COVID-19: role of the inflammasome

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Abstract

Covid-19 disease is caused by SARS Cov-2 virus. Despite its high transmissibility, the CFR (Case Fatality Rate) of COVID-19 seems to be lower than the SARS (9,5%) and MERS (34,4%) ones[93] , but higher than the influenza one (0-1%)[94,95] . The disease is asymptomatic or paucisymptomatic in most of the patients, although in few cases it can be characterized by serious complications. The main causes of hospitalization in intensive care are represented by ALI (Acute Lung Injury), ARDS (Acute Respiratory Distress Syndrome), cardiovascular problems and coagulopathies (diffuse thrombosis, microthrombosis, embolisms, myocarditis, arrhytmias, heart failure, stroke)[96-98], acute nephropathy[99,100] and encephalopathies[101]. The virus presence in the vascular wall can cause endotheliitis, which triggers the process of diffuse coagulation that can lead to a worsening of the systemic inflammation. The exaggerated inflammatory response seems to be connected with the development of ARDS, MOF (Multiple Organ Failure) and coagulopathies[102-107].

Danger signs and cytokine storm

As defined, inflammation is an immunovascular response to an inflammatory stimulus. The main objectives of inflammation are the elimination of the pathogens and the repair of the damaged tissues[108-110]. The lack of an adequate inflammatory response can lead to chronic disease and acute damage, even death. The cytokine storm is a process where an uncontrolled immune response is responsible of serious complications observed in COVID-19 patients[111-113]. During the SARS Cov-2 infection, if the effects of viral replication an those of tissue damage add up to the pro-inflammatory effects of coagulation phenomena, there can be a generalized release of cytokines, chemokines and growth factors, which can start the "cytokine storm"[115-116]. **Fig. 1.** The warning sign capable of triggering inflammation can be represented by an infection, or by damage or tissue alteration[5]. Warning signs are defined PAMPs (Pathogen-Associated Molecular Patterns) and DAMPs (Damage-Associated Molecular Patterns)[114]. PAMPs derive from microorganisms and, consequently, trigger inflammations related to infections. DAMPs derive from host cells and are the basis of the so-called sterile inflammation. Often, however, DAMPs are also involved in infectious forms. In fact, sterile inflammation can subsequently complicate with bacterial overlap.

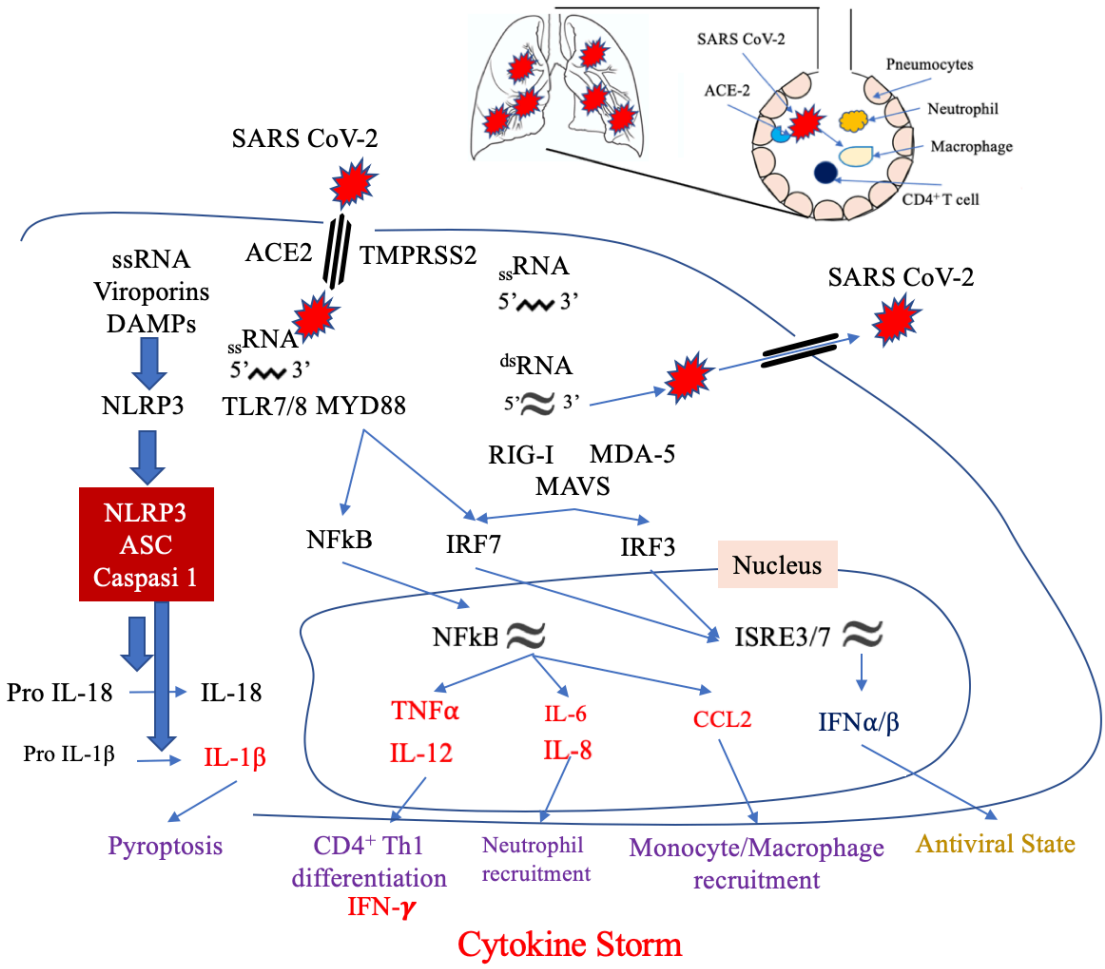

Fig. 1. Cytokine storm. SARS CoV-2 virus enters alveolar epithelial cells thanks to the action of the TMPRSS2 cell protease, and to the interaction with the ACE2 membrane receptor. Therefore, it is recognized by intracellular sensors: a) viral RNA sensors (RIGI-I and MDA5) b) NLRP3 inflammasome sensors. The activation of the NLRP3 sensor, after binding to the ASC adapter, activates the caspase1 enzyme. Capsase1 activates the proteolytic cleavage that transforms the immature interleukins pro IL-1β and pro IL-18 into the active forms IL-1β and IL-18. RIG-I and MDA-5 activate IRF3 / 7, with the production of IFNα / β. TLR7 / 8 activate MYD88 and NFκB, and casuses an induction of pro-inflammatory cytokines (TNFα, IL-6, IL-12, IL8). IL-1β promotes piroptosis. The IFNs α and β determine the development of the antiviral state in adjacent cells and promote the inflammatory state through the products of the activity of the ISGs. IL-8 recalls neutrophils, which can give rise to NETosis. IL-12 stimulates the differentiation of CD4 + Th0 lymphocytes into CD4 + Th1 lymphocytes, producers of IFN-γ. Innate immunity, in addition to aiming to eliminate the virus, orchestrates the adaptive immune response through the cytokines. There is a risk that, due to the initiation of self-maintenance and self-amplification loops, there will be the appearance of an exaggerated immunoinflammatory response, called cytokine release syndrome or cytokine storm.

There are receptors capable of detecting the presence of warning signs, called PRRs (pattern-recognition receptors). The inflammatory response is triggered when PRRs bind PAMPs / DAMPs. There are several types of PRRs: TLRs, RLRs, NLRs, ALRs 2. TLRs are found on the host cell membrane and in endosomes [3,4]. RLRs, NLRs, ALRs are localized in the cytoplasm of the host cell. While RLRs (RIG-I and MDA5) recognize cytoplasmic RNA (RNA virus), ALRs recognize cytoplasmic DNA (DNA virus)[4]. The NLRs family corresponds to the inflammasomes and includes various members, among which the best known is the NLRP3.

The first antiviral defense initiates after the SARS CoV-2 virus has overcome the anatomical barrier,

and is represented by the IFN-I / III system. IFN-III works locally, while IFN-I α / β has systemic actions and can contribute to the abnormal inflammation. The same pathway, in fact, activates the genes associated with the IFN (ISGs: interferon-stimulated genes) and the transcription factor NFkB.

Inflammasomes

Inflammasomes are cytosolic protein complexes that mediate the activation of powerful inflammation factors, triggering a cascade of inflammatory responses. Known since 2002, they are part of innate immunity[19-23]. The NLRP3 inflammasome is one of the main intracellular inflammatory pathways of the innate immune system. Activation of the inflammasome determines the production and release of the pro-inflammatory cytokines IL-1β and IL-18 **Fig. 2**.

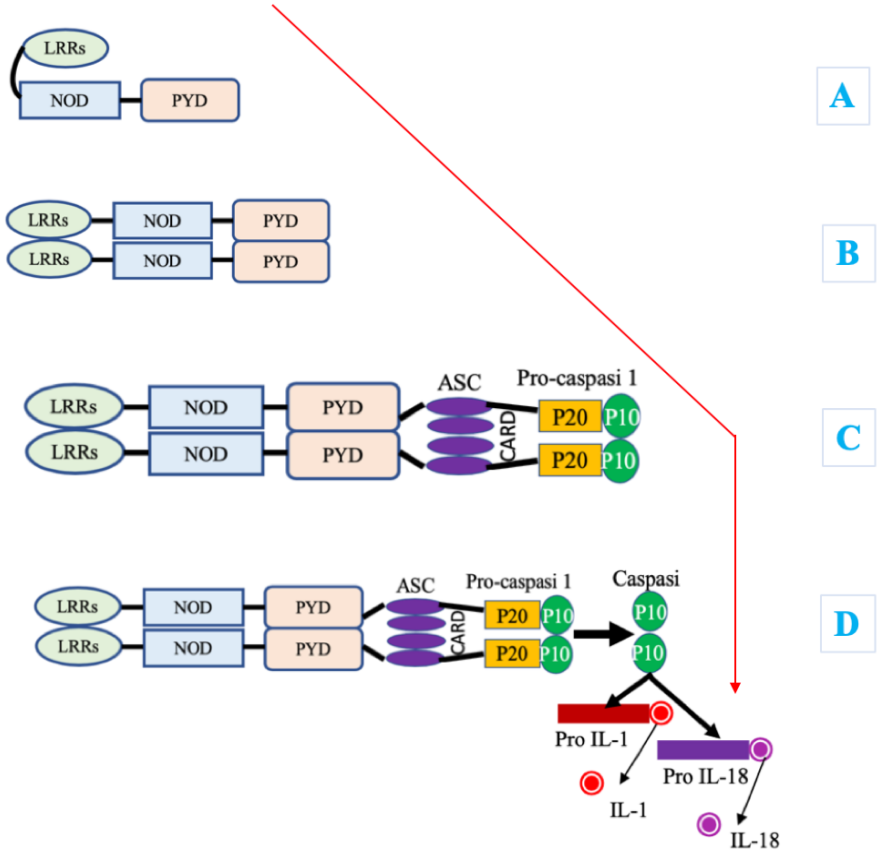

Fig. 2. ***Inflammasome.*** *A) The NLRP3 has a tripartite structure, being formed by a C-terminal domain (LRR), a central domain (NOD) and a N-terminal domain (PYD). LRR represents the binding domain between NRLP3 and the pathogen (PAMP / DAMP). It includes a sequence of 20-30 amino acids rich in leucine residues. The NLRP3 sensor, through the LRR domain, recognizes and interacts with the pathogen (PAMP and / or DAMP). The NOD domain facilitates the oligomerization and activation of the inflammasome. The PYD domain binds procapsase 1 thanks to the involvement of an adapter called ASC. B) Following the stimulus, the NOD domain promotes the activation of the inflammasome (multimeric protein ≅ 760KDa). C) The activated inflammasome recruits the inactive pro-caspase 1, which includes two heterodimers P20 and P10, and through auto-cleaving turns into active caspase 1. The recruitment of pro-caspase 1 requires the intervention of the ASC adapter which, on one hand, binds to the PYD domain of the NLRP3, and on the other, through the CARD domain, binds pro-caspase 1. D) Caspase 1 determines the proteolytic cleavage of the inactive pro-IL1β (33KDa) and pro-IL18 cytokines, transforming them into the active forms IL-1β (18KDa) and IL-18. IL-1β and IL-18 are then released.*

Therefore, the inflammasome is a multimeric protein complex that functions as a sensor. The NLRP3 inflammasome can be activated by a wide range of molecular stimuli, represented by PAMPs, released during viral, bacterial, fungal or protozoan infection[24-27], or by DAMPs, of endogenous or exogenous origin, linked to cellular events[48] such as extracellular release of ATP, disturbances of the cytoplasmic concentration of K^+ and Ca^{++} [53-57], mitochondrial dysfunction, stress Endoplasmic reticulum, reactive oxygen species (ROS)[48], release of oxidized mitochondrial DNA, release of cathepsin from lysosomes[50], cholesterol, monosodium urate crystals (MSU), beta amyloid (Aβ) plaques, silica or asbestos[28-33].

ROS play an important role in the activation of NLRP3. Oxidative stress promotes the accumulation of poorly folded proteins that cause strain in the endoplasmic reticulum and activate the NFkB. The destabilization of lysosomes can be at the origin of the activation of the NLRP3. Following the phagocytosis of large particles of silicon, asbestos, cholesterol [6,-9], uric acid, β-amyloid, they can release the cathepsin B protease, induce efflux of K^+ ions and release into the cytosol Ca^{++} ions, causing the activation of the inflammasome[58]. Mitochondria are fundamental in cellular homeostasis and constitute a platform for the activation of NLRP3. ROS, Extracellular acidosis[11], increased K + efflux and increased intracellular Ca ++ concentration are all factors that induce mitochondrial dysfunction, that causes release of mitochondrial DNA (oxidized by the action of ROS), cardiolipin and GTPase (Drp1 and mitofusin)[59]. Oxidized mitochondrial DNA, cardiolipin, Drp1 and Mitofusina, activate NLRP3[60,61,65]. The MAVS protein, in addition to mediating the activation of IFN-I, contributes in activating the inflammasome[62-64]. The presence of extracellular histones also activates the NLRP3. Extracellular histones have been found in BALF (Bronchial Alveolus Lavage Fluid) of mice and humans suffering from acute lung injury (ALI) which benefited significantly from the use of anti-histone antibodies[70-72]. A moderate activation of the NLRP3 has a defensive value, helping to eliminate pathogens and promote tissue repair phenomena. On the other hand, exaggerated or prolonged activation damages the tissues and contributes to the pathogenesis of serious auto-inflammatory disorders, mediated by an abnormal overproduction of inflammatory cytokines[49]. Indeed, NLRP3 has been implicated in the pathogenesis of a series of complex diseases, such as type II diabetes, atherosclerosis[35-39,9] , obesity and gout[40]. An emerging role of NLRP3 has been reported in neurological diseases, including Alzheimer's disease and Parkinson's disease[41,42]. Abnormal activation of the NLRP3 inflammasome may contribute to the pathogenesis of intestinal carcinomas and kerato-conjunctivitis[43-47].

The products of activated inflammasomes (IL-1β and IL-18) encourage the development of severe lung diseases associated with infectious diseases, sepsis, polytrauma (ALI / ARDS) and contribute to the development of VILI (Ventilator-Induced Lung Injury)[66-69]. After its activation, NLRP3 facilitates the self-cleavage of inactive pro-caspase 1 with active caspase 1 formation. Active caspase 1 promotes the proteolytic cleavage of immature pro-Il1β and pro-Il-18 cytokines with the formation of pro-inflammatory cytokines Il-1β and IL-18. IL-1 includes two isoforms: Il-1α and IL-1β, both of which are powerful pro-inflammatory cytokines with different functional profiles. Il-1α has a short range. Il-β, on the other hand, has a systemic action. Both act by binding to the same receptor (the IL-1RI) which, in turn, recruits an accessory protein responsible for the transduction of the intracellular signal that leads to the activation of a plethora of genes with pro-inflammatory purposes. Unlike IL-1α, IL-1β is produced in an inactive form (pro IL-1β) which needs to be processed to give rise to the active form[6]. Given the devastating self-toxic and self-inflammatory potential of the inflammatory tool represented by IL -1β, by the inflammasome and by a type of inflammatory cell death called pyroptosis, induced by IL-1β, it is necessary a strict control over the multiple levels of these useful but dangerous pathways.

Impaired control of IL-1β production and action may be responsible for rare but severe autoinflammatory genetic pathologies, characterized by an increased activation of the inflammasome and consequently by the synthesis and release of IL -1β (CAPS, TRAPS, FMF). Even the lack of modulation of its action plays a role (DIRA). The body produces a natural inhibitor, IL-1Ra, which functions as a bait, competitively binding to IL1RI, with greater affinity than the two cytokines,

without activating the accessory protein, limiting the effects of IL-1α / β. Mice without IL1Ra develop chronic synovitis[17] and lethal arteritis[18].

Inflammasome, endothelitis, platelets and thrombosis

The respiratory system represents the main way of penetration for the SARS CoV-2 virus. In addition, pneumonia is the most striking epiphenomenon of COVID-19 disease. However, considering the pathogenesis of the most severe forms, COVID-19 disease can be considered a vascular pathology[137]. That's because the endothelium and the coagulation process are fundamental in the progression of the pathology, up to the possible exitus[138-140]. The distinction is not purely speculative but has important therapeutic implications. Endothelial cells do not represent a simple mechanical barrier but a real regulatory organ, essential for vascular homeostasis and for host's defenses[141]. In physiological conditions the endothelium prevents thrombosis by regulating the behavior of platelets and the balance of the factors involved in coagulation and fibrinolysis[141], and it helps to maintain local vascular tone and to modulate inflammation through the activation of leukocytes. Endothelial cells produce thrombomodulin, which activates protein C which, in turn, inactivates thrombin and prevents clot formation. In addition, the endothelium produces nitric oxide (NO) and prostacycline with a vasodilating action[148]. Some stress conditions, such as hypoxia and oxidative stress, activate the endothelium making it dysfunctional, so the antithrombotic mechanism becomes prothrombotic and antifibrinolytic[148]. The endothelium, once activated, expresses adhesion molecules and receptors and recruits neutrophils[149,150]. Endothelial cells release endothelin and the platelet activation factor, which contributes to vasoconstriction and platelet activation. The interaction of endothelial cells with platelets, leukocytes and pro-inflammatory mediators promotes blood clotting[150]. Therefore, under pathological conditions, the endothelium can promote thrombosis[136]. DAMPS can activate inflammasomes in various types of cells, both immune and epithelial: in platelets, neutrophils, monocytes, macrophages, epithelial cells, fibroblasts and even in endothelial cells. The inflammasome can act in any organ and system of the body. In vitro and in vivo researches in animals confirmed the ability of DAMPs to activate inflammasome in endothelial cells[152-153]. In vivo (mice), hemorrhagic shock activates the NLRP3, the production of IL-1β and the pyroptosis in the endothelial cells of the pulmonary vessels[144,145]. The inflammasome when activated at the endothelial cell level, modulates platelets and coagulation factors. The activated inflammasome causes local cell damage associated with a release of DAMPs (sterile inflammation). This creates a loop, with a self-amplifying effect, which contributes to the genesis of organ damage and to the propagation of the inflammatory response[142]. In addition to the effect of DAMPs, the innate immune system activates in response to the SARS CoV-2 virus, which penetrates the endothelial cell thanks to the presence of the ACE2 receptor expressed on its surface. Even if the trigger is represented by the virus, the formation of DAMPs, resulting from tissue damage, self-amplifies and propagates inflammation, helping to perpetuate local damage and generate the cytokine storm, spreading inflammation beyond the initial site. ROS also activate NLRP3 in pulmonary microvascular endothelial cells[146], increasing the presence of IL-1β in the BALF. Endothelial damage causes: neutrophilic infiltration, vascular losses, alveolar and interstitial edema, release of pro-inflammatory cytokines in the lungs, loss of platelet regulation and coagulation factors, with thrombotic phenomena[136]. NETs are another way with which the the inflammasome NLRP3 can help determine mcyrothrombosis and thromboembolism. Neutrophil extracellular traps (NETs) are web-like nuclear material derived from neutrophilic granulocytes and extruded into the extracellular environment in response to appropriate inflammatory stimuli. NETs formation are triggered in response to microbial cues and endogenous danger signals: reactive oxygen species (ROS), produced by NADPH oxidase or mitochondria, which activate myeloperoxidase (MPO), neutrophil elastase (NE) and protein-arginine deiminase type 4 (PAD4) to promote chromatin decondensation[1]. NETs promotes thrombo-occlusive disorders and tissue damage during acute inflammation or chronic inflammation[2,14,15,154,155]. The role of platelets goes beyond coagulation homeostasis. Indeed, platelets are involved in the inflammatory response. In response to

DAMPs, platelets, together with leukocytes, form aggregates that adhere to the parietal endothelium. Platelets synthesize inflammation mediators that increase the expression of adhesion molecules and the secretion of chemokines by endothelial cells. Hence, platelets modulate endothelial functions. Platelets promote the adhesion of leukocytes to the microvascular walls and their activation. White blood cells are then recruited at the vascular damage site level. Platelets, promoting phagocytosis and degranulation in neutrophils, reinforce the negative loop, accentuating and perpetuating organ damage. Inflammasomes and IL-1β are involved in the pro-inflammatory role of platelets, both in infectious and non-infectious pathologies. In fact, the NLRP3 can be activated in the platelets with the release of IL-1β. So, having been shown that NLRP3 activates endothelial cells and platelets and, under conditions of hypoxia[10], enhances thrombosis[153], we think that a better understanding of the role of inflammation in COVID-19 disease, understood as vascular disease, could help to identify new and effective therapeutic targets.

INFLAMMASOME, ALI/ARDS/VILI

An exaggerated inflammatory response, dependent on the inflammasome, is involved in the pathogenesis of ALI / ARDS / VILI[117,118]. ALI and ARDS are clinical disorders burdened by high mortality, characterized by an excessive, progressive and uncontrolled inflammatory response, by an extensive infiltrate of macrophages and neutrophils and by a highly inflammatory cell death, called pyroptosis[118,120]. The development of ALI / ARDS requires the involvement of the NLRP3 inflammasome[117, 136]. Recent studies have suggested that the NLRP3 inflammasome plays a key role in the progression of ALI / ARDS caused by various pathogenic microorganisms, such as the influenza virus A[122], Pseudomonas aeruginosa[121] and Staphylococcus aureus[123]. High levels of IL-18 were found in the ARDS, correlating with an unfavorable prognosis[66,124]. Antibodies against IL-1β and the IL-1R receptor antagonist attenuated the ALI in rodent models[66,125]. The presence of extracellular histones has been demonstrated in human and murine BALF of subjects with ALI. The administration of histone neutralizing antibodies attenuated disease[125]. IL-1β, IL-18 and caspase1 increased in the peripheral blood of ALI / ARDS patients [117].

Histones are activators of the NLRP3 inflammasome[127,128]. The primary source of extracellular histones is represented by the recruited neutrophils that infiltrate the pulmonary alveoli and form TRAPs[12,13]. Histones activate NLRP3 inflammasomes which, in turn, promote the recruitment of neutrophils and the formation of TRAPs, from which extracellular histones originate. This situation creates another loop, by self-amplifying the soil on which ALI / ARDS[117] develops, contributing substantially to the worsening of the COVID-19 disease. Therefore, inhibition of extracellular histones or IL-1β can be an interesting option to fight ALI / ARDS and other inflammatory diseases. Mechanical ventilation determines a sterile inflammatory response, implicated in the development of VILI, and confirmed by the increase in IL-1β and IL-18 in BALF[129-135]. The gene deletion of NLP3, caspase1, IL-18 and the use of neutralizing antibodies against IL-1β and IL-18 significantly reduce VILI. Cellular biomechanical trauma related to mechanical ventilation[132] induces the release of DAMPs that activate the inflammasome in ventilated mice.

Conclusions

The NLRP3 inflammasome plays a crucial role in the pathogenesis of many auto inflammatory diseases, including severe forms of COVID-19. The modulation of the NLRP3 could be exploited, acting in the window of therapeutic opportunity, delimited by well-defined critical points, to prevent the progression of the disease towards ALI / ARDS, towards thrombosis and microthrombosis, towards multiple organ failure (MOF). For these reasons, randomized clinical trials are desirable to evaluate the effectiveness of NLRP3 inhibitors, to offer valid and personalized alternatives in the approach to a complex disease, such as COVID-19.

Abbreviations:

ALI: acute lung injury
ARDS: **:** Acute respiratory distress syndrome
ALRs: AIM2-like receptors
BALF: Bronchoalveolar lavage fluid
CFR: Case Fatality Rate
CAPS: cryopyrin-associated periodic syndrome (CAPS)
CARD: caspase activation and recruitment domain
DAMPs: Damage-associated Molecular Patterns
DIRA: Deficiency of the interleukin-**1**–receptor antagonist
Drp1: Dynamin-related Protein Drp1
FMF: familial Mediterranean fever
GAD: Gasdermin-D
HLA-DR: human leucocyte antigen DR
IFN: Interferon
IL-1β: interleukin 1β
IL-12: Interleukin 12
IL-6: Interleukin 6
IL-8: Interleukin 8
IL-10: Interleukin 10
IL-18: Interleukin 18
IL1Ra: Interleukin-1 Receptor Antagonist
ISGs: interferon-stimulated genes
LRR: leucine-rich repeat
MDA-5: Melanoma differentiation-associated protein 5
MAVS: Mitochondrial antiviral-signaling protein
MERS: Middle East Respiratory Syndrome
NETs: Neutrophil Extracellular Traps
NFkB: nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3: NLR family pyrin domain containing 3
NOD: nucleotide-binding oligomerization domain
NLRs: NOD-like receptors
PAMPs: pathogen-associated molecular patterns
PRRs: pattern-recognition receptors
PYD: Pyrin Domain
RIG-I: retinoic acid-inducible gene I
ROS: Reactive oxygen species
RLRs: RIG-I-like receptors
SARS: Severe acute respiratory syndrome
TNF-α: Tumor Necrosis Factor α
TLRs: Toll-like receptors
TRAPS: TNF receptor-associated periodic syndrome
VILI: ventilator-induced lung injury

Declaration of interests:
We declare no competing interests.

References

[1] Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol*. 2018;18(2):134-147.

[2] Brill, A., Fuchs, T. A., Savchenko, A. S., Thomas, G. M., Martinod, K., De Meyer, S. F., Bhandari, A. A., & Wagner, D. D. (2012). Neutrophil extracellular traps promote deep vein thrombosis in mice. *Journal of thrombosis and haemostasis : JTH*, *10*(1), 136–144.

[3] Arpaia N, and Barton GM (2011). Toll-like receptors: key players in antiviral immunity. Curr. Opin. Virol 1, 447–454.

[4] Iwasaki A (2012). A virological view of innate immune recognition. Annu. Rev. Microbiol 66, 177– 196.

[5] Kono H, and Rock KL (2008). How dying cells alert the immune system to danger. Nat. Rev. Immunol 8, 279–289.

[6] Peter Libby, MD. Interleukin-1 Beta as a Target for Atherosclerosis Therapy: The Biological Basis of CANTOS and

Beyond. J Am Coll Cardiol. 2017 October 31; 70(18): 2278–2289.

[7] Duewell P, Kono H, Rayner KJ, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals [published correction appears in Nature. 2010 Jul 29;466(7306):652]. Nature. 2010;464(7293):1357-1361.

[8] Rajamäki K, Lappalainen J, Oörni K, et al. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. *PLoS One*. 2010;5(7):e11765. Published 2010 Jul 23.

[9] Abe J, Berk BC. Atheroprone flow activation of the sterol regulatory element binding protein 2 and nod-like receptor protein 3 inflammasome mediates focal atherosclerosis. *Circulation*. 2013;128(6):579-582.

[10] Folco EJ, Sukhova GK, Quillard T, Libby P. Moderate hypoxia potentiates interleukin-1β production in activated human macrophages. *Circ Res*. 2014;115(10):875-883.

[11] Rajamäki K, Nordström T, Nurmi K, et al. Extracellular acidosis is a novel danger signal alerting innate immunity via the NLRP3 inflammasome. *J Biol Chem*. 2013;288(19):13410-13419.

[12] Abi Abdallah DS and Denkers EY (2012) Neutrophils cast extracellular traps in response to protozoan parasites. Front. Immun. 3:382.

[13] Alasmari SZ. In Vivo Imaging of Neutrophil Extracellular Traps (NETs): Visualization Methods and Outcomes. Biomed Res Int. 2020;2020:4192745. Published 2020 Feb 1.

[14] Fuchs TA, Brill A, Duerschmied D, et al. Extracellular DNA traps promote thrombosis. Proceedings of the National Academy of Sciences of the United States of America. 2010 Sep;107(36):15880-15885.

[15] M. Saffarzadeh, C. Juenemann, M. A. Queisser et al., "Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones," *PLoS One*, vol. 7, no. 2, Article ID e32366, 2012.

[16] C. Carmona-Rivera, W. Zhao, S. Yalavarthi, and M. J. Kaplan, "Neutrophil extracellular traps induce endothelial dysfunction in systemic lupus erythematosus through the activation of matrix metalloproteinase-2," *Annals of the Rheumatic Diseases*, vol. 74, no. 7, pp. 1417–1424, 2015.

[17] Horai, R., S. Saijo, H. Tanioka, S. Nakae, K. Sudo, A. Okahara, T. Ikuse, M. Asano e Y. Iwakura. 2000. Sviluppo di artropatia infiammatoria cronica simile all'artrite reumatoide in topi con deficit di antagonisti del recettore dell'interleuchina 1. J. Exp. Med. 191: 313-320.

[18] Nicklin, M. J., D. E. Hughes, J. L. Barton, J. M. Ure e G. W. Duff. 2000. Infiammazione arteriosa nei topi privi del gene antagonista del recettore dell'interleuchina 1. J. Exp. Med. 191: 303-312.

[19] S. R. Ali, M. Karin, and V. Nizet, "Signaling cascades and inflammasome activation in microbial infections," Inflamma- some, vol. 2, no. 1, 2016.

[20] F. Gentile, A. L. Cuenca, A. G. Cuenca et al., "Improved emergency myelopoiesis and survival in neonatal sepsis by caspase-1/11 ablation," Immunology, vol. 145, no. 2, pp. 300–311, 2015.

[21] I. Jorgensen and E. A. Miao, "Pyroptotic cell death defends against intracellular pathogens," Immunological Reviews, vol. 265, no. 1, pp. 130–142, 2015.

[22] K. Schroder and J. Tschopp, "The inflammasomes," Cell, vol. 140, no. 6, pp. 821–832, 2010.

[23] H. Yaribeygi, N. Katsiki, A. E. Butler, and A. Sahebkar, "Effects of antidiabetic drugs on NLRP3 inflammasome activ- ity, with a focus on diabetic kidneys," Drug Discovery Today, vol. 24, no. 1, pp. 256–262, 2019.

[24] Kanneganti T.-D., Özören N., Body-Malapel M., et al. Bacterial RNA and small antiviral compounds activate caspase-1 through cryopyrin/Nalp3. *Nature*. 2006;440(7081):233–236.

[25] Mariathasan S., Weiss D. S., Newton K., et al. La criopirina attiva l'inflammasoma in risposta a tossine e ATP. Natura. 2006; 440 (7081): 228-232.

[26] Hise A. G., Tomalka J., Ganesan S., et al. An essential role for the NLRP3 inflammasome in host defense against the human fungal pathogen candida albicans. *Cell Host and Microbe*. 2009;5(5):487–497.

[27] Shio M. T., Eisenbarth S. C., Savaria M., et al. Malarial hemozoin activates the NLRP3 inflammasome through Lyn and Syk kinases. *PLoS Pathogens*. 2009;5(8, article e1000559).

[28] F. Martinon, V. Petrilli, A. Mayor, A. Tardivel, and J. Tschopp, "Gout-associated uric acid crystals activate the NALP3 inflammasome," Nature, vol. 440, no. 7081, pp. 237–241, 2006.

[29] Tschopp J., Schroder K. NLRP3 attivazione dell'inflammasoma: la convergenza di molteplici vie di segnalazione sulla produzione di ROS? Immunologia. 2010; 10 (3): 210-215.

[30] Dostert C., Pétrilli V., Van Bruggen R., Steele C., Mossman B. T., Tschopp J. Attivazione immunitaria innata attraverso il rilevamento inflammasome di Nalp3 di amianto e silice. Scienza. 2008; 320 (5876): 674-677.

[31] Halle A., Hornung V., Petzold G. C., et al. The NALP3 inflammasome is involved in the innate immune response to amyloid-β . *Nature Immunology*. 2008;9(8):857–865.

[32] Pazár B., Ea H.-K., Narayan S., et al. I cristalli basici di fosfato di calcio inducono la secrezione di IL-1β dei monociti/macrofagi attraverso l'inflammasoma NLRP3 in vitro. Journal of Immunology. 2011; 186 (4): 2495-2502

[33] Duewell P., Kono H., Rayner K. J., et al. Gli inflammasomi NLRP3 sono necessari per l'aterogenesi e attivati dai cristalli di colesterolo. Natura. 2010; 464 (7293): 1357-1361.

[34] H. Yaribeygi, MT Mohammadi, R. Rezaee, and A. Sahebkar, "Fenofibrate improves renal function by amelioration of NOX-4, IL-18, and p53 expression in an experimental model of diabetic nephropathy," Journal of Cellular Biochemistry, vol . 119, no. 9, pp. 7458–7469, 2018.

[35] A. Grebe, F. Hoss, and E. Latz, "NLRP3 inflammasome and the IL-1 pathway in atherosclerosis," Circulation Research, vol. 122, no. 12, pp. 1722–1740, 2018.

[36] H. Wen, J. P. Y. Ting, and L. A. J. O'Neill, "A role for the NLRP3 inflammasome in metabolic diseases — did Warburg miss inflammation ?," Nature Immunology, vol. 13, no. 4, pp. 352–357, 2012.

[37] H. Zhang, X. Gong, S. Ni, Y. Wang, L. Zhu, and N. Ji, "C1q / TNF-related protein-9 attenuates atherosclerosis through AMPK-NLRP3 inflammasome singling pathway," International Immunopharmacology, vol. 77, 2019.

[38] B. A. Ference, H. N. Ginsberg, I. Graham et al., "Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel, "European Heart Journal, vol. 38, no. 32, pp. 2459–2472, 2017.

[39] Z. Hoseini, F. Sepahvand, B. Rashidi, A. Sahebkar, A. Masoudifar, and H. Mirzaei, "NLRP3 inflammasome: its regulation and involvement in atherosclerosis," Journal of Cellular Physiology, vol. 233, no. 3, pp. 2116–2132, 2018.

[40] H. Y. Kim, H. J. Lee, Y. J. Chang et al., "Interleukin-17-pro- ducing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity," Nature Medicine, vol. 20, no. 1, pp. 54–61, 2014.

[41] C. Ising, C. Venegas, S. Zhang et al., "NLRP3 inflammasome activation drives tau pathology," Nature, vol. 575, no. 7784, pp. 669–673, 2019.

[42] S. Wang, Y. H. Yuan, N. H. Chen, and H. B. Wang, "The mechanisms of NLRP3 inflammasome /pyroptosis activation and their role in Parkinson's disease," International Immuno-pharmacology, vol. 67, pp. 458–464, 20.

[43] M. S. J. Mangan, E. J. Olhava, W. R. Roush, H. M. Seidel, G. D. Glick, and E. Latz, "Erratum: Targeting the NLRP3 inflammasome in inflammatory diseases," Nature Reviews Drug Discovery, vol. 17, no. 9, p. 688, 2018.

[44] E. Tourkochristou, I. Aggeletopoulou, C. Konstantakis, and C. Triantos, "Role of NLRP3 inflammasome in inflammatory bowel diseases," World Journal of Gastroenterology, vol. 25, no. 33, pp. 4796–4804, 2019.

[45] L. Liu, Y. Dong, M. Ye et al., "The pathogenic role of NLRP3 inflammasome activation in inflammatory bowel diseases of both mice and humans," Journal of Crohn's and Colitis, vol. 11, no. 6, pp. 737–750, 2017.

[46] C. de Torre-Minguela, P. Mesa Del Castillo, and P. Pelegrin, "The NLRP3 and pyrin inflammasomes: implications in the pathophysiology of autoinflammatory diseases," Frontiers in Immunology, vol. 8, p. 43, 2017.

[47] X.Yang, G.Zhao, J.Yanetal., "Pannexin1channelscontrib- ute to IL-1β expression via NLRP3 / caspase-1 inflammasome in Aspergillus FumigatusKeratitis," Current Eye Research, vol. 44, no. 7, pp. 716–725, 2019.
[48] T. Prochnicki and E. Latz. ‘’Inflammasomes on the crossroads of innate immune recognition and metabolic control’’. Cell Metabolism, vol. 26, no. 1, pp. 71–93, 2017.

[49] Tőzsér J, Benkő S. Natural Compounds as Regulators of NLRP3 Inflammasome-Mediated IL-1β Production. Mediators Inflamm. 2016;2016:5460302.

[50] Elliott E. I., Sutterwala F. S. Initiation and perpetuation of NLRP3 inflammasome activation and assembly. *Immunological Reviews*. 2015;265(1):35–52.

[53] Perregaux D., Gabel C. A. Interleukin-1 beta maturation and release in response to ATP and nigericin. Evidence that potassium depletion mediated by these agents is a necessary and common feature of their activity. *The Journal of Biological Chemistry*. 1994;269(21):15195–15203.

[54] Kahlenberg J. M., Lundberg K. C., Kertesy S. B., Qu Y., Dubyak G. R. Potentiation of caspase-1 activation by the P2X7 receptor is dependent on TLR signals and requires NF-κB-driven protein synthesis. Journal of Immunology. 2005; 175 (11): 7611-7622.

[55] Muñoz-Planillo R., Kuffa P., Martínez-Colón G., Smith B., Rajendiran T., Núñez G. K + efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. Immunity. 2013; 38 (6): 1142-1153.

[56] Pétrilli V., Papin S., Dostert C., Mayor A., Martinon F., Tschopp J. Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. Cell Death and Differentiation. 2007; 14 (9): 1583-1589.

[57] Murakami T., Ockinger J., Yu J., et al. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. *Proceedings of the National Academy of Sciences of the United States of America*. 2012;109(28):11282–11287.

[58] Hornung V., Bauernfeind F., Halle A., et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nature Immunology*. 2008;9(8):847–856.

[59] Dan Dunn J., Alvarez L. A. J., Zhang X., Soldati T. Reactive oxygen species and mitochondria: a nexus of cellular homeostasis. Redox Biology. 2015;6:472–485.

[60] Shimada K., Crother T. R., Karlin J., et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity*. 2012;36(3):401–414.

[61] Iyer S. S., He Q., Janczy J. R., et al. Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. Immunity. 2013;39(2):311–323.

[62] Wang X., Jiang W., Yan Y., et al. RNA viruses promote activation of the NLRP3 inflammasome through a RIP1-RIP3-DRP1 signaling pathway. *Nature Immunology*. 2014;15(12):1126–1133.

[63] Ichinohe T., Yamazaki T., Koshiba T., Yanagi Y. Mitochondrial protein mitofusin 2 is required for NLRP3 inflammasome activation after RNA virus infection. *Proceedings of the National Academy of Sciences of the United States of America*. 2013;110(44):17963–17968.

[64] Subramanian N., Natarajan K., Clatworthy M. R., Wang Z., Germain R. N. The adaptor MAVS promotes NLRP3 mitochondrial localization and inflammasome activation. Cell. 2013;153(2):348–361.

[65] Shaw S. Y., Tran K., Castoreno A. B., et al. Selective modulation of autophagy, innate immunity, and adaptive immunity by small molecules. *ACS Chemical Biology*. 2013;8(12):2724–2733.

[66] Dolinay T, Kim YS, Howrylak J, Hunninghake GM, An CH, Fredenburgh L, Massaro AF, Rogers A, Gazourian L, Nakahira K, Haspel JA, Landazury R, Eppanapally S, Christie JD, Meyer NJ, Ware LB, Christiani DC, Ryter SW, Baron RM, Choi AM. Inflammasome-regulated cytokines are critical mediators of acute lung injury. Am J Respir Crit Care Med. 2012;185:1225–1234.

[67] Makabe H, Kojika M, Takahashi G, Matsumoto N, Shibata S, Suzuki Y, Inoue Y, Endo S. Interleukin-18 levels reflect the long-term prognosis of acute lung injury and acute respiratory distress syndrome. J Anesth. 2012;26:658–663.

[68] Kuipers MT, Aslami H, Janczy JR, van er Sluijs KF, Vlaar AP, Wothuis EK, Choi G, Roelofs JJ, Flavell RA, Sutterwala FS, Bresser P, Leemans JC, van der Poll T, Schultz MJ, Wieland CW. Ventilator-induced lung injury is mediated by the NLRP3 inflammasome. Anesthesiology. 2012;116:1104–1115.

[69] dos Santos G, Kutuzov MA, Ridge KM. The inflammasome in lung diseases. Am J Physiol Lung Cell Mol Physiol. 2012;303:L627–633.

[70] Xu J, Zhang X, Pelayo R, Monestier M, Ammollo CT, Semeraro F, Taylor FB, Esmon NL, Lupu F, Esmon CT. Extracellular histones are major mediators of death in sepsis. Nat Med. 2009;15:1318–1321
[71] Huang H, Evankovich J, Yan W, Nace G, Zhang L, Ross M, Liao X, Billiar T, Xu J, Esmon CT, Tsung A. Endogenous histones function as alarmins in sterile inflammatory liver injury through Toll-like receptor 9 in mice. Hepatology. 2011;54:999–1008.

[72] Bosmann M, Grailer JJ, Russkamp NF, Ruemmler R, Monestier M, Zetoune FS, Sarma JV, Ward PA. Extracellular histones are essential effectors of C5aR and C5L2-dependent tissue damage and inflammation in acute lung injury. FASEB J. 2013;27:5010–5021

[73] Park A, Iwasaki A. Type I and Type III Interferons - Induction, Signaling, Evasion, and Application to Combat COVID-19. Cell Host Microbe. 2020;27(6):870-878.

[74] Lazear HM, Schoggins JW, Diamond MS. Funzioni condivise e distinte di interferone di tipo I e di tipo III. Immunità. 2019 aprile; 50 (4): 907-923.

[75] Crouse, J., Kalinke, U., and Oxenius, A. (2015). Regulation of antiviral T cell responses by type I interferons. Nat. Rev. Immunol. 15, 231–242.

[76] Garcıa-Sastre, A. (2017). Dieci strategie di evasione dell'interferone da parte dei virus. Microbo ospite cellulare 22, 176–184.

[77] Hoffmann, H.H., Schneider, W.M. e Rice, C.M. (2015). Interferoni e violette: una corsa agli armamenti evolutiva di interazioni molecolari. Trends Immunol. 36, 124–138.

[78] Ingle, H., Peterson, S.T. e Baldridge, M.T. (2018). Distinti effetti degli interferoni di tipo I e III sui virus enterici. Virus 10, E46.

[79] Kotenko, S.V., Gallagher, G., Baurin, V.V., Lewis-Antes, A., Shen, M., Shah, N.K., Langer, J.A., Sheikh, F., Dickensheets, H., and Donnelly, R.P. (2003). IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. Nat. Immunol. 4, 69–77.

[80] Lazear, H.M., Nice, T.J., and Diamond, M.S. 2015b. Interferon-l: immune functions at barrier surfaces and beyond. Immunity 43, 15–28.

[81] Schoggins, J.W. (2018). Recent advances in antiviral interferon-stimulated gene biology. F1000Res. 7, 309..

[82] Schreiber, G. (2017). The molecular basis for differential type I interferon signaling. J. Biol. Chem. 292, 7285–7294.

[83] Snell, L.M., McGaha, T.L., and Brooks, D.G. (2017). Type I Interferon in Chronic Virus Infection and Cancer.

Trends Immunol. 38, 542–557.

[84] Sorgeloos, F., Kreit, M., Hermant, P., Lardinois, C., and Michiels, T. (2013). Antiviral type I and type III interferon responses in the central nervous system. Viruses 5, 834–857.

[85] Wack, A., Terczynska-Dyla, E., and Hartmann, R. (2015). Guarding the fron- tiers: the biology of type III interferons. Nat. Immunol. 16, 802–809.

[86] Wells, A.I., and Coyne, C.B. (2018). Type III Interferons in Antiviral Defenses at Barrier Surfaces. Trends Immunol. 39, 848–858.

[87] Ivashkiv, L.B., and Donlin, L.T. (2014). Regulation of type I interferon re- sponses. Nat. Rev. Immunol. 14, 36–49.

[88] Kotenko, S.V., Rivera, A., Parker, D. e Durbin, J.E. (2019). IFN di tipo III: oltre la protezione antivirale. Semin. Immunol. 43, 101303.

[89] Schoggins, J.W., and Rice, C.M. (2011). Interferon-stimulated genes and their antiviral effector functions. Curr. Opin. Virol. 1, 519–525.

[90] Lim, Y.X., Ng, Y.L., Tam, J.P., and Liu, D.X. (2016). Human Coronaviruses: A Review of Virus-Host Interactions. Diseases 4, 26.

[91] Nelemans, T. e Kikkert, M. (2019). Viral Innate Immune Evasion e la patogenesi delle infezioni emergenti da virus RNA. Virus 11, 961.

[92] Totura, A.L., and Baric, R.S. (2012). SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. Curr. Opin. Virol. 2, 264–275.

[93] Smits SL, de Lang A, van den Brand JM, et al. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog. 2010;6(2):e1000756. Published 2010 Feb 5.

[94] Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A novel coronavirus emerging in China—key questions for impact assessment. N Engl J Med. 2020;382:692–694.

[95] de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14:523–534

[96] Fauci AS, Lane HC, Redfield RR. Covid-19—navigating the uncharted. N Engl J Med. 2020 doi: 10.1056/NEJMe2002387. published online Feb 28.

[97] Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. *J Am Coll Cardiol*. 2020;75(18):2352-2371.

[98] Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763-1770.

[99] Batlle D, Soler MJ, Sparks MA, et al. Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. *J Am Soc Nephrol*. 2020;31(7):1380-1383.

[100] Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*. 2020;382(23):2268-2270.

[101] Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. 2020;94:55-58.

[102] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(6):1421-1424.

[103] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020;18(4):844-7.

[104] Lippi G, Favaloro EJ. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. *Thromb Haemost*. 2020;120(5):876-878.

[105] Teuwen, L., Geldhof, V., Pasut, A. *et al.* COVID-19: the vasculature unleashed. *Nat Rev Immunol* **20,** 389–391 (2020).

[106] Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147.

[107] Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *J Thromb Haemost*. 2020;18(6):1517-1519.

[108] Newton, K., & Dixit, V. M. (2012). Signaling in innate immunity and inflammation. *Cold Spring Harbor perspectives in biology*, *4*(3), a006049.

[109] Cui, J., Chen, Y., Wang, H. Y., & Wang, R. F. (2014). Mechanisms and pathways of innate immune activation and regulation in health and cancer. *Human vaccines & immunotherapeutics*, *10*(11), 3270–3285.

[110] Trine H. Mogensen. Pathogen Recognition and Inflammatory Signaling in Innate Immune Defenses. linical Microbiology Reviews Apr 2009, 22 (2) 240-273.

[111] Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev*. 2020;53:25-32.

[112] Soy, M., Keser, G., Atagündüz, P. *et al.* Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol* **39,** 2085–2094 (2020).

[113] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *J Infect*. 2020;80(6):607-613.

[114] Tang D, Kang R, Coyne CB, Zeh HJ, Lotze MT. PAMPs and DAMPs: signal 0s that spur autophagy and immunity. *Immunol Rev*. 2012;249(1):158-175.

[115] Sinha P, Matthay MA, Calfee CS. Is a “Cytokine Storm” Relevant to COVID-19? *JAMA Intern Med.* Published online June 30, 2020.

[116] Howard Hughes Medical Institute. (2020, May 21). Preventing 'cytokine storm' may ease severe COVID-19 symptoms. *ScienceDaily*. Retrieved July 6, 2020

[117] Grailer JJ, Canning BA, Kalbitz M, et al. Critical role for the NLRP3 inflammasome during acute lung injury. *J Immunol*. 2014;192(12):5974-5983.

[118] Li, D., Ren, W., Jiang, Z., & Zhu, L. (2018). Regulation of the NLRP3 inflammasome and macrophage pyroptosis by the p38 MAPK signaling pathway in a mouse model of acute lung injury. Molecular Medicine Reports, 18, 4399-4409.

[119] Aggarwal NR, King LS and D'Alessio FR: Diverse macrophage populations mediate acute lung inflammation and resolution. Am J Physiol Lung Cell Mol Physiol. 306:L709–L725. 2014.

[120] Han, S., and Mallampalli, R. K. (2015). The acute respiratory distress syndrome: from mechanism to translation. *J. Immunol.* 194, 855–860.

[121] Cohen, T. S., and Prince, A. S. (2013). Activation of inflammasome signaling mediates pathology of acute P. *aeruginosa pneumonia*. *J. Clin. Invest.* 123, 1630–1637.

[122] Allen, I. C., Scull, M. A., Moore, C. B., Holl, E. K., McElvania-TeKippe, E., Taxman, D. J., et al. (2009). The NLRP3 inflammasome mediates in vivo innate immunity to influenza A virus through recognition of viral RNA. Immunity 30, 556–565.

[123] Miller, L. S., Pietras, E. M., Uricchio, L. H., Hirano, K., Rao, S., Lin, H., et al. (2007). Inflammasome-mediated production of IL-1beta is required for neutrophil recruitment against Staphylococcus aureus in vivo. J. Immunol. 179, 6933–6942.

[124] Makabe H., M. Kojika, G. Takahashi, N. Matsumoto, S. Shibata, Y. Suzuki, Y. Inoue, S. Endo. 2012. Interleukin-18 levels reflect the long-term prognosis of acute lung injury and acute respiratory distress syndrome. J. Anesth. 26: 658–663.

[125] Jordan J. A., R. F. Guo, E. C. Yun, V. Sarma, R. L. Warner, L. D. Crouch, G. Senaldi, T. R. Ulich, P. A. Ward. 2001. Role of IL-18 in acute lung inflammation. J. Immunol. 167: 7060–7068.

[126] Bosmann M., J. J. Grailer, R. Ruemmler, N. F. Russkamp, F. S. Zetoune, J. V. Sarma, T. J. Standiford, P. A. Ward. 2013. Extracellular histones are essential effectors of C5aR- and C5L2-mediated tissue damage and inflammation in acute lung injury. FASEB J. 27: 5010–5021.

[127] Allam, R., M. N. Darisipudi, J. Tschopp, and H. J. Anders. 2013. Histones trigger sterile inflammation by activating the NLRP3 inflammasome. Eur. J. Immunol. 43: 3336-3342.

[128] Huang H., H. W. Chen, J. Evankovich, W. Yan, B. R. Rosborough, G. W. Nace, Q. Ding, P. Loughran, D. Beer-Stolz, T. R. Billiar, et al. 2013. Gli istoni attivano l'inflammasoma NLRP3 nelle cellule di Kupffer durante una lesione infiammatoria del fegato sterile. J. Immunol. 191: 2665–2679

[129] Kuipers MT, Aslami H, Janczy JR, et al. Ventilator-induced lung injury is mediated by the NLRP3 inflammasome. *Anesthesiology*. 2012;116(5):1104-1115.

[130] Frank JA, Pittet JF, Wray C, Matthay MA: Protection from experimental ventilator-induced acute lung injury by IL-1 receptor blockade. Thorax 2008; 63:147–53

[131] Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. JAMA 1999; 282:54–61

[132] Tremblay LN, Slutsky AS: Ventilator-induced lung injury: From the bench to the bedside. Intensive Care Med 2006; 32:24–33

[133] Liu H, Gu C, Liu M, et al. Ventilator-induced lung injury is alleviated by inhibiting NLRP3 inflammasome activation. *Mol Immunol*. 2019;111:1-10.

[134] dos Santos CC. The role of the inflammasome in ventilator-induced lung injury. *Am J Respir Crit Care Med*. 2012;185(11):1141-1144.

[135] Mizushina Y, Karasawa T, Aizawa K, et al. Inflammasome-Independent and Atypical Processing of IL-1β Contributes to Acid Aspiration-Induced Acute Lung Injury. *J Immunol*. 2019;203(1):236-246.

[136] Bortolotti P, Faure E, Kipnis E. Inflammasomes in Tissue Damages and Immune Disorders After Trauma. Front Immunol. 2018 Aug 16;9:1900. doi: 10.3389/fimmu.2018.01900. PMID: 30166988; PMCID: PMC6105702.

[137] Zamboni P. COVID-19 as a Vascular Disease: Lesson Learned from Imaging and Blood Biomarkers. *Diagnostics (Basel)*. 2020;10(7):E440. Published 2020 Jun 29.

[138] Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. *Thromb Res*. 2020;192:23-26.

[139] Edler C, Schröder AS, Aepfelbacher M, et al. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany [published correction appears in Int J Legal Med. 2020 Jun 19;:]. *Int J Legal Med*. 2020;134(4):1275-1284.

[140] Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol*. 2020;127:104362.

[141] Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol*. 2007;7(10):803-815.

[142] Greven J, Pfeifer R, Zhi Q, Pape HC. Update on the role of endothelial cells in trauma. *Eur J Trauma Emerg Surg*. 2018;44(5):667-677.

[143] Chen S, Sun B. Negative regulation of NLRP3 inflammasome signaling. *Protein Cell*. 2013;4(4):251-258.

[144] Xiang M, Shi X, Li Y, et al. Hemorrhagic shock activation of NLRP3 inflammasome in lung endothelial cells. *J Immunol*. 2011;187(9):4809-4817.

[145] Yang J, Zhao Y, Zhang P, et al. Hemorrhagic shock primes for lung vascular endothelial cell pyroptosis: role in pulmonary inflammation following LPS. *Cell Death Dis*. 2016;7(9):e2363.

[146] Long Y, Liu X, Tan XZ, et al. ROS-induced NLRP3 inflammasome priming and activation mediate PCB 118-induced pyroptosis in endothelial cells. Ecotoxicology and Environmental Safety. 2020 Feb;189:109937.

[147] Qiao J, Wu X, Luo Q, et al. NLRP3 regulates platelet integrin αIIbβ3 outside-in signaling, hemostasis and arterial thrombosis. *Haematologica*. 2018;103(9):1568-1576.

[148] Chanchal S, Mishra A, Singh MK, Ashraf MZ. Understanding Inflammatory Responses in the Manifestation of Prothrombotic Phenotypes. *Front Cell Dev Biol*. 2020;8:73.

[149] van Hinsbergh, V. W. (2012). Endothelium - role in regulation of coagulation and inflammation. *Semin. Immunopathol.* 34, 93–106.

[150] Incalza, M. A., D'Oria, R., Natalicchio, A., Perrini, S., Laviola, L., and Giorgino, F. (2018). Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. *Vascul. Pharmacol.* 100, 1–19.

[151] Yau, J. W., Teoh, H., and Verma, S. (2015). Endothelial cell control of thrombosis. *BMC Cardiovasc. Disord.* 15:130.

[152] Xia, M., Boini, K. M., Abais, J. M., Xu, M., Zhang, Y., and Li, P. L. (2014). Endothelial NLRP3 inflammasome activation and enhanced neointima formation in mice by adipokine visfatin. *Am. J. Pathol.* 184, 1617–1628.

[153] Gupta, N., Sahu, A., Prabhakar, A., Chatterjee, T., Tyagi, T., Kumari, B., et al. (2017). Activation of NLRP3 inflammasome complex potentiates venous thrombosis in response to hypoxia. *Proc. Natl. Acad. Sci. U.S.A.* 114, 4763–4768.

[154] Perdomo, J., Leung, H.H.L., Ahmadi, Z. *et al.* Neutrophil activation and NETosis are the major drivers of thrombosis in heparin-induced thrombocytopenia. *Nat Commun* **10,** 1322 (2019).

[155] Mohammed Saied Mohammed Bakeer, Yossef Nassar, Mahmoud A Allam. Neutrophil Extracellular Trap (NET): The Interplay Between Infection, Inflammation and Thrombosis. Archives of Microbiology & Immunology. Arch Microbiol Immunology 2016; 1 (1): 19-26.