiviral host defenses, but inflammasomes overactivation often lead to uncontrolled inflammation and pathological tissue injury during infection. Several studies have reported that during SARS-CoV, MERS-CoV or SARS-CoV-2 infection aberrant activation of NLRP3 inflammasome is observed which contribute to cytokine storm and pyroptosis in target cells [41].

What concerning the signalling pathways of NLRP3 inflammasome activation in response to SARS-CoV infection it is known that SARS-CoV E protein induces Ca2+ leakage to the cytosol from Golgi storage and ORF3a protein induce K + efflux at the plasma membrane to the extracellular spaces [41,42]. The imbalance in the ionic concentration in the cells, generated by damaged mitochondria ROS lead to NLRP3 inflammasome activation. Also, ORF3a viroporin protein helps inflammasome assembly through TRAF3-mediated ubiquitination of ASC. While ORF8b viroporin protein directly interacts with the leucine-rich repeat of NLRP3 to stimulate its activation independent of ion channel activity. Active NLRP3 induces IL-1β and IL-18 secretion, and pyroptosis [41,43].

The signalling pathways of inflammasomes activation in response to SARS-CoV-2 infection is still under research. Scientists present different signalling pathways that may lead to NLRP3 inflammasome activation. Up to date, it is known that activation of the renin–angiotensin–aldosterone system (RAAS) leads to elevated levels of angiotensin II, which, after binding to the AT1 receptor, triggers the NLRP3 inflammasome in cells [44]. Also, the SARS-CoV-2 virus N proteins may activate the ComC in an MBL–MASP-2-dependent manner. In turn, the ComC cleavage fragments (the C3a and C5a anaphylatoxins), and C5b/C9 membrane attack complex (MAC), can trigger the NLRP3 inflammasome in cells. Moreover, there is the supposition that SARS-CoV-2 can directly activate the NLRP3 inflammasome in target cells by binding to ACE2 only via the spike protein [44]. Active NLRP3 initiates activation caspase-1, which causes the transformation of pro-IL-1β and pro-IL-18 cytokines into IL-1 β and IL-18, respectively and by creating gasdermin D pore channels in cell membranes lead to cell death by pyroptosis [3].

Based on the strong inflammatory potential of the NLRP3 inflammasome during infections caused by MERS- and SARS-CoVs, inhibition of the NLRP3 inflammasome activity may attenuate the cytokine storm and be a therapeutic target in the treatment of tissue inflammation in SARS patients [33,41].

3. Interplays between inflammasomes and pathogenic bacteria

Several studies have demonstrated that infection of cells with pathogenic bacteria induces the assembly of inflammasome complexes and IL-1β and IL-18 secretion. During host defense against bacterial infection, a prominent role play pattern recognition receptors (PRRs). There are two major classes of PRRs: first-class - PRRs that include membrane-bound Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), and second class - non-membrane bound intracellular receptors such as the AIM2-like receptor (ALR), RIG-I-like receptor (RLR), nucleotide-binding protein domain and leucine-rich repeat-containing (NLR) proteins. Activation of these receptors also upregulates inflammasome activity that takes part in controlling replication and dissemination of microbial pathogens in the organism [13]. Pathogenic microorganisms, in turn, evolve virulence factors aimed to antagonize inflammasome pathways and in this way, increase their ability to survive in the host organism and cause disease. Competition occurs between the pathogen and host to control pyroptosis and pro-inflammatory cytokine secretion, and the outcome dictates the life or death of the host [13,45].

Helicobacter pylori (H. pylori) is a Gram-negative, helically shaped, microaerophilic bacterium that colonizes the human stomach and is a leading cause of certain types of human gastric diseases such as chronic gastritis, gastric ulcers and gastric carcinomas [45]. Pachathundikandi et al. [46] demonstrated that infection of mice by *H. pylori* leads to stimulation of the expression of the NLRP3 inflammasome. Analysis of bacterial pathogenicity factors and molecular mechanisms of inflammasome activation shows that by engagement of the immune receptor TLR2, *H. pylori* triggers NLRP3 and caspase-1 stimulation of IL-1β production. *H. pylori* also stimulates TLR9 and TLR10 and induces the secretion of IL-8 and TNF. Highers levels are induced by the bacterial microRNA hsa-miR-223-3p, which can control the expression of NLRP3. During *H. pylori* infection, TLR-dependent pathways can impact pro- and anti-inflammatory cytokine expression to reduce the immune attack, allowing *H. pylori* to colonize and survive in the stomach [46]. Few reports have shown that *H. pylori* controls inflammation and inflammasome activity via its virulence factors: cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), withaferin A (WA), flagellin (FlaA), and CagPAI. Recognition of host innate immune system PRRs of PAMPs from *H. pylori* leads to the production of chemokines and pro-inflammatory cytokines and activation of NF-κB and STAT3 in activated B cells. Activation of these transcription factors induces expression of IL-1β, IL-6, IL-8, IL-18, IL-23 and TNFα, which are responsible for a state of inflammation and in this way may induce gastric carcinomas [45].

Mycobacterium tuberculosis (M. tuberculosis) is a genetically related group of *Mycobacterium* species that can cause tuberculosis in

humans and animals. In 2016, Wei et al. [47] found that *M. tuberculosis* infection of the human acute monocyte leukaemia cell line THP-1 could promote NLRP3 activation and inflammatory cytokine secretion. The authors discovered that NLRP3 activation was regulated by DNA methylation modification, and DNA methylase Sss I methylation decreased NLRP3 promoter activity. These data suggest that during *M. tuberculosis* infection, DNA methylation is involved in NLRP3 inflammasome activation [47]. Clinical *M. tuberculosis* isolates compared to the laboratory strain H37Rv have been shown to induce lower IL-1β release than H37Rv, suggesting different inflammasome activation abilities. IL-1β maturation involves NLRP3, AIM2, and an additional unknown sensor. Pharmacological blockade of NLRP3 with MCC950 leads to a reduction of bacterial survival [48].

The Salmonella enterica* serovar *Typhimurium (S. typhimurium) is a pathogenic Gram-negative bacteria that is predominately found in the gut lumen and causes gastroenteritis in humans and animals. *S. typhimurium* invasion of the mucosa can lead to its migration to mesenteric lymph nodes, liver, and spleen, causing a life-threatening infection. Its toxicity is due to an outer membrane consisting largely of lipopolysaccharides that protect the bacteria from the environment [49]. The role of inflammasomes during *Salmonella* infection are conflicting in the literature. Some scientists have reported that in Nlrp3$^{-/-}$, Caspase-1/11 and NLRC4 –deficient mice, not in all animals show enhanced susceptibility to systemic infection [50,51]. For survival within host cells, *S. typhimurium* needs the appropriate expression of TCS proteins SsrA and SsrB. In an experiment on murine bone-marrow-derived macrophages, infection by *S. typhimurium* led to an increase in SsrB transcription (controlling bacterial motility) and a decrease in inflammasome activation. An evolved SsrB-binding region upstream of flhDC causes repression in *S. typhimurium* and inflammasome activation in host defense [52]. Hausmann et al. [53] using intestinal epithelial cells (IECs), found that blockade of bacterial dissemination during *S. typhimurium* infection mainly involved intestinal epithelial NAIP/NLRC4. In IECs, the NAIP/NLRC4 inflammasome specifically limited *S. typhimurium* migration from the intestines to draining lymph nodes. Additionally, NLRP3 and Caspase-11 fail to restrict *S. typhimurium* mucosa traversal, migration to lymph nodes, and systemic pathogen growth. These data show that due to site-specific bacterial PAMP expression, intestinal epithelial NAIP/NLRC4 restricts systemic dissemination of the adapted pathogen *S. typhimurium* [53].

Escherichia coli (E. coli) is a Gram-negative, facultatively anaerobic, rod-shaped, coliform bacterium of the genus *Escherichia*. *E. coli* is part of the physiological bacterial flora of the human large intestine and other warm-blooded animals. In the intestine, this symbiotic bacteria performs a useful role, mainly participating in food digestion and vitamins B and K synthesis.

Some serotypes of *E. coli* are pathogenic to humans under certain conditions and cause gastrointestinal and urinary disorders [54]. For inflammasome activation during Enteropathogenic and enterohemorrhagic *E. coli* infection, important roles are played by specific molecules expressed by bacteria: EprJ, EscI, EprI, NleA, NleB, NleF. EprJ can activate the murine NLRC4 inflammasome; EscI can induce the murine NLRP4 inflammasome in a Naip2-dependent manner; EprI can induce the murine and human of NLRC4 inflammasome in a Naip2-dependent manner; NleA suppresses NLRP3-inflammasome formation; NleB inhibits NLRP3 inflammasome activation and inhibits NF-κB and FADD/Caspase-8 apoptosis by suppressing FADD/Caspase-8; NleF blocks non-canonical NLRP3 inflammasome activity and inhibits Caspase-4,-8, and –9-associated cell death [55]. In contrast, in a study on females suffering from urinary tract infections caused by uropathogenic *E. coli,* an upregulation of NLRP3, NAIP, NLRC4, ASC, and CASPASE-1 at both mRNA and protein levels, as well as pro-inflammatory cytokines (IL-6, IL-8, IFN-γ, TNF-α, and MCP-1), was found. In that analysis, the inflammatory response during urinary tract infection caused by uropathogenic *E. coli* in females had a dominant role in NLRP3 and NLRC4 inflammasomes [56]. *in vitro,* bladder epithelial cell lines incubated with uropathogenic *E. coli* isolates displayed increasing caspase-1 activity and IL-1β release that was mediated by α-hemolysin activation of the NLRP3 inflammasome in an NF-κB-independent manner. The phase-locked type-1-fimbrial ON variant of *E. coli* (CFT073) also inhibited caspase-1 activation and IL-1β release. The uropathogenic *E. coli* colonization ability was associated with a reduced ability of CFT073 host cell adhesion in NLRP3-deficient cells in comparison to wild-type cells. These data show that both type-1 fimbriae and α-hemolysin can participate in the modulation of the activity of the NLRP3 inflammasome and that the NLRP3 inflammasome is important for type-1 fimbriae-dependent colonization of bladder epithelial cells [57].

Brucellais a Gram-negative, nonmotile, non-spore-forming, rod-shaped (coccobacilli) bacteria that causes chronic diseases such as Brucellosis. Four pathogens infect humans: the causative agent of brucellosis in small cattle (*Brucella melitensis*), the causative agent of brucellosis in cattle (*Brucella abortus*), the causative agent of pig brucellosis (*Brucella suis*) and *Brucella. canis*, which infects dogs [58]. In peripheral blood samples obtained from patients with acute brucellosis, no effect on caspase-1 and *NLRP3* was observed, but an increase in serum IL-18, IFN-γ levels and *AIM2* and *NLRC4* inflammasome expressions was documented in comparison to healthy controls [58]. Gomes et al. [59] also found that NLRC4 did not need to induce caspase-1 activation and further secretion of IL-1β by *B. abortus* in macrophages, whereas AIM2, which senses Brucella DNA, and NLRP3 were required for caspase-1 activation and IL-1β secretion, and AIM2 knockout mice were more susceptible to Brucella infection than wild-type control mice [59]. Pretreatment of *B. abortus*-infected alveolar epithelial cells with a specific caspase-1 inhibitor leads to a reduction of IL-1β production in cells, which may suppress inflammation in the lung [60]. Overall, these data suggest that multiple ASC-dependent inflammasomes participate in host defense against Brucella infection.

Streptococcus pneumoniae (***S. pneumoniae***) or *pneumococcus*, is a pathogenic Gram-positive, spherical bacteria, alpha-haemolytic (under aerobic conditions) or beta-haemolytic (under anaerobic conditions), which is a facultative anaerobic member of the genus *Streptococcus. S. pneumoniae* can cause several invasive diseases, such as otitis media, meningitis and pneumonia [61]. Inflammasomes have been shown to participate in host protection against *S. pneumoniae* infection. For example, primary mouse macrophages infected with *S. pneumoniae* showed increased expression of the NLRP3 and AIM2 inflammasome, and inflammasome activation requires Syk and JNK signalling. It should be noted that a putative virulence factor, pneumolysin (PLY), of the *Streptococcus pneumoniae* is also critical for Syk/JNK activation, and inhibitors of Syk and JNK can abolish the oligomerization of apoptosis-associated speck-like protein containing a caspase-activating and recruitment domain and subsequent caspase-1 activation and IL-1β secretion [62]. Zhang et al. [63] using mouse peritoneal neutrophils, discovered that *S. pneumoniae* infection induced IL-1β secretion, which played a leading role in NLRP3 inflammasome but had no significant effect on the AIM2 and NLRC4 inflammasomes. Similarly to the experiment on primary mouse macrophage JNK kinase, ASC oligomerization modulation and consequent caspase-1 activation and IL-1β secretion in mouse neutrophils have been observed. Additionally, during *S. pneumoniae* infection, neutrophil serine protease can mediate IL-1β processing. These data support a role for the Syk/JNK signalling pathway in inflammasome activation and modulation of host immune responses against *S. pneumoniae* [50].

4. Interactions between inflammasomes and probiotic bacteria

Probiotic bacteria have no impact on inflammasome activation and pro-inflammatory cytokine synthesis in healthy individuals, but probiotics may regulate inflammasome activation in organisms that have previously experienced some degree of inflammation due to pathogenic bacterial infection [64,65].

Enterococcus faecium (E. faecium) is a Gram-positive, facultative

anaerobic lactic acid bacteria in the genus Enterococcus that does not form spores and capsules. *E. faecium* and *E. faecalis* colonize the human intestine in the first days of life and are part of the healthy gut microflora of humans and animals. *E. faecium* has gained particular importance thanks to beneficial strains marketed as probiotics [65]. This addition of probiotic *E. faecium NCIMB* 10415 to the diet of healthy pigs did not affect mRNA expression of NLRP6, NLRP3, caspase-1, IL-1β, and IL-18, but it increased the ASC expression level in the jejunum and ileum in comparison to the control group. In contrast, in an *ex vivo* experiment using chambers (an apparatus for measuring epithelial membrane properties), pre-incubation of porcine jejunum with the probiotic *E. faecium* led to an increase in IL-1β release during incubation with enterotoxigenic *E. coli* (ETEC), but it did not affect the mRNA expression of inflammasome components [65]. Additionally, preincubation of porcine monocyte-derived DC (MoDC) cells with *E. faecium NCIMB* 10415 did not influence NLRP3, NLRP6 and NLRC4 inflammasome activation in comparison to cells infected with ETEC alone [66]. Schmitz et al. have obtained similar results [67] in their experiment on dogs with chronic enteropathy. The authors showed that supplementation with probiotic *E. faecium* NCIMB 10415 did not alter NLRP3, IL-1β, or IL-18 mRNA expression in the duodenum and colon [67].

Enterococcus faecalis (E. faecalis) It has further been reported that pretreatment of the human leukaemia monocytic THP-1 cell line with heat-killed probiotic *E. faecalis* (strain KH2) or NLRP3 siRNA can inhibit NLRP3 inflammasome activation in macrophages in response to fecal content or commensal microbes, *P. mirabilis* or *E. coli*, according to the reduction of caspase-1 activation and IL-1β maturation. Moreover, E. faecalis attenuates the phagocytosis that is required for full activation of the NLRP3 inflammasome [68].

Lactobacillus rhamnosus (L. rhamnosus) is a probiotic Gram-positive heterofermentative facultative anaerobic non-spore-forming rod bacterium. The *L. rhamnosus* most commonly inhabits the healthy female genitourinary tract and is often used to control pathogenic bacterial and yeast overgrowth during an active infection. *L. rhamnosus* is also used in yogurt and dairy products. Scientific data have shown that pretreatment of primary bovine mammary epithelial cells (BMEC) with L. rhamnosus GR-1 attenuates NLRP3 activation and reduces E. coli-induced increases in expression of the NLRP3 inflammasome and caspase-1. Additionally, pretreatment of BMEC with L. rhamnosus GR-1 counteracts the E. coli-leading to an increase in TNF-α, IL-1β, IL-6, IL-8, and IL-18 expression [69]. During influenza A virus infection of human primary macrophages, *L. rhamnosus* GG and *L. rhamnosus* LC705 induce the expression and synthesis of the NALP3 inflammasome, IL-1β, and IL-18 in macrophages. These data suggest that *L. rhamnosus* has antiviral potential in human macrophages [70]. Tohno et al. [71] examined the ability of Lactobacillus strains (L. delbrueckii subsp. bulgaricus NIAI B6 and L. gasseri JCM1131^{T}) to activate NLRP3 in gut-associated lymphoid tissues (GALT) of new-borne and adult swine, and they found that both strains could enhance NLRP3 expression in adult and new-borne GALT. The authors also showed that bacterial components are recognized by porcine TLR2 and TLR9 and that the *Lactobacillus* strain could directly promote NLRP3 expression via TLR and NOD-mediated signalling [71].

Escherichia coli Nissle 1917 (EcN) and commensal E. coli K12 wild-type strain (***E. coli K12)*** are Gram-negative probiotic bacteria that are used in the treatment of ulcerative colitis, diarrhea, and constipation. Incubation of Caco-2 cells (enterocyte model) with *E. coli Nissle 1917 (EcN) and E. coli K12* strains led to NALP3 inflammasome activation and caspase-1 and IL-18 secretion. Of note, *E. coli* K12 led to higher levels of IL-18 compared with stimulation with the EcN strain, which suggests that commensal *E. coli* K12 causes more pro-inflammatory and proapoptotic signalling in enterocytes compared with the EcN strain [72].

5. Interactions between inflammasomes and yeasts

The innate immune system is also the first line of defense against fungal pathogens. Pattern recognition receptors recognize fungal particles and initiate cellular responses and killing mechanisms to destroy the pathogenic yeasts. Upon organism entry, yeasts can induce often recurring and equally difficult-to-treat mucosal or skin infections. Finally, multiple evidence shows that the host initiates defense mechanisms in numerous fungal pathogens that involve inflammasome activation and robust production of pro-inflammatory cytokines [73].

Malassezia yeasts are a group of lipophilic yeasts of the genus Malassezia. These yeasts form clusters consisting of 18 species living exclusively on the skin and mucosal sites of warm-blooded vertebrates. *Malassezia* yeasts are part of the healthy human skin flora and also play a role in skin diseases, including seborrheic dermatitis, pityriasis versicolor, seborrheic dermatitis, atopic eczema, folliculitis and dandruff. Kistowska et al. [74] examined the effect of clinical isolates of Malassezia species, *M. japonica, M. slooffiae* and *M. sympodialis,* on inflammatory protein expression in human dendritic cells (DCs) (derived from freshly isolated human CD14-positive monocytes) and mouse bone-marrow-derived dendritic cells (BMDCs). The authors reported that *Malassezia spp*. could induce NLRP3 inflammasome activation and IL-1β maturation in the cell lines. They also demonstrated that human monocytic THP1 cells transduced with NLRP3-shRNA showed reduced IL-1β secretion upon *M. furfur* exposure in comparison to THP1 cells transduced with lamin-shRNA. Yeast exposure of BMDCs from NLRP3-deficient mice strongly reduced IL-1β secretion when compared to wild-type cells. Syk and Dectin-1 were required for *Malassezia spp*.-induced inflammasome activation in human mono-DCs and murine BMDCs. These findings demonstrate that *Malassezia* yeasts activate pro-inflammatory responses in antigen-presenting cells by activation of the NLRP3 inflammasome [74].

Microsporum canis (M. canis) is a pathogenic, highly contagious and asexual fungus of the phylum Ascomycota. *M. canis* causes infections of the scalp and body sites, creating inflammatory lesions associated with hair loss. In humans, *M. canis* is associated with tinea pedis, onychomycosis, tinea corporis, and tinea capitis. In animals, *M. canis* induce multifocal alopecia, scaling and circular lesions. The ability of *M. canis* to activate inflammasome revealed the role of the NLRP3 inflammasome in host defence against *M. canis* infection and the control of this infection by regulating the activation of inflammasomes. In human monocytic THP-1 cells and mouse dendritic cells, the clinical strain of *M. canis* isolated from patients with tinea capitis could induce IL-1β secretion in a NLRP3 activation-dependent manner. The pathways responsible for NLRP3 inflammasome activation required ROS production, Cathepsin B release, K^{+} efflux, Syk, Dectin-1, and Card9 [75].

Candida albicans (C. albicans) is a diploid yeast that colonizes digestive and vaginal mucosal surfaces and is an agent of opportunistic infections of humans that are transmitted through the mouth and genitals. Roselletti et al. [76] studied mechanisms of inflammation in women with vulvovaginal candidiasis infected with *C. albicans* and discovered overexpression of genes encoding NLRP3 and caspase-1 inflammasome components, as well as increased IL-1β and IL-8 production. Based on the data mentioned above, the authors supposed that the NLRP3 inflammasome might be a key player in human vulvovaginal disease caused by *C. albicans* [76]. There is also information that the NLRC4 inflammasome is also essential in protection against *C. albicans* infection. In bone marrow chimeric mouse models, C. albicans le to upregulation of NLRP3 and NLRC4 expression in the oral mucosa, but in contrast to NLRP3, which decreased the severity of infection when present in either the hematopoietic or stromal compartments, NLRC4 played a significant role in limiting mucosal candidiasis when functioning at the level of the mucosal stroma. These data underscore the tissue-specific role of inflammasomes in innate immune responses against mucosal *C. albicans* infection [77].

Aspergillus is a highly aerobic group of conidial fungi that represents over 185 fungal species. Some invasive pulmonary *Aspergillus* species can cause infections such as asthma, fibrosis, tuberculosis and other lung infections [78]. In pulmonary aspergillosis in mice caused by *Aspergillus*

fumigatus (A. fumigatus), AIM2 and NLRP3 participate in the induction of protective immune responses and recognize intracellular A. fumigatus. In mice infected with *A. fumigatus* and simultaneously lacking AIM2 and NLRP3 receptors, hyphal dissemination to lung blood vessels leads to increased susceptibility to infection in comparison to wild type mice. Interestingly, mice lacking either AIM2 or NLRP3 showed similar susceptibility to hyphal dissemination in comparison to wild type mice. Additionally, AIM2 and NLRP3 activation initiated the assembly of a single cytoplasmic inflammasome platform containing the adaptor protein ASC with caspase-1 and caspase-8, which subsequently caused pro-inflammatory cytokine IL-1β and IL-18 expression [79].

Paracoccidioides brasiliensis (P. brasiliensis) is a thermally dimorphic fungus of the genus Paracoccidioides. *P. brasiliensis* causes a disease known as paracoccidioidomycosis characterized by slow, progressive granulomatous changes in the head mucosa (nose and sinuses) or the skin. Paracoccidioides sometimes affect the central nervous system, gastrointestinal tract, lymphatic system and skeletal system [80]. Several studies have shown that the NLRP3 inflammasome is involved in recognition of *P. brasiliensis* by human cells. In monocytes isolated from the blood of patients suffering from Paracoccidioidomycosis, an increase in gene expression of the NLRP3 inflammasome, CASP-1, and ASC and of IL-1β and TNF-α secretion was observed. This analysis also involved patients who smoked, who showed enhanced expression of components of the NLRP3-inflammasome [81]. Similar data have been obtained in *in vitro* experiments on human dendritic cells (DCs) in response to *P. brasiliensis* yeast cells, demonstrating an increasing level of NLRP3 inflammasome and cytokine production by dendritic cells and inflammasome activation in a manner dependent on endosome acidification, ROS generation, and K^+ efflux production. Additionally, *P. brasiliensis* recognition involves dectin-1 and Syk phosphorylation. Moreover, NLRP3 inflammasome is essential for Th1/Th17 cell activation, which may influence host defence against *P. brasiliensis* yeasts [82].

6. Interactions between inflammasomes and parasites

Numerous scientific data have confirmed the important role of the inflammasomes in the host response to pathogenesis of many parasitic infections [83].

***Neospora caninum* (*N. caninum*)** is a coccidian parasite that, due to structural similarities, is also misclassified as *Toxoplasma gondii*. *N. caninum* is a significant cause of spontaneous abortion in infected livestock. In bovine macrophages, *N. caninum* induced NLRP3 inflammasome activation-mediated caspase-1 activation and inhibition of caspase-1 in infected cells, leading to the presence of more parasites in the parasitophorous vacuole. These findings suggested that the bovine inflammasome may be a potential target for the future development of drugs or vaccines against N. caninum infection in cattle [84]. Earlier, Wang et al. [85] using murine bone marrow-derived macrophages infected with *N. caninum*, noticed NLRP3 inflammasome activation accompanied by IL-1β and IL-18 release, caspase-1 cleavage and induction of cell death. The authors discovered that K^+ efflux induced NLRP3 activation. *N. caninum*infection in mice deficient in NLRP3, ASC, and caspase-1/11 resulted in decreased production of IL-18 and IFN-γ in serum. These data suggest that the NLRP3 inflammasome plays a key role in host defence against parasites [85].

Leishmania is a parasitic protozoan belonging to the Trypanosomatidae family representing over 50 species. Leishmania species are widely distributed in South America, Africa, Asia and Europe. Leishmania is transmitted in the body by bites from infected sand flies. After entering an organism, the parasites reside intracellularly in monocytes and travel to internal organs via the bloodstream to cause visceral leishmaniasis [86]. Each species of Leishmania acts differently during NLRP3 inflammasome activation. For example, L. amazoniensis and L. major activate, whereas L. mexicana and L. donovani inhibit the NLRP3 inflammasome [72,73]. The inhibitory action of L. infantum on the NLRP3 inflammasome could be beneficial in Alzheimer's disease, as in an experiment on THP-1 derived macrophages showing a reduction synthesis of ASC-speck formation and increases in TNFα, caspase 5, IL-1β, and IL-10. These data suggest that parasite infection by down-regulation of NLRP3 inflammasome activation can reduce neuroinflammation and could play a protective role against Alzheimer's disease development [87]. Additionally, in patients suffering from mucosal or cutaneous leishmaniasis induced by L. braziliensis, high levels of AIM2 gene expression were observed in mucosal leishmaniasis compared with cutaneous leishmaniasis, suggesting that AIM2 is an important factor in the disease course of these patients [88].

Schistosoma is a blood fluke tropical parasite that when introduced into the skin leads to the development of dermatitis, fever, intoxication, urticaria, splenomegaly, eosinophilia, liver fibrosis, and damage to the intestines or urogenital organs. The clinical picture in schistosomiasis is mainly due to the development of an immuno-allergic reaction to parasite eggs. During a schistosomal infection, the eggs are trapped in the host liver, and products derived from eggs induce a polarized Th2 cell response, resulting in granuloma formation and eventually fibrosis. People who have been infected for a long time may experience kidney failure, infertility, liver damage, or bladder cancer [89]. The literature shows that Schistosomes can interact with host inflammasomes and activate apoptosis during inflammation. In mouse livers infected with *Schistosoma mansoni* (*S. mansoni*), activation of the NLRP3 and AIM2 inflammasomes and an increase in the release of ROS, NF-κB (p65) and superoxides in livers were observed [90]. In mice suffering from *S. japonicum* infection, liver fibrosis and high levels of IL-1β, ALT/AST in plasma, and high expression of NLRP3 and NF-κB in liver tissue were observed. Inhibition of NLRP3 inflammasome production alleviated liver inflammation and collagen deposition in infected mice [63]. It was also found that stimulation of mouse hepatic stellate cells HSCs with soluble egg antigen could activate the NLRP3 inflammasome in cells and that NLRP3 activation in the spleen required tyrosine kinase enzyme (Syk), Dectin-1 and JNK [78].

***Entamoeba histolytica* (E. histolytica)** is an anaerobic parasitic amoebozoan belonging to the Entamoeba genus. E. histolytica causes bloody diarrhea and fatal abscesses outside the intestine. *E. histolytica* can also disseminate to other tissues and cause abscesses in the liver or brain [91]. Several studies have shown that *E. histolytica* induces strong production of IL-1α in human epithelial and stromal cells, and EhCP5 (cysteine proteinase) of E. histolytica can cleave and inactivate recombinant IL-1β and IL-18 [91]. Moreover, using integrin-binding cysteine protease EhCP5 located on its surface, E. histolytica can activate α5β1 integrin located on macrophages, resulting in ATP release into the extracellular space through the opening of pannexin-1 channels that signal through P2 × 7 receptors to deliver a critical co-stimulatory signal that activates the NLRP3 inflammasome. These data show that α5β1 is an inflammatory response initiator during E. histolytica infection [92].

7. Factors responsible for inflammasomes activity

Inflammasomes are activated by a wide range of stimuli such as: pathogenic toxins and components (eg. LPS, bacterial flagellin, protein PB1-F2, HIV ssRNA40, SARS-CoV E,ORF3a and ORF8b viroporin proteins) (Table 1); endogenous components (eg. DAMPs, HAMPs, PAMPs, K + efflux, ATP, cathepsin B release, MSU, cholesterol crystals, calcium crystals, uric acid, amyloid-β, α-synuclein) (Table 2); chemical irritants (eg. alum, silica, asbestos, UVB irradiation, trinitrophenylchloride, silver nanoparticles) (Table 3) or pharmacological substances (eg. imiquimod, amodiaquine, nevirapine, propofol, morphine) (Table 4).

The regulation of inflammasome activity involves intracellular and extracellular mechanisms [93]. Intracellular regulators of inflammasome activity include mechanisms associated with the level of calcium and potassium ions in the cell. For example, in cells with a low concentration of potassium and chlorine, dehydration leads to mobilization of calcium ions to initiate TGF-β-activated kinase 1 (TAK1), which leads

Table 1
Some pathogenic agents capable of inflammasome activation.

Pathogenic agents	Action	Source
Ligands of TLRs, CLRs, ALR and RLR receptors, NLR proteins	Pathogenic virulence factors eg. LPS, LeTx, CagA, VacA, WA, FlaA, by binding to these receptors activate the secretion of an appropriate inflammasome.	[98]
Cytosolic dsDNA	Cytosolic dsDNA from virus, bacteria, or the host itself can activate the AIM2 inflammasome.	[4]
PB1-F2	Activate signal 2 of the NLRP3 inflammasome and thereby mediate the activation of the NLRP3-inflammasome.	[17]
HIV ssRNA40	Activates the NLRP3 inflammasome and increases the expression and extracellular secretion of pro-inflammatory cytokines (IL-1β, IL-18) and neurotoxic cytokines (TNF-α, IL-1α, C1q).	[22]
SARS-CoV E, ORF3a and ORF8b viroporin proteins	SARS-CoV E induces Ca2+ leakage to the cytosol from Golgi storage and ORF3a protein induce K + efflux at the plasma membrane to the extracellular spaces. The imbalance in the ionic concentration in the cells, generated by damaged mitochondria ROS lead to NLRP3 inflammasome activation. Also, ORF3a viroporin protein helps inflammasome assembly through TRAF3-mediated ubiquitination of ASC. While ORF8b viroporin protein directly interacts with the leucine-rich repeat of NLRP3 to stimulate its activation independent of ion channel activity.	[41, 42]

TLRs - Toll-like receptors, **CLRs** - C-type lectin receptors, **ALR** - AIM2-like receptor, **RLR** - RIG-I-like receptor, **NLR** - leucine-rich repeat-containing proteins, **IpaH7.8** - effector from the bacterium Shigella flexneri, **(CagA)** cytotoxin-associated gene A, **(VacA)** vacuolating cytotoxin A, **(WA)** withaferin A, **(FlaA)** flagellin - *H. pylori* virulence factors, **LPS** - lipopolysaccharide, **LeTx** - *Bacillus anthracis* lethal toxin, **protein PB1-F2** - influenza A virus component, **ssRNA40** - specific GU-rich single-stranded RNA from the HIV long terminal repeat region.

to deubiquitination of NLRP3 [93,94]. Also, a change in the concentration of extracellular calcium leads to a decrease in the level of cyclic AMP (cAMP) through inhibition of adenylate cyclase and an increase in the cytoplasmic concentration of Ca2+ through activation of phospholipase C and the production of secondary calcium-mobilizing mediators. Concerning the role of potassium, it is known that activation of NLRP3 and NLRP1B inflammasomes serves as a response to the low concentration of potassium inside cells that promotes ASC assembly. In contrast, a high level of extracellular potassium may block the release of IL-1β after NLRC4 and AIM2 inflammasome formation [9,94]. Moreover, adenosine triphosphate (ATP) is a NLRP3 inflammasome agonist that can bind to P2 × 7 receptor and cause the outflow of potassium and formation of pannexin channels in cells, through which it may alter the cell-extracellular signals responsible for inflammasome activity [93,95].

In contrast, extracellular upregulation of inflammasome activity can occur through cytokine receptors that activate NLRP3 transcription. In addition, NLRP3 transcription can be triggered by the deubiquitination of NLRP3, which occurs only in response to the stimulation of PRRs [96]. The suppression of inflammasome activity can ensure according to the type of negative feedback in cells or activity of type I interferon (IFN). IFN reduces NLRP3 inflammasome activity through activation of inducible nitric oxide synthase, leading to inhibition of the production of pro-IL 1β and pro-IL-18 [97].

8. Substances that can inhibit inflammasome activity

It should be noted excessive activation of the NLRP3 inflammasome may cause various diseases, including metabolic syndrome, cardiovascular and neurodegenerative diseases, diabetes, or atherosclerosis.

Table 2
Some endogenous agents capable of inflammasome activation.

Endogenous agents	Action	Source
DAMPs, HAMPs, PAMPs	All these molecular patterns trigger the generation of ROS and in the ROS-dependent pathway triggers NLRP3 inflammasome complex formation.	[5]
K^+ efflux	Decrease of intracellular K^+ concentration in cells is a common trigger for canonical and noncanonical NLRP3 inflammasome activation.	[5]
ATP	Extracellular ATP, triggers P2 × 7-dependent pore formation by the pannexin-1 hemichannel, allowing extracellular NLRP3 agonists to enter the cytosol and formation of NLRP3 inflammasome.	[5]
Cathepsin B	Lysosomal permeabilization leads to the release of cathepsin B that triggers the activation of the Nlrp3 inflammasome.	[99]
MSU	An increase in intracellular Na^+, causing water influx and cellular swelling, which in turn lowers the intracellular K^+ concentration and induce NLRP3 inflammasome activation.	[100]
Cholesterol crystals	Cholesterol crystals cause lysosome rupture, resulting in the release of cathepsin B in cytosol and activate the NLRP3 inflammasome.	[101]
Calcium crystals	Calcium phosphate crystals (hydroxyapatite and tricalcium phosphate) through lysosomal rupture, potassium efflux, ROS generation and cathepsin B induce NLRP3 inflammasome activation.	[102]
Uric acid	Uric acid released from injured cells via uric acid-dependent pathways can activate the inflammasome NALP3 inflammasome leading to IL-1β production.	[5]
Amyloid-β	Amyloid β may directly interact with NLRP3 and initiate inflammasome activation resulting in caspase-1 activation and subsequent maturation and release of IL-1β.	[103, 104]
α-synuclein	α-synuclein by disrupting the lysosome and facilitating the release of cathepsin B induces NLRP3 inflammasome activation.	[103]

DAMPs- danger-associated molecular pattern molecules, **HAMPs** - homeostasis-altering molecular processes, **PAMPs** - pathogen-associated molecular patterns, **MSU** - monosodium urate, **amyloid-β** – protein that contribute to Alzheimer's disease, **α-synuclein** - protein that contribute to Parkinson's disease.

Table 3
Some chemical irritants capable of inflammasome activation.

Chemical irritants	Action	Source
Alum	Phagocytosed alum-containing lysosomes rupture and release their components to the cytosol. The released contents and molecules generated during this process contribute to NLRP3 inflammasome activation.	[102]
Silica	Inflammasome activation is triggered by reactive oxygen species, which are generated by a NADPH oxidase upon particle phagocytosis.	[105]
Asbestos	NLRP3 inflammasome activation upon asbestos stimulation is dependent on endocytosis and ROS production.	[105]
UVB irradiation	UVB irradiation increases intracellular free Ca2+, resulting in the activation of the NALP3 inflammasome	[106]
TNP-Cl	Treatment mice with 0.15 mL 5% TNP-Cl initiate tissue inflammation and activation of Nalp3 inflammasome.	[107]
AgNPs	AgNPs stimulate ASC speck assembly formation, caspase-1 activation, and mature IL-1β secretion, indicating the activation of NLRP3 inflammasomes in human THP-1 monocytes and hepatic cells.	[102]

TNP-Cl – trinitrophenylchloride, **AgNPs** - silver nanoparticles.

Therefore, more and more specific scientific experiments occur in the literature concerning the discovery of potential inhibitors of inflammasomes with the goal of using them in the future as specific targets for inflammasome regulation and inflammation control.

Obovatol is a biphenolic natural chemical compound isolated from

Table 4
Some pharmacological substances capable of inflammasome activation.

Pharmacological substances	Action	Source
Imiquimod	Imiquimod suppress the quinone oxidoreductases mitochondrial Complex I and NQO2 what lead to a burst of ROS and thiol oxidation, and via NEK7 led to NLRP3 activation. Also, K^+ efflux is dispensable for NLRP3 activation.	[108]
Amodiaquine and Nevirapine	Reactive metabolites of these drugs cause the release of DAMPs, which in turn activate inflammasomes.	[109]
Propofol	Propofol overdose can trigger NLRP3 inflammasome activation via mitochondrial ROS-dependent pathway	[110]
Morphine	Morphine by binding to TLR4 activates NF-κB and induce the secretion of NLRP3	[111]

Imiquimod is a small-molecule ligand of TLR7 that is licensed for the treatment of viral infections and cancers of the skin. **Amodiaquine**is a medication used to treat malaria. **Nevirapine** is a medication used to treat and prevent HIV/AIDS, specifically HIV-1. **Propofol (Diprivan)**, is a short-acting medication that results in a decreased level of consciousness and a lack of memory for events. **Morphine** is a pain medication of the opiate family.

Magnolia obovata that has anti-inflammatory and neurotrophic properties. Numerous research shows that obovatol has anti-inflammasome properties and may be used for the treatment of Alzheimer's disease (AD), various types of cancer and atherosclerosis. For example, in AD model mice obovatol administration suppresses inflammation in microglial cells and improves cognitive function in animals [112]. It has been reported that obovatol may inhibit cancer cells proliferation via the inhibition of NF-kB signal transduction and apoptosis increase [113]. Moreover, by inhibiting the expression of cyclins and cyclin-dependent kinases obovatol reduces the number of vascular smooth muscle cells [114]. Also, in *in vitro* experiments on mouse bone marrow-derived macrophages and *in vivo* studies on mice, obovatol was found to inhibit NLRP3, AIM2, and non-canonical inflammasome expression. Obovatol affects the priming step of inflammasome activation and suppresses transcription of pro-inflammatory cytokine synthesis. Additionally, the inhibitory mechanism of obovatol relies on inhibition of mitochondrial ROS generation and Asc pyroptosome formation [115].

Mucin 1 (MUC1) is an epithelial membrane antigen (glycoprotein with extensive O-linked glycosylation of its extracellular domain) that is synthesized by the apical surface of mucosal epithelial cells (stomach, intestines, lungs, and several other organs) and protects against bacteria and enzymes. It was stated that by regulation of the NLRP3 inflammasome activity MUC1 protects against *H. pylori* and *H. influenzae* pathogenesis. For example, in the experiment on mouse macrophage was found that MUC1 inhibits activation of the NLRP3 inflammasome during *H. pylori* and *H. influenzae* infections and suppresses IL-1β produced via the NLRP3 inflammasome. No effect of MUC1 on the NLRP1b, NLRC4 and AIM2 inflammasomes have been observed that support the role of MUC1 in the regulation of NLRP3 activation by bacteria [116].

Catechin is a flavan-3-ol, a type of natural phenol, and has antioxidant properties. Catechin is present in many dietary products, green tea, red wine, beer, chocolate, and cocoa, among others, and possesses a range of beneficial health effects. There is evidence that emphasizes the protective effects of catechin against periodontitis and gouty inflammation. Such, in mice suffering from periodontitis induced by *Porphyromonas gingivalis,* downregulation of NLRP3 and AIM2 inflammasome activation was observed. Catechin also suppresses the production of IL-1β by inhibiting pro-IL-1β expression via the downregulation of nuclear factor-κB, p38 mitogen-activated protein kinase, and TLR signaling in THP-1 cells [117]. Similarly, subcutaneous injection of catechin decreases monosodium urate (MSU)-induced IL-1β and IL-6 secretion in C57BL/6 mice (*in vivo*) and inhibits MSU-induced IL-1β secretion, intracellular calcium and NLRP3 inflammasome activation in MSU-challenged THP-1 cells (*in vitro*) [118]. These data suggest that catechin has anti-inflammatory properties by reducing inflammasome activity and pro-inflammatory cytokine synthesis in periodontitis and gout attack.

Dicer or helicase with RNase motif is a ribonuclease from the RNase III family (RNase III) that cleaves double-stranded RNA and pre-miRNA molecules to produce short double-stranded RNA fragments called small interfering RNAs (siRNAs) and microRNAs (miRNAs). Dicer promotes activation of the RNA-induced silencing complex (RISC), which is essential for RNA interference. In the experiment on the mouse suffering from retinal pathologies, genetic suppression of Dicer1 leads to focal retinal pigmented epithelium atrophy and aberrant retinal neovascularization in the eye [119]. In addition, dicer-deficient murine bone marrow macrophages show disturbances in NLRP3 inflammasome activation. Dicer is required for optimal secretion of mature IL-1β and caspase-1 following stimulation of the NLRP3 but not the AIM2 inflammasome. These data indicate that miRNAs are necessary for the production of mature micro-RNAs and NLRP3 inflammasome activation in bone marrow macrophages and underline key function of DICER1 in maintaining retinal homeostasis [119,120].

8.1. Heat-killed probiotics

It has been previously demonstrated that heat-killed probiotics can be useful for attenuation of NLRP3-mediated colitis and inflammation-associated colon carcinogenesis in mice. Treatment mice suffering from dextran sodium sulfate (DSS)-induced colitis with heat-killed *E. faecalis* amelioration of the severity of intestinal inflammation and the formation of colorectal cancer were observed. In contrast, *E. faecalis* cannot prevent DSS-induced colitis in NLRP3 knockout mice [68]. Moreover, in an experiment where THP-1-derived macrophages were incubated with heat-killed E. faecalis commensal bacteria, a reduction of NLRP3 and caspase-1 activation and IL-1β maturation was observed. Above mentioned data suggesting that application of heat-killed probiotic, E. faecalis could be useful for attenuation of NLRP3-mediated inflammation in the gut and may prevent colon carcinogenesis [68].

Selenium (Se) is an essential micronutrient that is necessary for proper antioxidant defense, reproduction, cancer prevention, immunity and health [121]. Several studies have demonstrated, that selenium by inhibition of the NLRP3 inflammasome activity attenuates *Staphylococcus aureus* mastitis and has an anti-inflammatory property in the mammary gland [122,123]. In a mouse model of *Staphylococcus aureus*-induced mastitis selenium administration in the diet was found to suppress NALP3 inflammasome expression and inhibit the maturation of caspase-1 and IL-1β in mammary tissue. Selenium decreases the production of IL-1β by inhibiting activation of the NF-κB/p65 signaling pathway induced by *Staphylococcus aureus,* and downregulation of the NALP3 inflammasome and ASC expression participates in inflammation reduction [122,123]

Quercetin is the natural biochemical substance of the flavonoid group isolated from foods of plant origin. Quercetin is used in alternative medicine and is part of several biologically active (BAA) food additives. Quercetin has antioxidant and anti-inflammatory properties. By inhibition of the NLRP3 inflammasome activity quercetin may prevent spinal degeneration and can be a potential therapeutic candidate for Kawasaki disease vasculitis and could be useful in preventing host epithelial damage induced by *E. coli* O157: H7 bacteria [124–126]. In *in vitro* experiments using the enterocyte model cells line Caco-2 infected with *E. coli* O157: H7, activation of the NLRP3 inflammasome and increased secretion of IL-1β and IL-18 were noticed. Incubation of infected Caco-2 cells with quercetin inhibited NLRP3 inflammasome activation and attenuated NLRP3 assembly through its ability to scavenge ROS and enhance autophagy. [126]. Also, quercetin in a dose-dependent manner inhibits IL-1β secretion by both the NLRP3 and AIM2 inflammasome and inhibits the cardiovascular lesions in the LCWE-induced vasculitis mouse model (i.p. injection of a cell wall extract from Lactobacillus

casei) [125].

Oridonin (Ori) is a bioactive ent-kaurane diterpenoid found in Rabdosia rubescens (an evergreen rainforest tree of the myrtle family Myrtaceae). Oridonin is widely used in traditional Chinese medicine and possesses anti-inflammatory and anticancer activity. Several data are showed that in an NLRP3 inflammasome-dependent manner oridonin exerts therapeutic effects on myocardial ischemia, liver fibrosis, neuroinflammation, colitis and sepsis. Also, there are reports that oridonin reduces lung inflammation and improves survival in SARS-CoV-infected animals [127–131]. The mechanism of oridonin action is based on the suppression of NF-κB or MAPK activity and inhibition of inflammasome-independent pro-inflammatory cytokines releases, such as TNF-α and IL-6 [132]. He et al. [133] in *in vitro* and in vivo experiments, demonstrated that oridonin is a covalent drug that can block NLRP3 inflammasome activation. They found that oridonin could form a covalent bond with cysteine 279 of NLRP3 in the NACHT domain to block the interaction between NLRP3 and NEK7, leading to inhibition of NLRP3 inflammasome assembly and downregulation of the expression of pro-inflammatory cytokines. [133]. This data suggest that oridonin could be used as a novel therapeutic against NLRP3-driven inflammation.

9. Conclusions

Based on literature data, the host activates the mechanism of inflammasomes formation as a defense response against the described pathogenic microorganisms, but in turn, some pathogens entering the organism using virulence factors may antagonize inflammasome pathways and increase their ability to survive in the host and cause disease. The host organism sometimes expresses excessive amounts of inflammasomes to remove harmful factors, which leads to the overproduction of inflammatory cytokines and can cause chronic inflammation and even autoinflammatory disease. Of note, probiotic bacteria do not impact inflammasome activation and pro-inflammatory cytokine synthesis in healthy individuals, but probiotics may regulate inflammasome activation in an organism that has previously experienced some degree of inflammation due to infection by pathogenic bacteria. Finally, by examining the signalling pathways responsible for the regulation of inflammasome activity, many biochemical substances have been discovered that have an inhibitory effect on inflammasome activity. Knowledge about the mechanisms responsible for the interactions between the host and certain types of microorganisms could contribute to the individuation of innovative strategies for the treatment of autoinflammatory diseases targeting a specific type of inflammasome activated by specific type of pathogen.

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Declaration of Competing Interest

The authors report no declarations of interest.

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