CD38 IN THE AGE OF COVID-19: A MEDICAL PERSPECTIVE

CLINICAL HIGHLIGHTS

Although morbidity and mortality rates secondary to the inflammatory and systemic fibrotic conditions of COVID-19 patients are of great concern, only a very few specific drugs are available for treatment.

Emerging evidence supports the hypothesis that the CD38 ectoenzyme and products controlled by the CD38/NAD\(^+\) axis may play significant roles in the pathogenesis of the disease.

The use of CD38-targeted therapies may be a new and viable treatment option in life-threatening COVID-19.

AUTHORS
Alberto L. Horenstein, Angelo C. Faini, Fabio Malavasi

CORRESPONDENCE
horenstein.al@gmail.com; fabio.malavasi@unito.it

KEY WORDS
CD38; COVID-19; NAD\(^+\) metabolome; SARS-CoV-2
CD38 IN THE AGE OF COVID-19: A MEDICAL PERSPECTIVE

Alberto L. Horenstein, Angelo C. Faini, and Fabio Malavasi
Department of Medical Science, University of Turin, Turin, Italy; and Centro Ricerca Medicina, Sperimentale (CeRMS) and Fondazione Ricerca Molinette Onlus, Turin, Italy

Abstract

This medical review addresses the hypothesis that CD38/NADase is at the center of a functional axis (i.e., intracellular Ca\textsuperscript{2+} mobilization/IFN\gamma response/reactive oxygen species burst) driven by severe acute respiratory syndrome coronavirus 2 infection, as already verified in respiratory syncytial virus pathology and CD38 activity in other cellular settings. Key features of the hypothesis are that 1) the substrates of CD38 (e.g., NAD\textsuperscript{+} and NADP\textsuperscript{+}) are depleted by viral-induced metabolic changes; 2) the products of the enzymatic activity of CD38 [e.g., cyclic adenosine diphosphate-ribose (ADPR)/ADPR/nicotinic acid adenine dinucleotide phosphate] and related enzymes [e.g., poly(ADP-ribose)polymerase, Sirtuins, and ADP-ribosyl hydrolase] are involved in the antiviral and proinflammatory response that favors the onset of lung immunopathology (e.g., cytokine storm and organ fibrosis); and 3) the pathological changes induced by this kinetic mechanism may be reduced by distinct modulators of the CD38/NAD\textsuperscript{+} axis (e.g., CD38 blockers, NAD\textsuperscript{+} suppliers, among others). This view is supported by arrays of associative basic and applied research data that are herein discussed and integrated with conclusions reported by others in the field of inflammatory, immune, tumor, and viral diseases.

CD38; COVID-19; NAD\textsuperscript{+} metabolome; SARS-CoV-2

1. GENERAL PREMISE

1.1. Starting Point

This perspective paper is grounded in observations from a 2018 study on the modulation of CD38 during respiratory syncytial virus (RSV) infection in monocytes and macrophages (1). Upon activation of the adaptive immune system during RSV infection, human monocyte-derived dendritic cells (hMDDCs) upregulate CD38 expression and affect the ability to activate T-cell proliferation (2). Similarly, during other viral infections, overexpression of CD38 by both CD4\textsuperscript{+} and CD8\textsuperscript{+} T lymphocytes results in nicotinamide adenine dinucleotide (NAD\textsuperscript{+}) depletion (3, 4). During viral infection, the infiltration of monocyte-derived macrophages is accompanied by release of high levels of reactive oxygen species (ROS) and proinflammatory cytokines (5). In the case of RSV, the innate immune response is initiated by recognition of single-stranded viral RNA (ssRNA) and secretion of type 1 interferon (IFN-\gamma) by infected cells.

IFNs engage autocrine- or paracrine-specific receptors to induce expression of a set of IFN-stimulated genes (ISGs), which inhibit viral replication by reprogramming the cellular metabolism. Moreover, ISGs are inhibited by the antioxidant N-acetyl cysteine, further highlighting the role of ROS in the process of antiviral responses (1, 6). It is known that CD38 is involved in angiotensin (ANG) II-induced intracellular Ca\textsuperscript{2+} release and ROS production (7). The ROS process in RSV-infected hMDDCs is under the control of CD38 (1), and its catalytical activity is upregulated as assessed by measuring the accumulation of adenosine diphosphate-ribose (ADPR) after adding NAD\textsuperscript{+} as a substrate (1, 8). This means that NAD\textsuperscript{+} consumption and generation of metabolic products by the enzymatic functions of CD38 are involved in the induction of anti-viral and proinflammatory responses.
This paper seeks to identify the underlying basis of CD38 involvement in the response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the coronavirus disease (COVID-19) pandemic (9). It does so by examining some of the key metabolic steps controlled by CD38 and its role in the immune response.

1.2. The COVID-19 Disease

SARS-CoV-2 causes COVID-19, which, at the time of this writing, has surpassed 100 million confirmed cases and resulted in over 2% deaths recorded in more than 200 countries (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports; accessed on February 2021).

1.3. The SARS-CoV-2 Virus and Cell Entry

Pathogenesis of SARS-CoV-2 infection (FIGURE 1, A-C) starts when the trimeric viral spike (S) glycoprotein binds to the human cell surface type I transmembrane angiotensin-converting enzyme 2 receptor (ACE2R), followed by proteolytic priming of the S protein. It contains two subunits: 1) S1, which has two major structural elements, the receptor-binding domain (RBD) and the NH2-terminal domain, and 2) S2, which mediates virus-cell membrane fusion after the RBD engages ACE2 (10). A two-step sequential protease cleavage model has been proposed for activation of S protein priming. A first cleavage between S1 and S2 activates a nick on S2’ site, by host proteases: the cellular transmembrane protease serine 2 (TMPRSS2) and furin, respectively (11, 12). Besides TMPRSS, other proteases have also been implicated in facilitating virus entry. Indeed, the extracellular protease plasmin is also able to nick the spike at the S1/S2, a furin cleavage site that increases its ability to bind with ACE2R of host cells (13).

Once the endocytic uptake is unlocked, the viruses uncoat the genome and release the genetic material, namely ss-RNA, to initiate replication. The coronavirus (CoV) genome does not encode for enzymes necessary for the synthesis of proteins, amino acids, lipids, or nucleotides. Therefore, SARS-CoV-2 exploits the host cell for its own replication and to protect its ss-RNA from antiviral immunity (14). To ensures its integrity, viral RNA is capped and methylated at the 5’-end by CoV-non-structural protein (nsp) [e.g., methyltransferase (MTase)] (15), thereby resembling host mRNA to promote translation and to prevent its degradation. All the successive events occur in the nucleus and cytoplasm (16).

ACE2 was originally identified as the receptor of other SARS CoVs (17) as well as of the RSV (1). Of note, ACE2 is also a metalloproteinase enzyme, which catalyzes the conversion of the substrate angiotensin (ANG)-II to ANG-1–7 in the renin-angiotensin system (RAS) (18), as shown in FIGURE 1B. Besides ACE2, it has also been suggested that CD26, the host receptor for MERS-CoV

![Figure 1](https://www.prv.org)
(19), and CD147 (20), serves as endocytic cell entry for SARS-CoV-2.

The ACE2R is expressed by endothelial and epithelial cells present in different organs, such as lungs, heart, gut, kidneys, brain, and placenta, which are all susceptible to viral infection (21–23). In the lungs, ACE2 is expressed by cells of the upper or lower respiratory tract, a critical step for initiation and clinical presentation of the viral infection. Both SARS-CoV-2 and RSV mainly affect the lower respiratory tract (FIGURE 1C). Pathognomonic signs generally found in human diseases and caused by respiratory virus (e.g., RSV and SARS-CoV-2) are involved in a hyperimmune response causing lung pathology (1, 23).

2. CD38 CHARACTERISTICS AND FUNCTIONS POTENTIALLY LINKED TO THE HOST RESPONSE TO SARS-COV-2 INFECTION

2.1. CD38

CD38 is a multifunctional cell protein endowed with signaling receptor and enzymatic features and was initially identified as a lymphocyte antigen by monoclonal antibody typing (24). CD38, present outside of the cell (25) and also intracellularly in the nucleus and organelles (26), is associated with important diseases, such as AIDS, autism, diabetes, chronic lymphocytic leukemia, and multiple myeloma (TABLE 1). These characteristics of CD38 have been comprehensively reviewed (36).

2.1.1. CD38 as an enzyme.

CD38 is a 43.7-kDa transmembrane glycoprotein, which also exists in a 39-kDa soluble form that retains its biochemical features in both normal and pathological fluids (37, 38). Recognition of structural and functional similarities between human CD38 and the enzyme ADP-ribosyl cyclase, purified from the sea mollusk Aplysia, allowed attribution of enzymatic activities to CD38 (39). Indeed, at physiological pH, CD38 catalyzes several enzymatic reactions: 1) the conversion of nicotinamide adenine dinucleotide (NAD\(^+\)) to adenosine diphosphate ribose (ADPR) (NAD\(^+\)-glycohydrolase activity); 2) the conversion of NAD\(^+\) to cyclic ADPR (cADPR) (cyclase activity); 3) the hydrolysis of cADPR to ADPR (hydrolase activity); and at acidic pH, CD38 runs 4) the conversion of NADP\(^+\), the phosphorylated equivalent of NAD\(^+\), to nicotinic acid adenine dinucleotide phosphate (NAADP) (NAADP-synthase activity) in the presence of nicotinic acid (NA) and the degradation of NAADP to ADPR. All of the reaction products are second messengers involved in the regulation of cytoplasmic Ca\(^{2+}\) fluxes (40). NAD\(^+\)-glycohydrolase, the main enzymatic activity of CD38, is not modified in the presence of anti-CD38 human or murine antibodies. On the contrary, cyclase activity is highly inhibited, while hydrolase activity is mildly activated (41–43). These data provide further support for considering extracellular CD38 primarily as a NAD\(^+\)-glycohydrolase (44). CD38 is also able to catalyze the degradation of intracellular NAD\(^+\) precursors [e.g., nicotinamide mononucleotide (NMN) and nicotinamide (NAM)] (45, 46).

Table 1. Potential and therapeutic approaches involving CD38 in diseases

| Disease                                           | Potential and Therapeutic Approaches                                      |
|---------------------------------------------------|-------------------------------------------------------------------------|
| Multiple myeloma                                  | Elimination of plasma cells through therapeutic anti-CD38 antibodies    |
|                                                   | (ADCC, ADCP, CDC, induction, or apoptosis) (27)                         |
| Amyloidosis                                       | Elimination of plasma cells (28)                                       |
| Systemic lupus erythematosus (SLE)                | Elimination of plasma cells and natural killer (NK) cells (29)         |
| Rheumatoid arthritis (RA)                         | Elimination of plasma cells (30)                                       |
| Systemic sclerosis (SS)                           | Mitigation of fibrosis by CD38-targeting of NAD\(^+\) metabolism (31) |
| Chronic active antibody-mediated kidney allograft rejection | Elimination of plasma cells (32)                                     |
| Neurodegeneration                                 | Age-related modulation of NAD\(^+\) metabolism (33)                    |
| Eye                                               | Interaction of neuronal CD38 with the soluble CD31 ligand (34)         |
| Olfactory                                         | Interactions among genes for oxytocin release, oxytocin receptor, and CD38 (35) |

For each disease or organ involved, a potential mechanism of action is suggested. References are included in parenthesis.
CD38 gene ablation experiments provide strong evidence that the enzymatic activity of CD38 is responsible for producing cADPR and NAADP, because formation of both nucleotide messengers is abrogated when the CD38 gene is deleted, indicating that CD38 is the dominant enzyme responsible for their synthesis (40). The nucleotide messengers regulate diverse cell functions by mobilizing intracellular Ca\(^{2+}\) stores: 1) NAADP elicited Ca\(^{2+}\) release, important for SARS-CoV-2 entry into cells (47), from the two-pore channels (TPCs), situated in acidic endolysosomes (EL) (48); and 2) cADPR enhances Ca\(^{2+}\) release via the activation of the ryanodine receptor (RyR) (36) situated in the membrane of the endoplasmic reticulum (ER). cADPR can also activate the Ca\(^{2+}\) influx channel transient receptor potential melastatin 2 (TRPM2) at the cell plasma membrane (PM), in synergy with ADPR (49) (FIGURE 3). Although physically separated, the Ca\(^{2+}\) stores in the ER and the EL can interact: in fact, Ca\(^{2+}\) released from the EL stores can be sequestered by the ER stores, boosting the latter for enhanced release of Ca\(^{2+}\) through RyRs by cADPR (FIGURE 3).

Further evidence for this view is that stimulation of the T-cell receptor-CD3 complex results in rapid NAADP formation in response to a stimulus. By contrast, an increase in cADPR concentration is delayed, which indicates that NAADP serves as a second messenger initiating role in T-cell Ca\(^{2+}\) signaling (50, 51).

It was initially thought that CD38 operated exclusively in the extracellular compartment containing the physiological substrates, with the products of the catalytic reaction being used inside the cell, creating a sort of topological paradox. Most immune and nonimmune cells express CD38 on the
surface, with the catalytic domain exposed to the outside. These are referred to as type II CD38. Extracellular NAD$^+$ and NADP$^+$ substrates are metabolized by type II CD38 into cADPR/ADPR and NAADP, respectively, acting in an autocrine mode for signaling (25). Substrates share the mechanism for extrusion either by cell lysis under pathological conditions (e.g., inflammation or oncogenesis) or by transportation through the connexin 43 (Cx43) hemichannels (52). Extracellular metabolites are able to reenter the cell using concentrative nucleoside transporters, where they can also act in a paracrine mode on neighboring cells (53). Type II CD38 is also compartmentalized in the EL/RE organelles (54). Accordingly, the intracellular exploitation of type II CD38 metabolites targeting intracellular Ca$^{2+}$ release machineries, give rise to this topological enigma, only recently partially disentangle (55).

These studies demonstrated the existence of a CD38 protein (referred to as type III CD38), whose catalytic domain faces the intracellular compartment. This functionally active molecule is expressed on the inner cell membrane and in the ER and produces intracellular cADPR with high efficiency (56). Type III CD38 is a nonglycosylated protein and thus devoid, in contrast to type II-CD38, of disulfide bridges (55), but whose formation during folding allows cADPR generation. The autocrine/paracrine mechanisms of type II- and type III-CD38 work in concert to harmonize the paradoxical regulatory issue. In mechanistic terms, and in line with previous observations on the pH dependency of CD38, the resulting cADPR and ADPR products are synthesized at neutral pH, while NAADP is synthesized at acidic pH (51, 57). The EL is highly acidic and therefore not favorable for the cyclase activity of CD38, thus pointing to EL the cellular compartment for the biogenesis of NAADP (FIGURE 3). Extracellular NAADP can also be transported into the cell cytoplasm, where NAADP, either from inflow or in situ generated, is delivered to the EL to induce Ca$^{2+}$ release from stores in response to various physiological stimuli (58). Additional findings were that cells expressing type III CD38 had the highest cADPR levels after induction by cytokines, and thus may be directly responsible for producing intracellular cADPR (59), targeting RyRs in the ER (FIGURE 3).

### 2.1.2. CD38 as a receptor.

Functional and structural data indicate that the promoter region of the human CD38 gene, located at chromosome 4, is regulated by several nuclear factors including the retinoic acid receptor (RAR$x$), retinoic acid-responsive element, glucocorticoid-responsive element (GRE), interferon-responsive element (IFN), and NF-κB (60). Furthermore, CD38 expression is induced and regulated by several soluble factors including cytokines and chemokines (61). The role of CD38 as a receptor was confirmed by comodulation experiments, indicating that the molecule displays lateral associations with other molecules sharing signal pathways. In this way, CD38 overcomes the steric hindrance of its very short cytoplasmic tail by interacting symbiotically with skilled receptors on different immune cells [e.g., T lymphocytes, natural killer (NK) cells, and monocytes] (36). The CD38 protein, assembled as a transmembrane receptor, influences both innate and adaptive immune responses by regulating the trafficking of cells (e.g., macrophages, dendritic cells, lymphocytes, and neutrophils) to the sites of inflammation (62). For migration purposes, CD38 expresses two hyaluronate-binding sites in the extracellular domain (63) and thus interacts with its counterreceptor CD31 (platelet/endothelial cell adhesion molecule-1 (64, 65). CD38 is also related to T-helper type 1 polarization and dendritic cells (DCs) chemotaxis (62, 66).

#### 2.2. The CD38 Catalytic Receptor and Inflammation

In addition to being a surface cell differentiation and activation marker, it was later observed that CD38 can induce the release of different cytokines after specific agonistic monoclonal antibody (mAb) ligation (61). Conversely, it was observed that IFN-γ alone induces CD38 in human macrophage/monocytes (67) and that vitamin D causes myeloid cells to express surface markers of monocytic cell differentiation (e.g., CD38, CD14, and CD11b), converting macrophages into potent immunosuppressive cells (68). CD38 activity in human macrophages is prevalently detected intracellularly, with its primary function being 1) the performance of cADPR and NAADP for Ca$^{2+}$ regulation; 2) the contribution to inflammatory cytokine secretion, and 3) cooperation in reprogrammed metabolic adaptations (e.g., increased glycolytic activity). Taken together, these data are consistent with the role of inflammatory marker for human macrophage/monocyte CD38 in inflammatory processes (69).

Type 1 interferons (IFNα/IFNβ) as well as other factors such as the RAS component ANG II (via activation of NF-κB) upregulate CD38 expression (70, 71) in proinflammatory cytotoxic human M1 polarized macrophages but not anti-inflammatory M2 (72–74). In turn, signaling through NF-κB, likely the primary transcription factor involved in the appearance of most of the proinflammatory genes, is amplified by CD38 (75). Furthermore, CD38 overexpression promotes a glycolytic adaptation in human macrophages (73).

Related to this metabolic event, nucleotides (such as NAD$^+$ and ATP) are released during the early phase of viral inflammation, acting as danger signals that alert the
immune system through binding to P2 type of purinergic receptors (P2Rs) (76, 77). Consumed nucleotides are rebuilt by enzymatic salvage pathways to restore extracellular homeostasis. As shown in **FIGURE 4**, NAD\(^+\) scavengers are nucleotide-catabolizing ectoenzymes (e.g., CD38/NADase, CD203a/ectonucleotide pyrophosphatase-phosphodiesterase, and CD73/5\(^{-}\)-ectonucleotidase) that generate adenosine (ADO) as end product, which can reenter the cell to reconstitute the pool of purine nucleotides (8, 36). Alternatively, extracellular ADO, and probably inosine (INO), activate purinergic P1 receptors (P1Rs) to dampen excessive inflammation, thus opposing inflammatory functions of P2R signaling (78).

Nucleotides released during viral inflammation also exert immunoregulatory roles in vivo (1, 45). For instance, macrophages not only express ACE2 but also high levels of CD38, the main consumer of human NAD\(^+\). A reasonable model is that in hyperstimulated macrophages, the NLR family pyrin domain containing protein 3 (NLRP3) inflammasome can be directly activated by SARS-CoV-2 via a CD38-mediated Ca\(^{2+}\)-dependent mechanism. This was posited during 2015 SARS epidemic (79).

A preliminary conclusion is that CD38 is involved in specific steps of viral inflammation by modulating immune response and by regulating Ca\(^{2+}\) signaling in different cell populations and tissues.

### 2.3. The CD38 Catalytic Receptor and Immune Response

The immune system exploits cell and humoral responses to attack viruses. Of all the various steps in COVID-19 immunity (80), here we analyze those potentially linked to CD38.

In SARS-CoV-2, innate immune response is activated when macrophages encounter viral pathogen-associated molecular patterns (PAMPs) from invading SARS-CoV-2 ss-RNA. PAMPs upregulates CD38 and activates innate immune pathways through Toll-like receptors (TLRs) and NLRP3 inflammasome activation (81). Downstream signaling drives the secretion of a range of proinflammatory cytokines, including IL1-\(\beta\), IL1RA, IL-6, IL-7, IL-18, IL-10, IFN\(\gamma\), and TNF\(\alpha\) (82). This leads to rapid recruitment of monocyte/macrophages to the lung in early phases of infection. The successive production of IFN\(\alpha\)/IFN\(\beta\) limits propagation of the virus (83). At the

---

**FIGURE 4.** Pathways for NAD\(^+\) biogenesis and consumption. Intracellular NAD\(^+\) is synthesized either from tryptophan (de novo pathway) or from nicotinamide riboside (NR), nicotinamide (NAM), or nicotinic acid (NA) (salvage pathways). Once internalized, NAM and NR merge at the step of nicotinamide mononucleotide (NMN), which is converted into NAD\(^+\). NA is converted to NA adenine dinucleotide (NAAD) and then to NAD\(^+\). Depletion of NAD\(^+\) is associated with enzymatic reactions that take place intracellularly: CD38/NAD\(^+\)-glycohydrolase, poly(ADP-ribose)polymerases (PARPs), and Sirtuins. NAD\(^+\) is also used as a cofactor by S-adenosylmethionine (SAM) for 1) the generation of intracellular adenosine from methionine, and 2) the activity of a viral SAM-dependent methyl transferase (MTase) enzyme, composed by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nonstructural proteins (nsp) 14 and 16, active for viral cap formation during viral replication. Extracellular NAD\(^+\) is metabolized by CD38, the first enzyme within a purinergic signaling cascade that, together with CD203 and CD73, generates exogenous adenosine.
same time, IFNs modulate the adaptive immune responses by increasing the expression of antiviral specific genes (ISGs) in neighboring cells (84).

For their part, CoVs escape immune responses by provoking a disbalance between antiviral and proinflammatory responses. It is hypothesized that SARS-CoV-2 exploit the upregulation of host ACE2R by increased expression of ISGs and CD38 in human lung epithelial cells, to enhance viral infection (7, 85). Other steps facilitating SARS-CoV-2 infection involve the suppression of IFN production by releasing damage-associated molecular patterns (DAMPs) into the extracellular environment and IL-1β amplifying in downstream signaling (81). Other cell types, including endothelial cells, are indirectly activated by circulating IL-6 and soluble IL-6 receptor complexes, with massive cytokine production and cell apoptosis (86). Apoptotic-infected endothelial and epithelial cells contribute to tissue inflammation by releasing damage-associated molecular patterns (DAMPs) into the extracellular environment and IL-1β upon NLRP3 inflammasome activation. The overproduction of IL-1β then activates macrophages, NK, and T cells, amplifying inflammation and facilitating tissue infiltration through the upregulation of adhesion molecules by lung endothelial cells. Indeed, IL-1β increases hyaluronan synthetase levels, and consequently matrix hyaluronate (87), which is reported as an adhesive ligand of CD38 (63).

2.4. The CD38 Catalytic Receptor in Cell Adhesion and Thrombosis

Upregulation of molecules involved in cell adhesion (i.e., CD38 and CD31) has twofold consequences: lymphopenia and thrombosis, which are both predictors of COVID-19 disease severity (88, 89).

Viral infection inducing excessive antigenic stimulation may cause a drastic decay in circulating immune cells with progressive T-cell anergy or exhaustion (90, 91). Mechanisms leading to lymphopenia can be due to 1) a direct effect on lymphocytes or indirect action destroying lymphatic organs; or 2) a disordered inflammatory cytokine reaction leading to lymphocyte apoptosis (92). CD38/NADase might be directly involved in these events. Indeed, CD38 activation by increased ANG II levels may intensify NAD+ depletion. In turn, this condition affects NAD+-dependent enzymes (e.g., Sirtuins and poly(ADP-ribose) polymerases [PARPs]), which are known regulators of cell viability and death (44).

CD38 express by immune cells is reported as interacting with extracellular matrix hyaluronate and with CD31 (64). The balance between dissemination of immune cells (CD38+ cells) to peripheral blood and tissue retention in the respiratory tract is the result of the interplay between these molecules. Indeed, CD38+ promotes cell attachment to hyaluronate, whereas the interaction of CD38 with CD31 on endothelial cells results in retention prevalently in tissues (in the lungs) and a weaker egress of immune cells to the peripheral blood, as has been shown in a leukemia model (93). Therefore, the trapping of exhausted T lymphocytes in the lungs may contribute to lymphopenia. Lastly, lymphocyte functions may be impaired by products derived from metabolic disorders, such as lactic acidemia (94) (vide infra).

COVID-19 comorbidities feature elevated levels of the extracellular plasmin, a protease involved in degradation of the fibrin matrix formed by the activity of thrombin during the process of thrombosis (88, 95). Furthermore, dysregulated ANG II due to loss of ACE2R by SARS-CoV-2, results in increased signaling through 1) purinergic P2R(s), and by 2) the serine protease thrombin, leading both to platelet activation and thrombosis, emerging features of COVID-19 (88). Thrombin induces platelets activation via mobilization of intracellular Ca2+, a process mediated by CD38 metabolic products, cADPR and NAADP (96). Moreover, as a platelet agonist, thrombin stimulates the association of CD38 enzymatic activities with the platelet cytoskeleton (97). As said, inflammatory conditions observed in COVID-19 are associated with the extracellular release of nucleotides, acting as ligands of purinergic receptors (88). P2Rs signaling is a key mechanism for platelet activation, which contributes to thromboinflammation and fibrosis (98). Indeed, an inflammatory P2R-associated release of IL-8 and elastase from neutrophils contributes to the pathogenesis of chronic obstructive pulmonary lung disease (COPD) (77). This finding suggests that nucleotide-activation of P2Rs can lead to inflammation, tissue fibrosis, as well as to a NAD+-dependent Sirtuins inhibition associated to ROS production (98). Purinergic and thrombotic-mechanisms can synergistically be activated during thrombosis (99). Therefore, antagonistic drugs that target thrombin or P2Rs may provide a useful therapy to blunt inflammatory diseases, such as COPD and COVID-19 (88). Similarly, catalyzing the conversion of ATP/NAD+ to ADO, thus terminatizing P2R effects, are already exploited in the treatment of inflammatory conditions in human patients (100).

Consequently, CD38 may serve as a molecular target for 1) immune cell trapping in the lungs and 2) monitoring a downmodulation of macrophages during viral respiratory diseases (1). Furthermore, it may help track 3) lymphopenia and thrombosis resulting from uncontrolled activation of immune cells.

2.5. The CD38 Catalytic Receptor and Immuno-Metabolic Adaptations

2.5.1. The NAD+ metabolome.

The metabolism of NAD+ (NAD+ metabolome) is involved in a variety of normal biological processes (101). As a
tunable component of innate immunity, the NAD$^+$ metabolome has become a target for therapeutic modulation of the NAD$^+$ status, which potentially curbs viral infection (102). Observations support the view that the immune response to viral infections is linked to the NAD$^+$ metabolome of the infected cells, as reported in Herpes virus and HIV-1 (103, 104).

NAD$^+$ operates both intra- and extracellularly (FIGURE 4). Extracellularly, NAD$^+$ elicits signals acting as a cytokine or serves as the substrate for a chain of nucleotidases led by CD38 to convert it to ADO, a nucleoside involved in the control of inflammation and immune responses (8, 105). The extracellular conversion of NAD$^+$ varies significantly according to the tissue environment or health conditions. Indeed, pathological settings are characterized by the NAD$^+$ metabolome acting as a target of multiple immunometabolic adaptations, as confirmed by a dysregulated NAD$^+$ gene system upon in vivo SARS-CoV-2 infection (106). Analyzes of RNaseq data involved comparison with a gene set representative of the NAD$^+$ transcriptome coding for the enzymes responsible for 1) NAD$^+$ biosynthesis, 2) NAD$^+$ phosphorylation to NADP$^+$, and 3) NAD$^+$ consumption. First, primary cells infected by SARS-CoV-2 feature more than threefold depression of cellular NAD$^+$ and NADP$^+$, as compared to control cells. CD38 (and its paralogue CD157) (36) are overexpressed (>2.5- and >1.5-fold, respectively) by infected human lung. CD38 upregulation and NAD$^+$ depletion are paralleled by activation of the IFN-induced (mono) ADPribosyl transferase (mART) (107). The SARS-CoV-2 genome encodes for nsp (15): among them, an ADP-ribosylhydrolase (ARH), an enzyme required for virulence that removes ADPR from proteins ribosylated by mART (FIGURE 4). (108, 109).

The NAD$^+$ metabolome is linked to the RAS/ACE2 system. On one side, NAD$^+$ biosynthesis is regulated by the nutritional supply of NAD$^+$ precursors through de novo pathway, which uses tryptophan (Trp), and the salvage pathway, which uses NAM/NA/NR (all referred to as vitamin B3), as primary sources (FIGURE 4) (46). Trp catabolism in chronic viral infections reduces circulating levels of NAD$^+$, resulting in exacerbated inflammation and low CD4$^+$ T-cell recovery (110). On the other, the RAS system exerts a protective role in acute lung injury via ACE2 and by modulating Trp levels in peripheral blood (17). Indeed, in aminoacidic malnutrition, increasing Trp and vitamin B3 sources restores ACE2 activity and prevents worsening of inflammation (111). In conclusion, epigenetic and pharmacological evidence links the NAD$^+$ metabolome to the RAS/ACE2 system. CD38 is activated by ANG II after ACE2 viral blocking (FIGURE 18), and once the human lungs are infected, the virus may even try to suppress NAD$^+$ production by the cells (112). NAD$^+$ depletion leads to suppression of both mitochondrial NAD$^+$-dependent signaling and resolution of inflammation (113).

Metabolomic studies indicate that under nonredox conditions NAD$^+$ is mainly consumed by CD38/NAD$^+$-glycohydrolase and NAD$^+$-dependent Sirtuins and PARPs (FIGURE 4) (101). Because of such continuous NAD$^+$ enzymatic degradation, its metabolite NAM and the other amidated and deamidated NAD$^+$ sources (e. g., NR, NMN, and NA) needed for resynthesis of NAD$^+$ are perforce scavenged (44). In fact, the antiviral host defenses mounted by NAD$^+$-dependent PARPs and Sirtuins are removed by depleting the cell of NAD$^+$ (1, 44). This is supported by mice models showing that increased NAD$^+$ levels augment the enzymatic activity of PARPs and Sirtuins, hindering CoV from hijacking the host cellular machinery for replication (114).

CD38 is a crucial regulator of Sirtuins which modulate normal and pathological energy metabolism (115). Sirtuins are dependent on NAD$^+$ biogenesis, and thus regulated by Trp or by nicotinamide phosphatidyltransferase (NAMPT), the rate-limiting enzyme that converts NAM into NAD$^+$ (FIGURE 4). Sirtuins and NAMPT participate in macrophage antiviral activity (116). In addition, CD38 activates the Sirtuin/NF-κB pathway in a NAD$^+$-dependent manner, since CD38 blocking increases NAD$^+$ levels and Sirtuin-1 activity in the nuclear, cytoplasmic, and mitochondrial compartments (26, 117). The pharmacological inhibition of NAMPT and Sirtuins, components of the macrophage IFN antiviral cascade, promotes growth of cytomegalovirus in both fibroblasts and macrophages (116). The central role of the NAD$^+$ metabolome in these cells is further supported by the notion that extracellular NAMPT behaves as a DAMP (118), which is elevated in COVID-19 patients with comorbidities (119).

The NAD$^+$-consuming enzyme PARPs and the aryl hydrocarbon receptor (AhR) are overexpressed in COVID-19 pathophysiology and in other lung conditions (RSV and COPD) (120, 121). Endogenous AhR ligands include Trp metabolite quinolinic acid in the de novo pathway and NA and NAM in the salvage pathway of NAD$^+$ biogenesis (FIGURE 4). As a transcription factor, AhR is involved in microbial defense, cell proliferation, immunity and NAD$^+$ metabolism (120). AhR targets NAD$^+$ metabolome functional elements such as CD38 and PARPs that are regulating glucose and lipid metabolism via Sirtuins. Deregluation of these pathways may facilitate COVID-19 and age-dependent pathologies (122). Indeed, a proinflammatory milieu leads to upregulation of the AhR which in turn activates PARPs. Mucin overproduction by lung epithelial cells triggered by IFN-signaling thickens the blood-air barrier and leads to hypoxia (123). Because mucin upregulation is driven by AhR, this factor involved in NAD$^+$ homeostasis in cooperation with CD38,
PARPs and Sirtuins, is a potential target for the treatment of hypoxia in COVID-19 patients (124).

Overexpression of CD38 and PARPs in COVID-19 causes cell death mainly by depletion of NAD$^+$ (125). NAD$^+$ boost improves blood flow and vascular vitality by promoting Sirtuins dependent increase of the levels of hydrogen sulfide (H2S), an endothelial signal regulator of NAD$^+$ levels (126, 127). Since H2S intracellular activity ensures vascular repair after injury, the relevance of the integrity of the NAD$^+$ metabolome should be considered in an eventual SARS-CoV-2 infection of endothelial cells, known to express ACE2 receptors (128).

Oral administration of amidated NAD$^+$ precursors (NR, NAM, and NMN) has been demonstrated to be the most effective approach to replenishing NAD$^+$ levels in vivo. Of these NAD$^+$ precursors, NR has been shown to have anti-inflammatory effects in different disease conditions in both preclinical and clinical settings (129). Currently, a clinical trial of NR as a therapeutic option in COVID-19 patients is ongoing (130).

NAM is a potent PARPs inhibitor that boost NAD$^+$/NADP$^+$ synthesis. Hence NAM reverses lung injury caused by ischemia, inhibits proinflammatory cytokines and is effective against HIV-1 infection (119, 122). Another aspect of NAM effects that is relevant to the metabolome rewiring of NAD$^+$ is their contribution to maintaining homeostasis through the involvement of gut microbiota in NAD$^+$ biogenesis (131). NAM suppliers (such as NR and NMN) are thus potential candidates for use in COVID-19 treatment by replenishing NAD$^+$ levels (45, 125, 129). NMN plays an anti-inflammatory role in preclinical models decreasing the levels of lactic acidosis and IL-6. By reducing IL-6, NMN improves shock-induced hyperglycemia, reducing inflammation (45).

All of the evidence seems to confirm that key events of the biosynthesis and consumption of NAD$^+$ play significant roles in the antiviral immune response. Consequently, NAD$^+$ refueling by modulating the biosynthetic pathways or, alternatively, by reducing NAD$^+$ consumption (117) may be of help in controlling the hyperimmune response to SARS-CoV-2 infection.

### 2.5.2. Alternative NAD$^+$-consuming enzymes.

CD38 consumes NAD$^+$ in multiple ways, such as by 1) mobilizing extracellular or intracellular NAD$^+$ pools, depending on its membrane topological conformation (55), and by 2) degrading extracellular NAD$^+$ to generate NAM, which can cross the plasma membrane and be converted to NMN and NAD$^+$ through NAMPT and NMNAT (33, 46). Although CD38 is the major ectoenzyme responsible for NAD$^+$ metabolization in mammalian tissues (36), there is evidence for cADPR and NAADP generation by other molecules. Indeed, depletion of extracellular NAD$^+$ also occurs through the highly conserved CD38 homolog CD157/Bst1, a molecule that, however, exhibits very low NAD$^+$-consuming activity (36). Another ectoenzyme that degrades extracellular NAD$^+$ is CD73/e5’NT, which successively metabolizes NAD$^+$ to NMN, and further to NR (132), to support intracellular NAD$^+$ biosynthesis. In particular, the cADPR levels in the brain of CD38-KO mice are consistent (66), indicating the existence of a cADPR-synthesizing enzyme. This enzyme was identified in the brain as SARM1 (sterile alpha and Toll/interleukin receptor motif-containing protein 1) (133, 134), which features NAD$^+$-cyclizing activity much higher than CD38, already known by its low (2%) cADPR yield after NAD$^+$ dismantling activity (57). The SARM1 molecule has no sequence similarity but has the same cytosolic orientation as type III CD38, and is able to catalyze the same set of NAD$^+$-depleting multireactions after being activated by endogenous NMN (33, 133, 135). CD38 is the main enzyme involved in the degradation of NMN in vivo (33). As an NMNase, CD38 controls the paracrine availability of extracellular NMN (but not NR or NA) (45) and thus influences the accessibility of NMN to SARM1.

For extracellular signaling activities in immune cells, NAD$^+$ uses purinergic P1 and P2 receptors and metabolizing ectoenzymes (CD38, CD203a, and CD73) (8). Notably, recent data showed that CD203a/ENPP1 also metabolizes 2’,3’-cyclic GMP-AMP dinucleotide (cGAMP), generating AMP and GMP (136), all acting as modulators of immunity (137). Indeed, DNA/RNA released in the cytoplasm during viral infection activates a cyclic GMP-AMP synthase (cGAS), forming cGAMP from cAMP/cGMP. Interesting, cGAMP is an activator of STING (stimulator of interferon genes), which integrates together with SARM1, a subset of Toll-Interleukin receptor (TIR) domain-containing proteins. Both proteins can degrade NAD$^+$ by acting as NAD$^+$-hydrolases producing ADPR and NAM, thus supporting TIR domain-mediated sensing of innate immunity (138). Links between the cGAMP-STING pathway with CD203a and NAD$^+$ have emerged whereby the hydrolysis of cGAMP by CD203a attenuates cGAS-STING signaling and, therefore, the depletion of NAD$^+$ (139). Consequently, inhibitors of CD203a (140) could help to combat viral activity by inhibiting cGAMP degradation and extracellular NAD$^+$ consumption.

New aspects of NAADP generation were reported indicating that the CD38-base exchange reaction is not the enzyme responsible for in vivo generation of this nucleotide in human myometrial cells (141). Of note, NAADP-dependent generation and the release of Ca$^{2+}$ were experimentally evidenced at physiological pH in response to histamine and oxytocin as modulators and with the use of pharmacological inhibitors. On the other hand, an insulin sensitization by NAADP was reported to
be produced through both CD38-dependent and CD38-independent pathways (142). CD38 is still the only molecule fully characterized as consuming NAD\(^+\) and synthesizing messengers (cADPR, ADPR, and NAADP) in a variety of cells (36) (and references herein).

A closer look at NAD\(^+\)-consuming enzymes therefore reveals differences in chemical structure, tissue distribution, compartmentalization, metabolism, substrate affinities and response to specific modulators, which might affect the performance among redundant enzymes. A sensitive proxy for hierarchical selectivity among NAD\(^+\)-consuming enzymes would be the level of physiological effects of each enzyme in different tissues and their different effects in clinical trial outcomes.

2.5.3. Metabolic acidosis and adenosinergic activities.

Cell homeostasis depends on adenine nucleotides (e.g., NAD\(^+\)/NADP\(^+\) and ATP). They produce energy on the one hand and generate anabolic products and second signal messengers (46) on the other. The production takes place in the cytoplasm, and glucose is transformed into pyruvate. Under normal oxygenation, pyruvate enters the mitochondria, where it undergoes enzymatic processes generating large quantities of ATP. In hypoxic cells (e.g., inflammation, tumors), pyruvate cannot enter the mitochondria but is converted to lactic acid. This step is marked by the generation of low ATP and higher production of NAD\(^+\). Lactic acid and NAD\(^+\) are transported to the extracellular environment, where the dinucleotide is consumed by CD38 to trigger intercellular communications and signaling mediated through nucleotides (i.e., cADPR, ADPR, and NAADP) and nucleosides (i.e., ADO) (143).

Patients with severe COVID-19 have been found to have high levels of lactic acid, leading to suppressed proliferation and functions of T lymphocytes (exhaustion). The results are a paresis of cellular and humoral immunities (144). Natural killer (NK) cells exposed to an acidic pH via lactic acid are driven to a state of anergy (145), while acidic conditions inhibit the maturation of DCs and antigen presentation (146). In contrast, myeloid-derived suppressor cells (MDSCs) and regulatory T lymphocytes (Treg) are functionally active in acidic environments (147). If these conditions of the immune compartment correlate in vivo with the viral infection, it is possible that a dysregulated inflammatory response may derive from metabolic acidosis (148). Similar observations have been made in multiple myeloma and severe bacterial sepsis (143, 149).

The dysregulated metabolic conditions observed during progression of SARS-CoV-2 infection may be brought about by the decay of CD4\(^+\) Treg cells, which influences hyperinflammation through production of anti-inflammatory ADO (150). ADO has a central role in mediating the pathophysiology of chronic lung diseases (151). The first evidence of a noncanonical adenosinergic pathway involving CD38 activity was described in the human Jurkat T-cell line (8). Recent studies have determined that NAD\(^+\) serves as a precursor to form ADO in the lungs where the dinucleotide is released from human airway epithelial cells and that ectoenzymes (CD38/CD203a/CD73) present in lung cells have the ability to metabolize NAD\(^+\) to ADO (152).

All lung NADase activity was impaired in CD38KO mice as well as in lung membranes suggesting that CD38 is the primary NADase in parenchymal lung cells, whose expression is upregulated by TNF-\(\alpha\) and inhibited by 78c, a pharmacologic blocker of CD38 enzymatic activity (153). The functional impact of the adenosinergic pathway led by CD38 in the lungs may be greater under pathologic conditions, given the overproduction of ADO and the high expression of its receptors in patients with chronic obstructive pulmonary diseases (COPD) (154), confirming the potential therapeutic value of CD38 in lung pathologies (e.g., acute respiratory distress syndrome (ARDS) and COVID-19).

Generated via a cascade of events triggered by the metabolization of NAD\(^+\) by CD38 or via ATP degradation (8, 155), ADO regulates innate and adaptive immune responses by stimulating A2A and A2B P1 purinergic receptors (76). ADO ligation to A2A leads to inhibition of the cytolytic activities of effector T lymphocytes (150) and IFN-\(\gamma\) release by NK cells (105). Moreover, when extracellular ADO levels are high, ligation of A2B (the low-affinity ADO receptor) influences the antigen-presenting activity of DCs (156) and activates normal infiltrating cells that block the immune response (such as Tregs, MDSCs, and macrophages). These effects lead to an established peripheral tolerance (151). Accordingly, extracellular ADO may act in diseases with essential inflammatory pathogenic components (e.g., tumors and COVID-19) as a negative immune checkpoint molecule (119, 143).

At early stages of COVID-19, a severe hypoxia may help induce physiological tissue-protecting mechanisms. If left unchecked, they may damage local host tissues. In this sort of scenario, ADO accumulates in the extracellular space of tissues under hypoxic conditions and is able to inhibit the acute inflammatory process via A2A and A2B ADO receptor engagement on immune cells (157, 158). Downstream increase of intracellular cAMP, which in turn inhibits NF-\(\kappa\)B-driven inflammation, reduces the damage due to an overactive immune system (78). However, SARS-CoV-2 induces a host proinflammatory critical life-threatening response, which eventually damages lung epithelial
and endothelial cells, impairing the exchange of O₂ and CO₂ (124). This immune response imbalance induces ARDS, which results in a massive release of inflammatory cytokines or cytokine storm syndrome (CSS).

2.5.4. Ca²⁺-mediated signals.

Mobilization of intracellular Ca²⁺ is a universal signaling mechanism to control proliferation, differentiation, transcription, replication, and metabolism (159).

The endocytic internalization of SARS-CoV-2, the delivery of the viral capsid into the cytoplasm for replication, and the activity of NAD⁺-dependent enzymes, all rely upon Ca²⁺ release from intracellular organelles (11, 106) (FIGURE 5). After viral entry, the pathogen-associated molecular patterns (PAMPs) from SARS-CoV-2 are recognized by TLRs (160). The interaction of the TLRs with NF-κB and the adaptor protein MyD88 induces an IFN-1 innate inflammatory response (161). TLRs, MyD88, and NF-κB expression is downregulated by ANG II receptor (AT₁R) blockers (ARB), reducing inflammation and protecting lung function (162). In this context, it has been previously established that CD38-mediated Ca²⁺ signaling that contributes to ANG II-induced human hepatic fibrosis and increased lung fibrosis in animal models is suppressed by ARB treatment. This adds a reasonable

**FIGURE 5.** Schematic model showing the potential role of CD38-mediated Ca²⁺ signals in COVID-19 pathogenesis. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cell entry/cytososis depends on the angiotensin-converting enzyme 2 (ACE2) catalytic receptor (ACE2R) and proteolytic priming (i.e., TMRPRSS2 peptidase) (shown in FIGURE 1). ANG II binds to the ANG II receptor (AT₁R) to induce activation of either type II- or type III-CD38 catalytic receptor, which in turn stimulates Ca²⁺ release through 2-pore channel (TPC) and ryanodine receptor (RyR). Ca²⁺ influx through TRPM2 channels also cooperates to provide a high concentration of Ca²⁺ in the cytosol. The overload of cytosolic Ca²⁺ is involved in the activation of the inflammatory cytokines or cytokine storm syndrome.
evidence in favor of the therapeutic use of ARB in SARS-CoV-2 infection (163, 164).

Activation of CD38 triggers a NAADP/cADPR-Ca\textsuperscript{2+} signaling pathway (FIGURE 5). NAADP is formed by CD38 catalysis at acidic pH by the exchange of the base NAM of NADP\textsuperscript{+} with NA and localized in EL stores (40, 57). In fact, blocking acidic EL stores by inhibiting the vacuolar H\textsuperscript{+}-adenosine triphosphatase (ATPase) with baflofimycin abrogated NAADP induced Ca\textsuperscript{2+} signaling (165). Downstream signaling then initiates DNA transcription for activation of ISGs controlled by the NF-κB transcription factor and of the NLRP3 inflammasome (166). The CD38/NAD\textsuperscript{+} pathway is found at the crossroads between adaptive (i.e., activation of immune cells) and innate immune (i.e., type I IFN-dependent anti-viral, the oxidative burst and the proinflammatory responses) defenses. The CD38-induced opening of intracellular Ca\textsuperscript{2+} channels promotes activation of inflammatory and anti-viral processes (167). However, the process of Ca\textsuperscript{2+} mobilization from intracellular stores is exploited by SARS-CoV-2 to trigger the production of highly inflammatory cytokines and profibrotic signals.

This proposed mechanistic model for COVID infection and disease (FIGURE 5) focuses on the CD38/NAD\textsuperscript{+} axis, which is at the junction between the oxidative burst (ROS), ISGs, and the hyperinflammatory response. This axis may therefore contribute to viral immunopathology by producing CD38-induced second messengers (cADPR, NAADP, and ADPR) with the opening of the RyRs and TPCs-Ca\textsuperscript{2+} channels and through Ca\textsuperscript{2+} influx via TRPM2. Furthermore, the accumulation of intracellular Ca\textsuperscript{2+} released from EL and ER stores would end with local production of ROS. The outcome would be a contribution of the CD38/NAD\textsuperscript{+} axis and Ca\textsuperscript{2+}-mediated signals to the COVID-19 process culminating in a cytokine storm syndrome (CSS) and tissue fibrosis.

3. CD38 AND RELATED MOLECULAR PATHWAYS MAY HELP MITIGATE COVID-19 EFFECTS

3.1. Viral Endocytosis and Ca\textsuperscript{2+}-Mediated Signals

During viral Ca\textsuperscript{2+}-dependent endocytosis, the S protein is cleaved by TRPMS2 and by other human enzymes at furin sites [i.e., furin (which is abundant in respiratory tract), and plasmin (involved in fibrinolysis)] to become active to bind to ACE2R. Noteworthy, comorbidities feature elevated levels of the extracellular protease plasmin (88, 95). Following this line, it has been hypothesized that a fibrinolytic inhibition may prove a promising therapeutic target for COVID-19 (95). Virus entry into cells can be also impeded by soluble human recombinant ACE2, which acts as a decoy receptor to hijack the virus from the host cellular receptor in very early stages of SARS-CoV-2 infections (168) and, downstream viral infection, by antagonists of Ca\textsuperscript{2+}-mediated signals (167). Among these, chloroquine and hydroxychloroquine interfere with Ca\textsuperscript{2+} release from acidic EL (and with the terminal glycosylation of ACE2), thus impairing virus-receptor endocytosis in SARS-CoV-2 infection (10, 11, 169). Cell infection generally depends on Ca\textsuperscript{2+} release gated by EL TPCs (170). As with MERS, NAADP-dependent Ca\textsuperscript{2+} signaling regulates SARS-CoV-2 translocation from the cell surface to the cytoplasm (171). After CD38 activation, TPCs activity is known to 1) alter endolyosomal Ca\textsuperscript{2+} content and pH (48), and to 2) regulate the activity of furin required for proteolytic activation of the viral S protein, fusion activity and cytoplasmic translocation (11, 12). Therefore, direct antagonists of cADPR/NAADP would prevent viral entry in the cell. Indeed, blocking TPCs by the inhibitor tetrandrine strongly inhibited entry of SARS-CoV-2 mediated by S protein (172).

3.2. CD38 Expression and Regulation of Intracellular Ca\textsuperscript{2+} Stores

Viral infection awakens different pathways that induce inflammatory conditions. One of these works by activating CD38. TPCs and RyRs are controlled by CD38 and contribute to Ca\textsuperscript{2+} signals responsible for inflammatory activation (48, 170). Thus inhibition of NAD\textsuperscript{+} and NAADP catabolism mediated by CD38 might interfere with SARS-CoV-2 infection and the inflammatory response.

EL is an acidic compartment ruled by a proton pump. CoV entry is blocked when the pump is inhibited (e.g., by baflofimycin) (173). Given that endosomal acidification depends on proton pump/Ca\textsuperscript{2+} release activities and that the entry of SARS-CoV-2 is reduced when TPCs are inhibited (172), it would be of considerable interest to know whether modulation of the NAADP-dependent Ca\textsuperscript{2+} signaling generated by CD38/NADase activity interferes with the SARS-CoV-2 pathological process.

The inflammatory conditions and the status of macrophages have been monitored using two types of CD38 inhibitor molecules. The first (kuromanin, apigenin, and rhein) originates from the flavonoid and anthraquinone families (174, 175), while the second (LX102) is a specifically designed chemical compound (176). When applied to explore the functional role of CD38 in macrophages, these treatments suppressed the IL-6 and IL-12 molecules, as well as pathways such as NF-κB, P2Rs, caspase-1, and ERK1/2, all of which are involved in the promotion of inflammation by CD38 (71, 177). Inhibition of CD38 may therefore increase NAD\textsuperscript{+} levels and reduce proinflammatory
macrophage polarization, thus improving related pathologies (178, 179).

cADPR, ISGs, and production of IFN-β are greatly reduced by 8-bromo-cADPR, a cADPR antagonist, and by kuromanin (1, 174). Both drugs block the release of intracellular Ca^{2+} mediated by the CD38/NAD^{+} axis, thus preventing the onset of a hyperinflammatory condition. Furthermore, kuromanin has an antioxidant function. The anti-oxidative effects of scavenging free radicals may also contribute to warding off inflammation. Inhibition of the enzymatic activities of CD38 may therefore be useful in the design of COVID-19 therapeutics.

Severe lung fibrosis in viral respiratory pathologies might be secondary to high expression of CD38 by endothelial cells. On this line, CD38 has been identified as a key regulator of hepatic stellate cells (HSC) activation and reported to increase following the progression of hepatic fibrosis produced as a result of viral infections (180). The fibrotic process in HSC is activated by ANG II and attenuated by angiotensin II receptor type 1 (AT1R) blockers (so-called ARB) (88), premises suggestive that the RAS system plays a major role in multiorgan fibrosis (31). The intracellular Ca^{2+} release-dependent profibrogenic effects of ANG II/CD38, are further supported by the findings of 1) association with increased concentration of transforming growth factor-β1 (181), and 2) ANG II-induced overproduction of extracellular matrix proteins (e.g., hyaluronate). The effects on Ca^{2+} elicited by ANG II can be reduced by inhibiting CD38 with 8-Br-cADPR or NAM (both cADPR antagonists) or with Ned-19 or dipyridamole (both NAADP competitive antagonists) (163, 182).

Furthermore, ANG II-induced Ca^{2+} release is inhibited by staurosporine (a protein kinase C inhibitor) and by scavengers of ROS (183). In addition, NAM prevents tissue damage in animal models with induced lung injury. Indeed, NAM inhibition of CD38 cyclase could attenuate tissue damage induced by Ca^{2+} signaling (184). In fact, NAM is now included among the treatments against COVID-19 (119, 185).

Lung fibrosis secondary to the SARS-CoV-2 virus is reminiscent of the macrophage activation syndrome (186) observed in autoimmune diseases. Examples include systemic lupus erythematosus and rheumatoid arthritis (RA), where CD38^{high} plasma cells play a key role (29). Anti-CD38 mAbs are currently used in the treatment of multiple myeloma (MM), a cancer of the plasma cells, and other hematologic malignancies (187, 188). The results obtained indicate that antibodies also modulate immune cells, including inflammatory monocytes and macrophages. The effects mediated by reacting the catalytic functions and intracellular Ca^{2+} release with CD38 antibodies still need to be evaluated in COVID-19 patients.

In a variety of cell types, Ca^{2+} homeostasis is regulated by the transcription factor early growth response-1 (Egr-1), which promotes Ca^{2+} entry across the PM upon ER-Ca^{2+} store depletion (189). Activation of Egr-1, mediated by inhibition of NAD^{+}-dependent Sirtuins, is critical for the replication of CoV (190). The uptick in the activity of acetylated Egr-1 seen in proinflammatory hyperglycemic atherosclerosis (191) highlights an eventual association between the comorbidities and Ca^{2+}-dependent mechanisms of SARS-CoV-2 infection in determining the aggressiveness of COVID-19 disease.

### 3.3. CD38 and Pregnancy-Associated Immunosuppression in COVID-19

Pregnant women are more susceptible to respiratory pathogens and severe pneumonia because of the conditions of tolerance established between the immune system of mother and embryo (22). In addition to immunogenetic factors, the ectoenzymatic adenosinergic networks working in closed environments metabolize nucleotides (ATP, NAD^{+}), providing nucleosides (ADO, INO) with immunosuppressive potential (8, 192). The existence of these networks and the contribution of ADO-producing ectoenzymes at the maternal/fetal interface have already been highlighted (193). Accordingly, the impact of COVID-19 infection on pregnant women appears to be less severe or similar to that reported for nonpregnant patients who developed COVID-19 pneumonia (194), due to protection of the lungs from CSS brought about by the immune system. Indeed, ADO, acting through the low-affinity A2B ADO receptor, stimulates IL-6 and acute-phase inflammatory proteins, such as C-reactive protein (CRP) production in macrophages and endothelial cells (195). In fact, reported data show that the majority of viral infected pregnant patients had increased IL-6 and CRP (194). A similar trend was reported during the development and progression of MM, where metabolic reprogramming contributes to increasing levels of immunosuppressive ADO (43). This experimental data make it reasonable to speculate that the induction of ADO within the close placental compartment in gestational patients (193) helps mitigate COVID-19 related pneumonia during pregnancy.

### 3.4. CD38 Connections and Pharmacological Control of COVID-19

Promising therapeutic options include neutralizing antibodies, vaccines, antibody transfer from convalescent-phase plasma, antiviral proteases, receptor-blocker inhibitors, and drug repurposing (196). Potential therapies (TABLE 2) include 1) small-molecules and drugs as modulators of the CD38/NAD^{+} axis (e.g., CD38 inhibitors, NAM, dexamethasone), 2) soluble factors such as ADO modulators (209), 3) immunomodulators of CD38.
expression (210), as well as 4) immunosuppressive cells
(e.g., cytokine-induced killer cells and mesenchymal
stem cells) (207, 208).

As previously mentioned, viral infection causes the
blocking of surface ACE2 (ACE2R) facilitating the actions
of ANG II, thus contributing to COVID-19 pathology (18).
It was therefore suggested (199) that an imbalance in the
action of ACE1 (that catalyzes ANG II from ANG I) and
ACE2 (that catalyzes ANG-1–7 from ANG II) may act as
primary driver of COVID-19 pathobiology (FIGURE 1B).

The ACE1/ACE2 imbalance occurs due to the viral inter-
ference in the ACE2 enzymatic activity; thus

Table 2. Summary of experimental drugs with potential use in SARS-CoV-2 infection therapy

| Drugs                                      | Bioactivity                                                                 |
|--------------------------------------------|------------------------------------------------------------------------------|
| Inhibitors SARS-CoV-2 endocytosis          |                                                                              |
| rhACE2 as decoy viral receptor             | Blockage of SARS-CoV-2 cell entry (168)                                      |
| Bafilomycin                                 | Inhibition of Ca\(^{2+}\) release (173)                                      |
| PanMTase inhibitor sinefungin              | Purine adenine metabolism (197)                                             |
| Repurposed drugs (HCQ, CQ)                 | Ca\(^{2+}\) metabolism (169)                                               |
| Modulators of the RAS system               |                                                                              |
| AT\(_1\)R blockers (ARBs)                  | AT\(_1\)R antagonists (162)                                                 |
| ACE1 inhibitors (ACEI)                     | Block the synthesis of ANG II (198)                                         |
| Agonists of MasR                           | Activation of angiotensin protective effects (199)                          |
| Drugs enhancing ACE2 activity              | Restoration of ACE1/ACE2 imbalance (198)                                     |
| Modulators of the CD38/NAD\(^{+}\) axis    |                                                                              |
| Kuromanin, apigenin, rhein, 78c, LX102     | CD38/NADase inhibitors (174–176, 200)                                       |
| NAD\(^{+}\), NMN, Vitamin B3 (NAM, NR, NA), Tryp | Restoration of NAD\(^{+}\) levels (45, 178, 201)                         |
| Dexamethasone                              | Downregulation of CD38 expression (202)                                     |
| Vitamins (retinoic acid, D3)               | Upregulation of CD38 expression (68, 203)                                   |
| NAM, 8Br-cADPR                              | cADPR antagonists (163, 201)                                                |
| Ned19, dipyridamole                         | NAADP antagonists (182, 204)                                                |
| Soluble immunomodulators                   |                                                                              |
| Anti-CD38 mAbs (isatuximab, daratumumab, MOR202, TAK-079) | AllostERIC inhibition of CD38 cyclase activity, cytotoxic effects, and clearance of CD38 + cells (187, 188) |
| Extracellular ADO                          | Protection of ARDS patients from hyperoxygenation damages (205, 206)     |
| Cellular immunomodulators                  |                                                                              |
| Cytokine-induced killer (CIK) cells        | Immunosuppression (207)                                                     |
| Mesenchymal stem cells (MSCs)               | Immunosuppression (208)                                                     |

Each drug is flanked by its mechanism of action controlled by CD38 (details in the text). References are included in brackets. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ADO, adenosine. NAADP, nicotinic acid adenine dinucleotide phosphate; cADPR, cyclic adenosine diphosphate ribose; ACE1, angiotensin-converting enzyme 1; AT\(_1\)R, ANG II receptor; NR, nicotinamide riboside; NAM, nicotinamide; NA, or niCOTINIC acid; Tryp, trypto-
phan; ARDS, acute respiratory distress syndrome.
it reduces ANG-1–7 signaling through its protective MasR (anti-inflammatory, antifibrogenic, and antioxidative). Several approaches have been proposed to treat COVID-19 by restoring ACE1/ACE2 steady-state: among these, 1) AT1R antagonists blockers (ARBs); 2) ACE1 inhibitors; 3) agonists of MasR; 4) recombinant human ACE2 as decoy receptor for the virus; and 5) the development of drugs enhancing ACE2 activity. Reducing ACE1/ACE2 imbalance is predicted to blunt COVID-19-associated morbidity and mortality, especially in elderly and vulnerable patients. Importantly, approved direct ARBs (AT1R antagonists) and ACE1 inhibitors (that block the synthesis of ANG II) can be repurposed to test their efficacy in treating COVID-19 (198). Related to this, it was reported that ANG II induces NAADP/cADPR production via CD38, both essential for the entire ANG II-mediated Ca2+ signaling. Indeed, 8-Br-cADPR antagonizes NAADP production, which was partially blocked by pretreatment with Ned19, a NAADP receptor blocker. Notably, antihypertensive ARB-drugs (i.e., losartan) abolished both ANG II-induced NAADP/cADPR production and Ca2+ increase (204).

The raw material for NAD+ biosynthesis, Trp, decreases as a consequence of health disorders (infection, inflammation), thus leading to reduce NAD+. Such COVID-19-associated conditions were corrected by prescription of NAD+ and/or its precursors (e.g., Trp, NAM, NR, and NMN) together with CD38 inhibitor (117). Moreover, clinical trials with ARDS patients, show indeed that NR depresses levels of IL-6, IL-5, IL-2, and TNF-α (129), supporting the view that NAD+ boosters might be tested for controlling CSS in COVID-19 patients.

In the human respiratory tract, CD38 expression is regulated by TNF-α, an inflammatory cytokine requiring NF-κB activation, resulting in increased Ca2+ responses to agonist corticosteroids (211). Among them, glucocorticoids are used in the management of airway hyperresponsiveness as a result of the negative regulation of genes that promote inflammation or the induction of genes that inhibit inflammation in lung cells (212). The CD38 promoter region includes NF-κB and GRE motifs (36). Thus CD38 increased expression is downregulated by dexamethasone through inhibition of NF-κB and its use in COVID-19 has been proposed (202).

The CD38 gene promoter is also sensitive to vitamins, hormones, cytokines, and different retinoids (36). All-trans retinoic acid (ATRA) is a highly specific inducer of CD38 expression in human myeloid cells mediated through RARα (203). CD38 expressed by immune cells has been induced by ATRA, which promotes adhesion of cells to endothelium, a feature which is responsible for respiratory distress caused by pulmonary interstitial cell infiltration (the so-called RA syndrome) (213). This event could be the first step toward CSS, which is characteristic of the late phases of COVID-19. In line with this observation, anti-CD38 mAbs specifically block binding of ATRA-treated CD4+CD45 T-cells to endothelium (214), mediated by CD38 interactions between leukocytes and the CD31 antigen present on the surface of lung endothelial cells.

Extracellular ADO levels govern the switch from the proinflammatory to the suppressive macrophage phenotype (209). This mechanism provides a rationale for targeting the purine metabolism by methotrexate to boost ADO production and reduce the dominance of proinflammatory macrophages. This happens in rheumatic diseases and, potentially, in COVID-19 patients (119, 215).

SARS-CoV-2 grows in the cell, where its ss-RNA is protected from the host’s cellular innate immunity (14). To ensure ss-RNA integrity, the viral nsp10, 14, and 16 are involved in a cap formation (by methylation of the ss-RNA molecule), a process essential for viral replication in host cells (15). Both nsp14 and nsp16 are methylated by S-adenosylmethionine (SAM)-dependent methyltransferase (MTase) enzymes (FIGURE 4). As a potential target for antiviral therapy, a complex between SARS-CoV-2 nsp10-nsp16 and a purine adenine (sinefungin) becomes a promising therapeutic approach as a pan-MTase inhibitor (197).

4. CD38 IMPACTS BIOLOGICAL MECHANISM (S) THROUGH WHICH SARS-COV-2 TARGETS ELDERLY PATIENTS WITH ACUTE DISEASE

COVID-19 is a biphasic illness with an innate immune response that transitions into an adaptive immune response except in many elderly patients, who develop severe disease with diffuse lung damage (82). Consequently, the high morbidity in the elderly is a striking feature of COVID-19 (216).

4.1. SARS-CoV-2 Cell Receptors and Senescence

Along with ACE-2, CD26 was also proposed as an endocytic cell receptor for SARS-CoV-2, interacting with the S-protein (19). Both ACE2 and CD26 are associated to senescence: ACE-2 is a known inhibitor of cell proliferation and the RAS system is upregulated in senescence (217). CD26 is known to be a bona fide cell surface marker of senescent cells (218). Similarly, myofibroblasts (which are considered to be senescent and profibrotic cells) also overexpress ACE-2 and CD26 (20, 219). Thus increased mortality in elderly COVID-19 patients may be related to an increased number of senescent lung cells, which are the main host target for COVID-19 viral infection (220).
4.2. **Host Defense and Maintenance of a Balanced Inflammatory Response in Aging**

Aging may contribute to the disease scenario through general dysregulation of the immune system, as evinced by increased levels of inflammatory cytokines. Aging is also characterized by increased expression of CD38 in immune cells, resulting in high consumption of the NAD$^+$ substrate (179, 221). The consequence is that NAD$^+$ depletion may exacerbate the cytokine storm and lead to fatal ARDS, which is most common in older COVID-19 patients (102).

Besides NAD$^+$ depletion, ROS detected during hypertension-induced vascular organ damage is also associated with aging endothelial cells and fibroblasts (222). This ROS-dependent cell weakness increases with age, and the same is true in older COVID-19 patients (216). ROS damage means that aging cells are unable to express prosurvival antioxidants and anti-inflammatory genes due to dysregulation of the nuclear factor erythroid 2-related factor 2 (NRF2) signaling transcription factor (223, 224). In addition, silencing of the antioxidant NRF2 gene results in an increased secretion of proinflammatory cytokines, which mediate CoV-induced CSS (225). Moreover, the cellular levels of the NRF2 protein are downregulated during RSV infection, promoting ROS damage by triggering NAD$^+$-dependent Sirtuins deacetylation of NRF2 (226). NRF-2 pathway activation is reduced by the CD38 inhibitor kuromamin, which supports the hypothesis of an involvement of the NAD$^+$ metabolome during viral infections (227).

4.3. **The NAD$^+$ Metabolome in the Elderly**

The question remains as to why NAD$^+$ declines during innate aging and premature aging syndromes (33, 200, 228). The main culprit is CD38, whose expression is physiologically upregulated during aging (117, 229), particularly in cells targeted by SARS-CoV-2 and expressing high levels of CD38 either at protein or mRNA contents (FIGURE 6). These considerations provide support to the pharmacological strategies for reversal of physiological- and pathological-related NAD$^+$ depletion and subsequent metabolic dysfunctions (117).

CD38 regulates NAD$^+$ homeostasis along with other normal and pathological NAD$^+$-dependent cellular processes (26, 118). Among these, CD38 expression is elevated in tissue repair and in fibrotic processes in different organs (31) in a way similar to CD38 upregulation and NAD$^+$ depletion seen in aging. This may suggest intriguing parallels between the biology of aging and fibrogenesis traceable to ANG II/CD38-dependent dysregulation of NAD$^+$ homeostasis (163).

Mitochondrial dysfunction occurs during aging due to reduced synthesis of NAD$^+$ (33, 231, 232), which could impact macrophage function (113). Interestingly, CD38 is highly expressed in proinflammatory macrophages (69), and genetic ablation or pharmacological inhibition of CD38 can reverse mitochondrial dysfunction and reduce inflammatory cytokines in human monocyte/macrophages and in mice (113, 200). Therefore, it is possible that increased circulating levels of inflammatory factors in an imbalanced metabolic cell microenvironment (e.g., in aging, oncogenesis, viral infection) induces CD38 expression, contributing to metabolic dysregulation and in turn promoting the inflammatory function of macrophages in the elderly.

NAD$^+$ depletion, and the deriving metabolic imbalance (e.g., hypoxia, glycolytic metabolism, and increased levels of lactic acid linked to a dysregulation of the immune system) driven by CD38, is believed to play a key role in cellular senescence (44). In senescent cells, DNA fragments of nuclear origin accumulated in the cytoplasm induce activation of the cGAS-STING cytoplasmic DNA-sensing machinery (233), with the acquisition of a senescence-associated secretory phenotype (SASP). SASP induces an increase of CD38 expression and subsequent NAD$^+$ consumption (45, 221). These SASP$^+$-senile cells do accumulate in different organs (liver and white adipose tissue) and produce proinflammatory cytokines that promote chronic inflammation and fibrosis (45). The senescent SASP cell is reported to upregulate CD38 expressed in peripheral macrophages (72); it is thus hypothesized that the accumulation of senescent cells releasing SASP factors increases the activity of CD38, with amplification of cytokine release and NAD$^+$ depletion (221, 234).

The senescence/age-related NAD$^+$ decline/COVID-19 link may appear paradoxical, since senescent cells do not themselves express high levels of CD38. It may be that the SASP factors upregulate CD38 expression in nonsenescent cells (for instance, endothelial cells or M1-macrophages). The SASP circuit might support the relation among cellular senescence, NAD$^+$ decline, and hyperinflammation, with disruption of cellular NAD$^+$ homeostasis and promotion of tissue deterioration (235). In the latter case, senescent cells also secrete proteases, growth factors, and extracellular matrix modifiers, which promote chronic inflammation and fibrosis. A proteomic database has been compiled of senescence-associated secretomes for aging and several diseases and provides a link between the accumulation of senescent cells and pathological process (236). This database is expected to shed light on the lesser known aspects of SASP in elderly COVID-19 affected patients and, at the same time, to help disentangle the CD38-
dependent mechanisms driving inflammation during SARS-CoV-2 infection in the elderly.

CD38 expression is regulated by transcription factor NF-κB (75), which plays a role in the silent inflammation frequently encountered in aging. This suggests that the COVID-19 process may alter the NAD⁺/CD38 axis, given that SARS-CoV-2 cell infection dysregulates the NAD⁺ gene set that includes enzymes required for the innate immune response, inducing a severe depletion of NAD⁺ by host cell (106).
The reported NAD\(^+\) attack during aging and the course of COVID-19 involves: 1) the CD38 NAD\(^+\)-glycohydrolase (102, 117); 2) the NAD\(^+\)-dependent Sirtuins, which suppresses both chronic inflammation and, by binding to the promoter region of ACE2, viral replication (237); and 3) PARPs, whose transcription is increased in individuals infected with SARS-CoV-2 (106). Other NAD\(^+\)-dependent enzymes are 4) ADP-ribosyltransferases (ARTs) and 5) ADP-ribosylhydrolases (ARHs). After ARTs transfer the ADPR unit from NAD\(^+\) onto an acceptor protein (ADPribosylation), ARHs release the ADPR from the target (109). SARS-CoV-2 possess an ARH involved in cell signaling, gene regulation, and apoptosis (102, 109), which contributes to the depletion of the already low NAD\(^+\) levels in aged people.

Among other mechanisms involved in age-related declines in NAD\(^+\) levels, one is the depletion of NAD\(^+\) precursors (e.g., NMN and NR). Indeed, NAMPT levels also reportedly declining during aging (238). Interestingly, it has been reported that NAMPT and NAD\(^+\) levels are significantly reduced by TNF-\(\alpha\) and ROS, impairing the activity of the senescence suppressor Siruin1 deacetylase and, therefore, contributing to the development of age-related illnesses and chronic inflammation. Hence, strategies to sustain NAD\(^+\) biosynthesis might be effective in suppressing physiological and pathological inflammation (117, 178). NAD\(^+\) boosting via dietary NR supplementation (FIGURE 4) was shown to improve hepatic fibrosis, while NMN supplementation was shown to reduce pulmonary fibrosis (239). Moreover, 78c, a thiazoloquin(az)olin(on) e-specific CD38 inhibitor, reversed NAD\(^+\) depletion and reduced the accumulation of inflammatory cells, with a substantial regression of pathological alterations (e.g., fibrotic and inflammatory changes) (153, 200) with therapeutic implications. Indeed, pharmacological approaches to boosting NAD\(^+\) by inhibiting CD38 activity, by NAD\(^+\) precursor supplementation or by a combination of both, represent potential therapeutic strategies for reversing the consequences of SARS-CoV-2 infection.

The main advantages provided by the supply of NAM/NR/NMNT in NAD\(^+\) depletion are that: 1) NAM inhibits PARP activity by competing with NAD\(^+\) for the CD38 active site, thus boosting NAD\(^+\) homeostatic levels; 2) the increased concentration of NAD\(^+\) provides the substrate for NAD\(^+\) kinase, leading to production of NADP\(^+\), which is a stronger PARP inhibitor (240); and 3) NAM is also able to inhibit Sirtuins (201), thereby replenishing NAD\(^+\) levels. Overall, the effects of amided sources for NAD\(^+\) biogenesis support its use in COVID-19 therapy.

Fibrosis is frequently seen in SARS-CoV-2 inflammation in elderly patients (241, 242). Fibrosis on the basis of persistent DNA damage signaling is reported in SARS-CoV-2 infection (243). Damaged DNA induced PARPs to accumulate free ADPR. Concurrently, NAD\(^+\) consumption by CD38 generates ADPR that binds to the TRPM2 channel, causing a Ca\(^{2+}\) influx across the plasma membrane (244). On the other hand, TPC and RyR, respectively, gated by NAADP and cADPR, release intracellular Ca\(^{2+}\) from the EL and ER organelles to provide high concentration of Ca\(^{2+}\) in the cytosol. The overload of cytosolic Ca\(^{2+}\) initiates cell apoptosis along with a cytokine hyperinflammation, potentially causing severe lung failure in COVID-19 patients (FIGURE 5). Indeed, the high number of fatalities in elderly COVID-19 patients is due to the macrophage overactivation, which leads to a CSS and to lung fibrosis (242).

Also relevant to the present topic is the recent observation that CD8\(^+\) tissue-resident memory T cells (Trm) in murine models drive age-associated chronic lung sequelae after viral pneumonia (245). The authors found that chronic nonresolving lung pathologies in mice are associated with an accumulation of Trm. However, Trm cells isolated from aged mice display reduced effector functions. The authors demonstrated this is a secondary effect of the lack of a subpopulation expressing molecules involved in TCR signaling. It is reasonable to anticipate that CD38 plays a role in this process. First, the enzymatic roles played by the molecule and derived products may contribute to the effects observed (31). Second, CD38 is reported as being associated to the TCR/CD3 complex and functionally dependent on it, at least in human models (246, 247). Finally, it would be of interest to investigate the presence of CD203a in the context of the lung environment, before and after viral infection, as a potential source of immunosuppressive ADO (143).

5. IMPLICATIONS OF CD38 FOR COVID-19 THERAPY

Despite the well-known multifaceted biology behind CD38 functions, so far, clinical applications in viral infections stay back and still need to be addressed. Moreover, to date, no specific drugs and therapeutics are approved by any regulatory agencies to prevent or treat SARS-CoV-2 infection. However, the strong groundwork on CD38 provided by theragnostic studies in multiple myeloma and other diseases (TABLE 1) leaves footprints for future research requiring further experimental and preclinical studies (248).

Indeed, the identification of CD38 as a key enzyme involved in NAD\(^+\) metabolism, cell signaling, and immunity strongly suggests its potential as a target in viral pathological conditions. Toward these goal, CD38 can be targeted using different pharmacological approaches.
such as small-molecule inhibitors and enzyme-modulating mAbs. For instance, during viral infection the ANG II dysregulation results in increased signaling through the CD38/NAD⁻¹-glycohydrolase and purinergic receptors, among others, leading to inflammation, thrombosis, fibrogenic alterations, and organ injury. Accordingly, approved drugs that modulate these targets or their ligands (herein discussed) may provide useful therapeutic approaches to blunt multiple aspects of COVID-19 pathology (TABLE 2). Pharmacological agents used to mitigate the detrimental actions of ACE/ANG II/AT₁R axis will not only preserve ACE2 anti-inflammatory functions but also blunt the cytokine storm elicited by SARS-CoV-2 infection. Indeed, ACEI or ARBs leading to reduce ANG II activities, and thus CD38 activation, will help to reduce fibrogenic tissue damages (249).

The disruption of ANG II/CD38 axis may also preserves mitochondrial and cellular wellness through AT₁R blocking and NAD⁺ boosting. Accordingly, as an ANGII/CD38 core-based therapy, a clinical trial has been recently launched to test whether (or not) ARBs reduce respiratory failure in COVID-19 patients (NCT04340557).

The COVID-19 pathological process is associated with increased inflammatory responses, oxidative stress, vascular damage, and fibrogenesis. The best clinical strategy for the treatment of COVID-19 patients is known to be a purely supportive care that includes 1) active hyperoxic ventilation (supplemental oxygen), and 2) measures to prevent infection and worsening of the pathological conditions (250, 251). Unfortunately, this means of oxygenation inhibits the local tissue hypoxia-driven ADO-A2AR-mediated anti-inflammatory protecting mechanism (252) and thereby exacerbates ARDS, a pathophysiologica process that leads to the death of COVID-19 patients (253, 254). As a proof-of-principle, it was reported that a COVID-19 patient with ARDS treated with ADO in high-flow 21% O₂ aerosol showed an improvement in clinical conditions (206). These effects were confirmed in a pilot trial with very promising clinical outcomes. Indeed, the pharmacological compensation for the oxygenation-associated loss of the generated extracellular ADO in the lungs of COVID-19 patients was achieved through intra-tracheal injection or inhalation of synthetic ADO (205). Importantly, the resolution of respiratory failure allowed the authors to concluded that the use of ADO is a valid therapeutic option in ARDS/COVID-19.

CD38 may be part of the multiple mechanisms explaining the low NAD⁺ levels observed in CD38-related diseases (TABLE 1). Therefore, inhibition of the CD38 enzymatic activity leading to increased NAD⁺ levels might be of interest for treatment. Unfortunately, the small-molecule inhibitors now available of CD38 enzymatic activity either have an affinity in the micromolar range (200) or trigger cell cytotoxicity like the therapeutic anti-CD38 mAbs. However, the observed immunosuppressive effects of anti-CD38 mAbs on malignant plasma cells could be useful after regulation of its functional effects. The consequence of a CD38 fine-tuning on the intracellular and extracellular NAD⁺ levels and related metabolites will help understanding how to modulate CD38 to maximize efficacy and lower potential adverse events (255).

To explore important aspects of COVID-19 therapeutic drugs, a number of small animal models (such as mice, hamsters, and ferrets) can be used (256, 257). Non-human primate models have also been explored for COVID-19. Interestingly, a characterization of CD38 from cynomolgus macaque was reported and demonstrates genetical, biochemical and immunological similarities of the primate CD38 with the human protein (258). The study opened new prospects for the pharmacological applications of this catalytic receptor. Indeed, a current study in cynomolgus macaque has focused on the effect of age on infection with SARS-CoV-2 (259, 260). To facilitate the study of SARS-CoV-2 pathogenesis and to test candidate COVID-19 therapeutic agents and drug repurposing, microengineered organs-on-chips and lung organoids as models have been developed (261).

6. CONCLUSIONS

The aim of this perspective review is to examine the connections between CD38 and COVID-19. It provides detailed analysis of the mechanisms 1) of viral invasion, 2) of viral evasion from innate and adaptive immune responses, and 3) of hyperinflammation associated to metabolic conditions; and examines the 4) protected immune status during pregnancy, and 5) clinical fragility of elderly patients. To achieve these goals the current review reanalyses hypotheses formulated in the context of RSV infection by exploiting the results about the role of multifaceted CD38 in other cellular systems. Associative basic and clinical research data are herein discussed and integrated with conclusions reported by others within the field.

We are led to conclude that CD38/NADase is at the center of a functional axis (i.e., intracellular Ca²⁺ mobilization/IFNs response/ROS burst) exploited by viral infections (e.g., RSV, SARS). Consequently, CD38-induced opening of intracellular Ca²⁺ channels would activate processes able to influence early steps of the disease, but whose persistence and worsening negatively affect the outcome of the COVID-19 disease.

The grounds for this hypothesis are that 1) the substrates of CD38 (i.e., NAD⁺ and NADP⁺) are depleted by
viral-induced metabolic rewiring; and 2) the products of the enzymatic activities of CD38 (i.e., cADPR/ADPR/NAADP) are involved in an anti-viral and proinflammatory response that may favor the onset of lung immunopathology (i.e., CSS and organ fibrosis). The role of the CD38/NAD\(^+\) axis at different stages of COVID-19 were also analyzed, along with different therapeutic possibilities. The conclusions are that pathological events of the current pandemic may be mitigated by distinct modulators of the CD38/NAD\(^+\) axis.

There are still many open questions to be answered concerning 1) the impact of the CD38/NAD\(^+\) axis in vivo during SARS-CoV-2 infection; 2) certain mechanisms underlying NAD\(^+\) involvement during SARS-CoV-2 infection, which remains unclear and requires further research for identifying the precise molecular mechanisms implicated in immunity and metabolic adaptations to SARS-CoV-2 infection; and 3) how to meet the challenge of discovering and developing new therapeutic agents, so critically in demand. However, many of today’s findings echo those from past viral infections (e.g., RSV and SARS), thus providing a foothold for dealing with COVID-19.

Of clinical relevance for the future in the strategy to fight COVID-19 is the identification of molecular metabolic pathways generally usurped by the viral pathogen and addressing the evaluation of the impact of agents that selectively target CD38’s receptorial and catalytic activities to confirm the potential of CD38 as a novel therapeutic target.

[ACKNOWLEDGMENTS](#)

Thanks are given to Laura McLean for assistance in the stylistic assembly of the review. We apologize to those whose work is not cited due to space limitations.

[GRANTS](#)

Contributions were provided by the Fondazione Ricerca Molinette, a non-profit organization located in Torino, Italy.

[CORRESPONDENCE](#)

A. L. Horenstein (e-mail: horenstein.al@gmail.com); F. Malavasi (e-mail: fabio.malavasi@unito.it).

[DISCLOSURES](#)

F.M. received honoraria for lectures given at Jenssen, Takeda, and Sanofi. A.L.H. and A.C.F. have no conflicts of interest.

[AUTHOR CONTRIBUTIONS](#)

A.L.H. conceived and designed research; A.L.H. drafted manuscript; A.C.F. and F.M. edited and revised manuscript; A.L.H., A.C.F., and F.M. approved final version of manuscript.

[REFERENCES](#)

1. Schiavoni I, Scagnolari C, Horenstein AL, Leone P, Pierangeli A, Malavasi F, Ausiello CM, Fedele G. CD38 modulates respiratory syncytial virus-driven proinflammatory processes in human monocyte-derived dendritic cells. *Immunology* 154: 122–131, 2018. doi:10.1111/imm.12873.

2. de Graaff PM, de Jong EC, van Capel TM, van Dijk ME, Roholl PJ, Boes J, Luxtjes W, Kimpen JL, van Bleek GM. Respiratory syncytial virus infection of monocyte-derived dendritic cells decreases their capacity to activate CD4 T cells. *J Immunol* 175: 5904–5911, 2005. doi:10.4049/jimmunol.175.9.5904.

3. Savarino A, Bottarel F, Malavasi F, Dianzani U. Role of CD38 in HIV-1 infection: an epiphenomenon of T-cell activation or an active player in virus/host interactions? *AIDS* 14: 1079–1089, 2000. doi:10.1097/00002030-200006160-00004.

4. Vollbrecht T, Brackmann H, Henrich N, Roeing J, Seybold U, Bogner JR, Goebel FD, Draenert R. Impact of changes in antigen level on CD38/PD-1 co-expression on HIV-specific CD8 T cells in chronic, untreated HIV-1 infection. *J Med Virol* 82: 358–370, 2010. doi:10.1002/jmv.21723.

5. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 20: 355–362, 2020. doi:10.1038/s41577-020-0331-4.

6. De Flora S, Grassi C, Carati L. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment. *Eur Respir J* 10: 1535–1541, 1997. doi:10.1183/09031936.97.10071535.

7. Lee S, Paudel O, Jiang Y, Yang XR, Sham JS. CD38 mediates angiotensin II-induced intracellular calcium release in rat pulmonary arterial smooth muscle cells. *Am J Respir Cell Mol Biol* 52: 332–341, 2015. doi:10.1165/rcmb.2014-0141OC.

8. Horenstein AL, Chillemi A, Zaccarello G, Bruzzone S, Quaroni V, Zito A, Serra S, Malavasi F. A CD38/CD203a/CD73 ectoenzymatic pathway independent of CD39 drives a novel adenosinergic loop in human T lymphocytes. *OncoImmunology* 2: e26246, 2013. doi:10.4161/onci.26246.

9. Helmy YA, Fawzy M, Elaswad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19 pandemic: a comprehensive review of taxonomy, genetics, epidemiology, diagnosis, treatment, and control. *J Clin Med* 9: 1225, 2020. doi:10.3390/jcm9041225.

10. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* 181: 281–292.e6, 2020. doi:10.1016/j.cell.2020.02.058.

11. Hoffmann M, Klein-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181: 271–280, 2020. doi:10.1016/j.cell.2020.02.052.
12. Jaimes JA, Millet JK, Whittaker GR. Proteolytic cleavage of the SARS-CoV-2 spike protein and the role of the novel S1/S2 site. iScience 23: 101212, 2020. doi:10.1016/j.isci.2020.101212.

13. Bestle D, Heindl MR, Limburg H, Van Lam van T, Pilgram O, Moulton H, Stein DA, Hardes K, Eckmann M, Dolnik O, Rohde C, Klenk HD, Garten W, Steinmetzer T, Böttcher-Friebertshäuser E, TMRPSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. Life Sci Allian 3: e202000786, 2020. doi:10.26580/lsa.202000786.

14. Ziebuhr J. The coronavirus replicase: insights into a sophisticated enzyme machinery. Adv Exp Med Biol 581: 3–11, 2006. doi:10.1007/978-0-387-33012-9_1.

15. Wang Y, Sun Y, Wu A, Xu S, Pan R, Zeng C, Jin X, Ge X, Shi Z, Ahola T, Chen Y, Guo D. Coronavirus nsp10/nsp16 methyltransferase can be targeted by nsp10-derived peptide in vitro and in vivo to reduce replication and pathogenesis. J Virol 89: 8416–8427, 2015. doi:10.1128/JVI.00948-15.

16. Fehr AR, Perlman PS. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 1282: 1–23, 2015. doi:10.1007/978-1-4939-2438-7.

17. Kuba K, Imai Y, Rao S, Gao H, Guo F, Pan R, Zeng C, Jin X, Ge X, Shi Z, Ahola T, Chen Y, Guo D. Coronavirus nsp10/nsp16 methyltransferase can be targeted by nsp10-derived peptide in vitro and in vivo to reduce replication and pathogenesis. J Virol 89: 8416–8427, 2015. doi:10.1128/JVI.00948-15.

18. Fehr AR, Perlman PS. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 1282: 1–23, 2015. doi:10.1007/978-1-4939-2438-7.

19. Kuba K, Imai Y, Rao S, Gao H, Guo F, Pan R, Zeng C, Jin X, Ge X, Shi Z, Ahola T, Chen Y, Guo D. Coronavirus nsp10/nsp16 methyltransferase can be targeted by nsp10-derived peptide in vitro and in vivo to reduce replication and pathogenesis. J Virol 89: 8416–8427, 2015. doi:10.1128/JVI.00948-15.

20. Kam YW, Okumura Y, Kido H, Ng LF, Bruzzone R, Altmeyer R. CD38 Antibody daratumumab for the treatment of chronic active anti-CD38 light-chain amyloidosis. Hematol Oncol Clin North Am 34: 1149–1159, 2020. doi:10.1016/j.hoc.2020.08.005.

21. Cole S, Walsh A, Yin X, Wechalekar MD, Smith MD, Proudfan SM, Veale DJ, Fearon U, Pitzalis C, Humby F, Bombardieri M, Axel A, Adams H, Chiu C, Sharp M, Alvarez J, Anderson I, Madakamutil L, Nagpal S, Guo Y. Integrative analysis reveals CD38 as a therapeutic target for plasma cell-rich pre-disease and established rheumatoid arthritis and systemic lupus erythematosus. Arthritis Res Ther 20: 85, 2018. doi:10.1186/s13075-018-1578-z.

22. Shi B, Wang W, Korman B, Kai L, Wang Q, Wei J, Bale S, Marangoni RG, Bhattacharya S, Miller S, Xu D, Akbarpour M, Chernes P, Proccissi D, Gursel D, Essalim-Netto JM, Chini CC, de Oliveira GC, Gudjonsson JE, Chini EN, Varga J. Targeting CD38-dependent NAD+ metabolism to mitigate multiple organ fibrosis. iScience 24: 101902, 2021. doi:10.1016/j.isci.2021.101902.

23. Doberer K, Kläger J, Gualdoni GA, Mayer KA, Eskandary F, Farkash EA, Agis H, Reiter T, Reindl-Schwaighofer R, Wahrmann M, Cohen G, Haslacher H, Bond G, Simonitsch-Klupp I, Halloran PF, Bohmig GA. CD38 Antibody daratumumab for the treatment of chronic active antibody-mediated kidney allograft rejection. Transplantation 105: 451–457, 2020. doi:10.1097/TP.0000000000003247.

24. Camacho-Pereira J, Tarragó MG, Chini CC, Nin V, Escande C, Warner GM, Puranik AS, Schoon RA, Reid JM, Galina A, Chini EN. CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. Cell Metab 23: 1127–1139, 2016. doi:10.1016/j.cmet.2016.05.006.

25. Guerreiro S, Privat AL, Bressac L, Doucet D. CD38 in neurodegeneration and neuroinflammation. Cells 9: 471, 2020. doi:10.3390/cells9040271.

26. Aksoy P, White TA, Thompson M, Chini EN, Regulation of intracellular levels of NAD: a novel role for CD38. Biochem Biophys Res Commun 345: 1386–1392, 2006. doi:10.1016/j.jbc.2005.06.042.

27. van de Donk NW, Richardson PG, Malavasi F, CD83 antibodies in multiple myeloma: back to the future. Blood 131: 13–29, 2018. doi:10.1182/blood-2017-06-740944.
39. Lee HC. Cyclic ADP-ribose: a calcium mobilizing metabolite of NAD+. *Mol Cell Biochem* 138: 229–235, 1994. doi:10.1007/BF00292846.

40. Lee HC. Cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate (NAADP) as messengers for calcium mobilization. *J Biol Chem* 287: 31633–31640, 2012. doi:10.1074/jbc.R112.349464.

41. Baum N, Fliegert R, Bauche A, Hambach J, Menzel S, Haag F, Bannas P, Koch-Nolte F, Daratumumab and nanobody-based heavy chain antibodies inhibit the ADPβR cyclase but not the NAD+-hydrolyase activity of CD38-expressing multiple myeloma cells. *Cancers* 13: 76, 2020. doi:10.3390/cancers13010076.

42. Horenstein AL, Faini AC, Morandi F, Bracci C, Lanza F, Giuliani N, Paulus A, Malavasi F. The circular life of human CD38 from basic science to clinics and back. *Molecules* 25: 4844, 2020. doi:10.3390/molecules25204844.

43. Horenstein AL, Quarona V, Toscani D, Costa F, Chillemi A, Pistoia V, Giuliani N, Malavasi F. Adenosine generated in the bone marrow niche through a CD38-mediated pathway correlates with progression of human myeloma. *Mol Med* 22: 694–704, 2016. doi:10.2119/molmed.2016.00198.

44. Hogan KA, Chini CC, Chini EN. The multi-faceted ecto-enzyme CD38: roles in immunomodulation, cancer, aging, and metabolic diseases. *Front Immunol* 10: 1187, 2019. doi:10.3389/fimmu.2019.01187.

45. Chini CC, Peclat TR, Warner GM, Kashyap S, Espindola-Netto JM, de Oliveira GC, et al. CD38 ecto-enzyme in immune cells is induced during aging and regulates NAD+ and NMN levels. *Nat Metab* 2: 1284–1304, 2020. doi:10.1038/s42255-020-00298-z.

46. Horenstein AL, Chillemi A, Quarona V, Zito A, Roato I, Morandi F, Mariampietri D, Bozani M, Toscani D, Oldham RJ, Cucchioloni M, Sasser AK, Pistoia V, Giuliani N, Malavasi F. NAD+-Metabolizing ectoenzymes in remodeling tumor-host interactions: the human myeloma model. *Cells* 4: 520–537, 2015. doi:10.3390/cells4030520.

47. Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z, Mu Z, Chen X, Chen J, Hu K, Jin Q, Wang J, Qian Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Cell surface antigen CD38 identifies an antigenic target: origin, genes and regulation of human CD38 and related molecules*. In: *Chemical Immunology and Allergy*, edited by Mehta K, Malavasi F. Berlin, Germany: Karger, 2000, p. 1–19.

48. Ausiello CM, Urbani F, la Sala A, Funaro A, Malavasi F. CD38 ligation induces discrete cytokine mRNA expression in human cultured lymphocytes. *Eur J Immunol* 25: 1477–1480, 1995. doi:10.1002/eji.1830250554.

49. Frasca L, Fedele G, Deaglio S, Capuano C, Palazzo R, Vaisitti T, Malavasi F, Ausiello CM. CD38 orchestrates migration, survival, and TH immune response of human mature dendritic cells. *Blood* 107: 2392–2399, 2006. doi:10.1182/blood-2005-07-2913.

50. Nishina H, Inagada K, Takahashi K, Hoshino S, Ikeda K, Katada T. Cell surface antigen CD38 identified as ecto-enzyme of NAD glycohydrolase has hyaluronate-binding activity. *Biochem Biophys Res Commun* 203: 1318–1323, 1994. doi:10.1016/0006-291X(94)91326-7.

51. Newman P, Berndt M, Gorski J, White G, Lyman S, Paddock C, Daratumumab and nanobody-based heavy chain antibodies inhibit the ADPβR cyclase but not the NAD+-hydrolyase activity of CD38-expressing multiple myeloma cells. *J Biol Chem* 289: 60855–60864, 2014. doi:10.1074/jbc.M114732200.

52. Partida-Sanchez S, Gasser A, Fliegert R, Siebrands CC, Dammermann W, Shi G, Mousseau BJ, Sumoza-Toledo A, Bhagat H, Walseth TF, Guse AH, Lund FE. Chemotaxis of mouse bone marrow neutrophils and dendritic cells is controlled by ADP-ribose, the major product generated by the CD38 enzyme reaction. *J Immunol* 179: 7827–7839, 2007. doi:10.4049/jimmunol.179.11.7827.

53. Musso T, Deaglio S, Franco L, Calosso L, Badolato R, Garbarino G, Dianzani U, Malavasi F. CD38 expression and functional activities are up-regulated by IFN-gamma on human monocytes and monocytic cell lines. *J Leukoc Biol* 69: 605–612, 2001.
CD38 IN THE PATHOPHYSIOLOGY OF COVID-19

68. Petin K, Weiss R, Müller G, Garten A, Grahnert A, Sack U, Hauschildt S. NAD metabolites interfere with proliferation and functional properties of THP-1 cells. Innate Immun 25: 280–293, 2019. doi:10.1177/1753425919844587.

69. Amici SA, Young NA, Narvaez-Miranda J, Jablonski KA, Arcos J, Rosas L, Papenfuss TL, Torrelles JB, Jarjour WN, Guerau-de-Anellano M. CD38 is robustly induced in human macrophages and monocyes in inflammatory conditions. Front Immunol 9: 1593, 2018. doi:10.3389/fimmu.2018.01593.

70. Chatterjee S, Daenthanasanmak A, Chakraborty P, Wyatt MW, Dhar P, Selvam SP, Fu J, Zhang J, Nguyen H, Kang I, Toth K, Al-Homrani M, Husain M, Beeson G, Ball L, Helke K, Husain S, Garrett-Mayer E, Hardiman G, Mehrotra M, Nishimura MI, Beeson CC, Bupp MG, Wu J, Ogretmen B, Paulos CM, Rathmell J, Yu XZ, Mehrotra S. CD38–NAD+ axis regulates immunotherapeutic anti-tumor T cell response. Cell Metab 27: 85–100.e8, 2018. doi:10.1016/j.cmet.2017.10.006.

71. Matalonga J, Glaria E, Bresque M, Escande C, Carbó JM, Kiefer K, Vicente R, León TE, Becerro S, Pascual-García M, Serret J, Sanjuño L, Morón-Ros S, Riera A, Paytubi S, Juarez A, Sottilo F, Lindbom L, Caelles C, Sarrias MR, Sancho J, Castrillo A, Chini EN, Valledor AF. The nuclear receptor LXR limits bacterial infection of host macrophages through a mechanism that impacts cellular NAD metabolism. Cell Rep 18: 1241–1255, 2017. doi:10.1016/j.celrep.2017.01.007.

72. Covarrubias AJ, Kale A, Perrone R, Lopez-Dominguez JA, Pisso AO, Kasler HG, et al. Senescence cells promote tissue NAD+ decline during ageing via the activation of CD38+ macrophages. Nat Metab 2: 1265–1283, 2020. doi:10.1038/s42255-020-00305-3.

73. Iqbal J, Zaidi M, TNF regulates cellular NAD+ metabolism in primary macrophages. Biochem Biophys Res Commun 342: 1312–1318, 2006. doi:10.1016/j.bbrc.2006.02.109.

74. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. J Clin Invest 122: 787–795, 2012. doi:10.1172/JCI95643.

75. Kang B, Tirumurugaan KG, Deshpande DA, Amrani Y, Panettieri RA, Walseth TF, Karman MS, Kang B, Tirumurugaan KG, Deshpande DA, Amrani Y, Panettieri RA, Walseth TF, Karman MS. Transcriptional regulation of CD38 expression by tumor necrosis factor-α in human airway smooth muscle cells: role of NF-κB and sensitivity to glucocorticoids. FASEB J 20: 1000–1002, 2006. doi:10.1096/fj.05-45859e.

76. Burnstock G, Boeynaems JM. Purinergic signalling and immune cells. Purinergic Signal 10: 529–564, 2014. doi:10.1007/s13302-014-0295-2.

77. Idzko M, Ferrari D, Eltzschig HK. Nucleotide signalling during inflammation. Nature 509: 310–317, 2014. doi:10.1038/nature13085.

78. Ohta S, Sitkovsky M. Role of G-protein-coupled adenosine receptors in downregulation of inflammation and protection from tissue damage. Nature 414: 916–920, 2001. doi:10.1038/414916a.

79. Nieto-Torres JL, Verdú-Báguena C, Jimenez-Guardo JM, Regla-Nava JA, Castaña-Rodríguez C, Fernandez-Delgado R, Torres J, Aguillera VM, Enjuanes L. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. Virology 485: 330–339, 2015. doi:10.1016/j.virology.2015.08.010.

80. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al. Immunology of COVID-19: current state of the science. Immunity 52: 910–941, 2020. doi:10.1016/j.immuni.2020.05.002.

81. Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. J Exp Med 217: e20200678, 2020. doi:10.1084/jem.20200678.

82. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med 383: 2255–2273, 2020. doi:10.1056/NEJMra2026131.

83. Lei X, Dong X, Ma R, Wang W, Xiao X, Tian Z, Wang C, Wang Y, Li L, Ren L, Guo F, Zhao Z, Zhou X, Ziang Z, Wang J. Activation and evasion of type I interferon responses by SARS-CoV-2. Nat Commun 11: 3810, 2020. doi:10.1038/s41467-020-17665-9.

84. Sajuthi SP, DeFord P, Li Y, Jackson ND, Montgomery MT, Everett JL, Rios CL, Pruesse E, Nolin JD, Plender EG, Wechsler ME, Mak AC, Eng C, Salazar S, Medina V, Wohlford EM, Huntsman S, Nickerson DA, Germer S, Zody MC, Abecasis G, Kang HM, Rice KM, Kumar R, Oh S, Rodriguez-Santana J, Burchard EG, Seibold MA. Type 2 and interferon inflammation strongly regulate SARS-CoV-2 related gene expression in the airway epithelium. Nat Commun 11: 5139, 2020. doi:10.1038/s41467-020-18781-2.

85. Zhuang MW, Cheng Y, Zhang J, Jiang XM, Wang L, Deng J, Wang PH. Increasing host cellular receptor-angiotensin- converting enzyme 2 expression by coronavirus may facilitate 2019-nCoV (or SARS-CoV-2) infection. J Med Virol 92: 2693–2701, 2020. doi:10.1002/jmv.26139.

86. Subbarao K, Mahanty S. Respiratory virus infections: understanding COVID-19. Immunity 52: 905–909, 2020. doi:10.1016/j.immuni.2020.05.004.

87. Bell TJ, Brand OJ, Morgan DJ, Salek-Ardakani S, Jagger C, Fujimori T, Cholewa L, Tilakaratna V, Ostling J, Thomas M, Day AJ, Snelgrove RJ, USSR T. Defective lung function following influenza virus is due to prolonged, reversible hyaluronan synthesis. Matrix Biol 80: 14–28, 2019. doi:10.1016/j.matbio.2018.06.006.

88. Srim K, Insel PA. Inflammation and thrombosis in COVID-19 pathophysiology: Proteinase-activated and purinergic receptors as drivers and candidate therapeutic targets. Physiol Rev 101: 545–556, 2020. doi:10.1152/physrev.00035.2020.

89. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, Wang Q, Miao H. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 5: 33, 2020. doi:10.1038/s41392-020-0164-4.

90. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, Chen L, Li M, Liu Y, Wang G, Yuan Z, Feng Z, Zhang Y, Wu Y, Chen Y. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 11, 2020. doi:10.3389/fimmu.2020.00827.

91. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 10: 102–108, 2020. doi:10.1016/j.jpha.2020.03.001.

92. Liao YC, Liang WG, Chen FW, Hsu JH, Yang JJ, Chang MS. Reduction and predictive study. J Pharm Anal 10: 102–108, 2020. doi:10.1016/j.jpha.2020.03.001.

93. Gallay N, Amani L, Lopez A, Colombat P, Binet C, Domenech J, Weksler BB, Malavasi F, Herault O. The role of platelet/endothelial cell adhesion molecule 1 (CD31) and CD38 antigens in marrow microenvironmental retention of acute myelogenous leukemia cells. Cancer Res 67: 8624–8632, 2007. doi:10.1158/0008-5472.CAN-07-0402.

94. Kamel KS, Oh MS, Haipern ML. Lactic acidosis: pathophysiology, classification, and causes; emphasis on biochemical and metabolic basis. Kidney Int 97: 75–88, 2020. doi:10.1016/j.kint.2019.08.023.
95. Ji HL, Zhao R, Matalon S, Matlabay MA. Elevated plasminogen as a common risk factor for COVID-19 susceptibility. Physiol Rev 100: 1065–1075, 2020. doi:10.1152/physrev.00013.2020.

96. Mushtaq M, Nam TS, Kim UH. Critical role for CD38-mediated Ca2+ signaling in thrombin-induced procoagulant activity of mouse platelets and hemostasis. J Biol Chem 286: 12952–12958, 2011. doi:10.1074/jbc.M110.207700.

97. Torti M, Festetics ET, Bertoni A, Sinagiglia F, Balduini C. The role of extracellular adenosine generation in the development of autoimmune diseases. Mediators Inflamm 2018: 1–10, 2018. doi:10.1155/2018/7019398.

98. Nikiforov A, Kulikova V, Ziegler M. The human NAD metabolome: functions, metabolism and compartmentalization. Crit Rev Biochem Mol Biol 50: 284–297, 2015. doi:10.1080/0201080X.2014.1064026.

99. Morandi F, Horenstein AL, Rizzo R, Malavasi F. The role of extracellular adenosine generation in the development of autoimmune diseases. Mediators Inflamm 2018: 1–10, 2018. doi:10.1155/2018/7019398.

100. Morandi F, Horenstein AL, Rizzo R, Malavasi F. The role of extracellular adenosine generation in the development of autoimmune diseases. Mediators Inflamm 2018: 1–10, 2018. doi:10.1155/2018/7019398.

101. Ferrari D, Idzko M, Dichmann S, Purišis D, Virchow C, Norgauer J, Chiozzi P, Di Virgilio F, Luttmann W. The molecular story of COVID-19; NAD+ as a common risk factor for COVID-19 susceptibility. Front Immunol 110: 2, 2020. doi:10.3389/fimmu.2020.00234.

102. Estevez B, Du X. New concepts and mechanisms of platelet activation signaling. Physiology (Bethesda) 32: 162–177, 2017. doi:10.1152/physiol.00020.2016.

103. Morandi F, Horenstein AL, Rizzo R, Malavasi F. The role of extracellular adenosine generation in the development of autoimmune diseases. Mediators Inflamm 2018: 1–10, 2018. doi:10.1155/2018/7019398.

104. Rajput V, Routy JP. Tryptophan catabolism in chronic viral infections: handling uninvited guests. Int J Tryptophan Res 8: JTR.2020. doi:10.2174/JTR.2020.026.

105. Hashimoto T, Perloto T, Rehman A, Trichereau J, Ishiguro H, Pulino M, Sigl V, Hanada T, Hanada R, Lipinski S, Wild B, Casamore SM, Singer D, Richter A, Kuba K, Fukushima A, Schreiber S, Clevers H, Verrey F, Rosenpooli T, Penninger JM. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 487: 477–481, 2012. doi:10.1038/nature1128.

106. Bianco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Muller R, Jordan TX, Oishi K, Panis M, Sachs D, Wang TT, Schwartz RE, Lim JK, Albrecht RA, teOever BR. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 181: 1036–1045, e9, 2020. doi:10.1016/j.cell.2020.04.026.

107. Minhas PS, Liu L, Moon PK, Joshi AU, Dove C, Mhatre S, Contrepois K, Wang Q, Lee BA, Coronado M, Bernstein D, Snyder MP, Migaud M, Majeti R, Mochly-Rosen D, Rabinowitz JD, Andresson KI. Macrophage de novo NAD+ synthesis specifies immune function in aging and inflammation. Nat Immunol 20: 50–63, 2019. doi:10.1038/s41590-018-0255-3.

108. Lehr J, Meyerholz DK, Ahel I, Perlman S. Coronavirus infection and PARP expression dysregulate the NAD+–consuming enzyme CD38: Searches of therapeutic options. Front Microbiol 10: 355, 2019. doi:10.3389/fmicb.2019.00355.

109. Koch-Nolte F. Mammalian ADP-ribosyltransferases and ADP-ribosylhydrolases. Front Biosci 6: 6716–6729, 2008. doi:10.2741/3184.

110. Mehraj V, Routy JP. Tryptophan catabolism in chronic viral infections: handling uninvited guests. Int J Tryptophan Res 8: JTR.2020. doi:10.2174/JTR.2020.026.

111. Katsuyama E, Suarez-Fueyo A, Bradley SJ, Mizui M, Marin AV, Mulki L, Krishfield S, Malavasi F, Yoon J, Sui SJ, Kyttarisd V, Tsokos GC. The CD38/NAD+/SIRT1/HEH2 axis mitigates cytotoxic CD8+ T cell function and identifies patients with se prone to infections. Cell Rep 30: 112–123, 2020. doi:10.1016/j.celrep.2019.12.014.

112. Danfott W, Robertson KA, Watkins WJ, Strobi B, Ghazali P. Metabolic regulators target at site 6 serially participate in the macrophage interferon antiviral cascade. Front Microbiol 10: 355, 2019. doi:10.3389/fmicb.2019.00355.

113. Chini EN, Chini CC, Espindola Netto JM, de Oliveira GC, van Schooten W. The pharmacology of CD38/NADase: an emerging target in cancer and diseases of aging. Trends Pharmacol Sci 39: 424–436, 2018. doi:10.1016/j.tips.2018.02.001.

114. Malavasi F, Deaglio D, Zaccarello G, Dietrich L, Audrite V, Serra S, Gandione M, Zitalla A, Tizzani A. The hidden life of NAD+-consuming ectoenzymes in the endocrine system. J Molecular Endocrinol 45: 183–191, 2010. doi:10.1677/JME-10-0082.

115. Sica A, Colombo MP, Trama A, Horn L, Garassino MC, Torri V. Immunometabolic status of COVID-19 cancer patients. Physiol Rev 100: 1839–1850, 2020. doi:10.1152/physrev.00018.2020.

116. Bock KW. Modulation of aryl hydrocarbon receptor (AhR) and the NAD+-consuming enzyme CD38: Searches of therapeutic options for nonalcoholic fatty liver disease (NAFLD). Biochem Pharmacol 175: 113905, 2020. doi:10.1016/j.bcp.2020.113905.

117. Grunewald ME, Shaban MG, Mackin SR, Fehr AR, Perlman S. Murine coronavirus infection activates the aryl hydrocarbon receptor in an indoleamine 2,3-dioxygenase-independent manner, contributing to cytokine modulation and proviral TCDD-inducible-PARP expression. J Virol 94: e01743-19, 2020. doi:10.1128/JVI.01743-19.

118. Gharote MA. Role of poly (ADP) ribose polymerase-1 inhibition by nicotinamide as a possible additive treatment to modulate host immune response and prevention of cytokine storm in COVID-19. JMedS 72: 25–28, 2020. doi:10.25259/JMEDS_29_2020.
123. Liu Y, Lv J, Liu J, Li M, Xie J, Lv Q, Deng W, Zhou N, Zhou Y, Song J, Wang P, Qin C, Tong WM, Huang B. Mucus production stimulated by IFN-α and NF-κB signaling triggers hypoxia of COVID-19. Cell Res 30: 1078–1087, 2020. doi:10.1038/s41422-020-00435-z.

124. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie Y, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497–506, 2020. doi:10.1016/S0140-6736(20)30183-5.

125. Yang G, Das A, Huang GX, Bonkowski MS, Longchamp A, Li C, Schultz MB, Badawy AA, Doroftei B, Ilie OD, Cojocariu RO, Ciobica A, Maftei R, Grab D, Anton Loring HS, Thompson PR. Emerging of SARM1 as a potential therapeutic target for wallerian-type diseases. Cell Chem Biol 27: 1–13, 2020. doi:10.1016/j.chembiol.2019.11.002.

126. Kato K, Nishimatsu H, Okawa D, Hirano S, Hiranâ K, Kasuya Y, Ishitan T, Tokunaga F, Nureki O. Structural insights into cGAMP degradation by ecto-nucleotide pyrophosphatase phosphodiesterase 1. Nat Commun 9: 4422, 2018. doi:10.1038/s41467-018-06922-7.

127. Loring HS, Thompson PR. Emergence of SARM1 as a potential therapeutic target for wallerian-type diseases. Cell Chem Biol 27: 1–13, 2020. doi:10.1016/j.chembiol.2019.11.002.

128. Onyedike Il, Wang M, Sintim HO, ENPP1, an old enzyme with new functions, and small molecule inhibitors—a STING in the tale of ENPP1. Molecules 24: 4192, 2019. doi:10.3390/molecules24224192.

129. Shamma M, Thode T, Weston A, Kaadige MR. Development of Enpp1 Inhibitors as a strategy to activate stimulator of interferon genes (STING) in cancers and other diseases. Int J Cell Sci Mol Biol 5: 555655, 2018. doi:10.19080/UCSB.2018.05.555655.

130. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for covid-19— interim who solidarity trial results. N Engl J Med 384: 497–511, 2021. doi:10.1056/NEJmaa2023184.

131. Doseffei B, Ilie OD, Cojocariu RO, Ciobica A, Maftei R, Grab D, Anton E, McKenna J, Dhunna N, Simionescu G. Bacillus subtilis reveals a novel enzymatic function of human CD73 related to NAD metabolism. Front Immunol 13: 2671, 2021. doi:10.3389/fimmu.2021.00760.

132. Fischer K, Hoffmann P, Voeikl S, Meidenbauer N, Ammer J, Edinger TIR domain proteins are an ancient family of NAD-consuming enzymes. Biochem J 480: 131–141, 2012. doi:10.1042/BJ20111263.

133. Essuman K, Summers DW, Sasaki Y, Mao X, Yim AK, DiAntonio A, Milbrandt J. TIR domain proteins are an ancient family of NAD+- consuming enzymes. Curr Biol 28: 421–430, 2018. doi:10.1016/j.cub.2017.12.024.

134. Loring HS, Thompson PR. A liquid-to-solid phase transition enhances the catalytic activity of SARM1. bioRxiv 2020.08.28.272377, 2020. doi:10.1101/2020.08.28.272377.

135. Zhao ZY, Xie XJ, Li WH, Liu J, Chen Z, Zhang B, Li T, Li SL, Lu JG, Zhang L, Zhang LH, Xu Z, Lee HC, Zhao YJ. A cell-permeant mimetic of NMN activates SARM1 to produce cyclic ADP-ribose and induce non-apoptotic cell death. iScience 15: 452–466, 2019. doi:10.1016/j.isci.2019.05.001.

136. Balka KR, Louis C, Saunders TL, Smith AM, Calleja DJ, D’silva DB, Moghaddas F, Taller M, Lawlor KE, Zhan Y, Burns CJ, Wicks IP, Miner JJ, Kile BT, Masters SL, De Nardo D, TBK1 and IKK paper. Act redun- dantly to mediate STING-induced NF-kB responses in myeloid cells. Cell Rep 31: 107492, 2020. doi:10.1016/j.celrep.2020.03.056.

137. Chhetri S, Khamis F, Pandak N, Al Khalili H, Said E, Petersen EA. Fatal case of COVID-19 due to metabolic acidosis following dysregulate inflammatory response (cytokine storm). iDCases 21: e00829, 2020. doi:10.1016/j.idc2020.e00829.
Candesartan could ameliorate the attenuation of hepatic fibrosis by CD38 ablation. *J Biol Chem* 285: 576–582, 2010. doi:10.1074/jbc.M109.076216.

164. Shrikirshna D, Astin R, Kemp PR, Hopkinson NS. Renin-angiotensin system blockade: a novel therapeutic approach in chronic obstructive pulmonary disease. *Clin Sci (Lond)* 123: 487–498, 2012. doi:10.1042/CS20120081.

165. Gerasimenko JV, Tepikin AV, Petersen OH, Gerasimenko OV. Calcium uptake via endocytosis with rapid release from acidifying endosomes. *Curr Biol* 8: 1335–1338, 1998. doi:10.1016/S0960-9822(07)00565-9.

166. Schneider WM, Chevillotte MD, Rice CM. Interferon-stimulated genes: a complex web of host defenses. *Annu Rev Immunol* 32: 513–545, 2014. doi:10.1146/annurev-immunol-032713-120231.

167. Murakami T, Ockinger J, Yu J, Byles V, McCall A, Hofer AM, Horng T. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. *Proc Natl Acad Sci U S A* 109: 11282–11287, 2012. doi:10.1073/pnas.1117765109.

168. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Hurtado D. P. C, Prosper F, Romero JP, Winzberger G, Zhang H, Slutsky AS, Conder R, Montserrat N, Mirazimi A, Penninger JM. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 181: 905–913, 2020. doi:10.1016/j.cell.2020.04.004.

169. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCov) in vitro. *Cell Res* 30: 269–271, 2020. doi:10.1038/s41422-020-0282-0.

170. Chen X, Cao R, Zhong W. Host calcium channels and pumps in viral infections. *Cells* 9: 94, 2019. doi:10.3390/cells9010054.

171. Gunaratne GS, Yang Y, Li F, Walseth TF, Marchant JS. NAADP-dependent Ca2+ signaling regulates Middle East respiratory syndrome-coronavirus pseudovirus translocation through the endolysosomal system. *Cell Calcium* 75: 30–41, 2018. doi:10.1016/j.ceca.2018.08.003.

172. Heister PM, Poston RN. Pharmacological hypothesis: TPC2 antagonist tetrandrine as a potential therapeutic agent for COVID-19. *Pharmacol Res Perspect* 8: e00653, 2020. doi:10.1002/prp2.653.

173. Gerasimenko JV, Charlesworth RM, Sherwood MW, Ferdek PE, Mikoshiba K, Parrington J, Petersen OH, Gerasimenko OV. Both RyRs and TPCs are required for intracellular Ca2+ release. *Cell Calcium* 58: 237–245, 2015. doi:10.1016/j.ceca.2015.05.005.

174. Escande C, Nin V, Price NL, Capellini V, Gomes AP, Barbosa MT, O’Neill L, White TA, Sinclair DA, Chini EN. Flavonoid apigenin is an inhibitor of the NAD+-ase CD38: implications for cellular NAD+ metabolism, protein acetylation, and treatment of metabolic syndrome. *Diabetes* 62: 1084–1093, 2013. doi:10.2337/db12-1139.

175. Sun H, Luo G, Chen D, Xiang Z. A comprehensive and system review for the pharmacological mechanism of action of rhein, an active anthraquinone ingredient. *Front Pharmacol* 7: 247, 2016. doi:10.3389/fphar.2016.00247.

176. Yang L, Li T, Li S, Wu Y, Shi X, Jin H, Liu Z, Zhao Y, Zhang L, Lee HC, Zhang L. Rational design and identification of small-molecule allosteric inhibitors of CD38. *ChemBioChem* 20: 2485–2493, 2019. doi:10.1002/cbic.201900169.

177. Shu B, Feng Y, Gui Y, Lu Q, Wei W, Xue X, Sun X, He W, Yang J, Dai C. Blockade of CD38 diminishes lipopolysaccharide-induced macrophage classical activation and acute kidney injury involving NF-κB.
signaling suppression. Cell Signal 42: 249–258, 2018. doi:10.1016/j.cellsig.2017.10.014.

178. Chini EN. CD38 as a regulator of cellular NAD: a novel potential pharmacological target for metabolic conditions. Curr Pharm Des 15: 57–63, 2009. doi:10.2174/13816129778185788.

179. Yarbro JR, Emmons RS, Pence BD. Macrophage immunometabolism and inflamming: roles of mitochondrial dysfunction, cellular senescence, CD38, and NAD. Immunometabolism 2: e200026, 2020. doi:10.20900/immunometab20200026.

180. March S, Graupera M, Rosa SM, Lozano F, Pizcueta P, Bosch J, Engel P. Identification and functional characterization of the hepatic stellate cell CD38 cell surface molecule. Am J Pathol 170: 176–187, 2007. doi:10.2353/ajpath.2007.051212.

181. Liu X, Li Z, Liu S, Sun J, Chen Z, Jiang M, Zhang Q, Wei Y, Wang X, Gressner AM, Weiskirchen R, Breitkopf K, Dooley S. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. Acta Pharm Sin B 10: 1205–1215, 2020. doi:10.1016/j.apsb.2020.04.008.

182. Naylor E, Arredouani A, Vasudevan SR, Lewis AM, Parkesh R, Mizote EN, Chini EN. Signaling suppression. Cell Signal 42: 249–258, 2018. doi:10.1016/j.cellsig.2017.10.014.

183. Song SB, Park JS, Chung GJ, Lee IH, Hwang ES. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD⁺ precursor vitamins in human nutrition. Annu Rev Nutr 28: 115–130, 2008. doi:10.1146/annurev.nutr.28.061807.155443.

184. Bogan KL, Brenner C. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD⁺ precursor vitamins in human nutrition. Annu Rev Nutr 28: 115–130, 2008. doi:10.1146/annurev.nutr.28.061807.155443.

185. Liu X, Li Z, Liu S, Sun J, Chen Z, Jiang M, Zhang Q, Wei Y, Wang X, Huang YY, Yi S, Yu X, Xian H, Bai F, Ou C, Xiong B, Lew AM, Cui J, Fang R, Huang H, Zao J, Hong X, Zhang Y, Zhou F, Luo HB. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. Acta Pharm Sin B 10: 1205–1215, 2020. doi:10.1016/j.apsb.2020.04.008.

186. Naylor E, Arredouani A, Vasudevan SR, Lewis AM, Parkesh R, Mizote EN, Chini EN. Signaling suppression. Cell Signal 42: 249–258, 2018. doi:10.1016/j.cellsig.2017.10.014.

187. Chini EN. CD38 as a regulator of cellular NAD: a novel potential pharmacological target for metabolic conditions. Curr Pharm Des 15: 57–63, 2009. doi:10.2174/13816129778185788.

188. Yarbro JR, Emmons RS, Pence BD. Macrophage immunometabolism and inflamming: roles of mitochondrial dysfunction, cellular senescence, CD38, and NAD. Immunometabolism 2: e200026, 2020. doi:10.20900/immunometab20200026.

189. Thiel G, Mayer SI, Müller I, Stefano L, Rössler OG. Egr-1–A Ca2+-regulated transcription factor. Cell Calcium 47: 397–403, 2010. doi:10.1016/j.ceca.2010.02.005.

190. Cai Y, Liu Y, Zhang X. Induction of transcription factor Egr-1 gene expression in astrocytes from murine coronavirus infection. Virology 355: 152–163, 2006. doi:10.1006/viro.2006.07.012.

191. Vedantham S, Thiagajaran D, Ananthakrishnan R, Wang L, Rosario R, Zou YS, Goldberg I, Yan SF, Schmidt AM, Ramasamy R. Aldose Reductase drives hyperacetylation of Egr-1 in hyperglycemia and consequent upregulation of proinflammatory and prothrombolic signals. Diabetes 63: 761–774, 2014. doi:10.2337/db13-0032.
206. Falcone C, Caracciolo M, Correale P, Macheda S, Vadala EG, La Scala S, Tescione M, Danielli R, Ferrarelli A, Tarasino MG, Romano L, De Lorenzo A. Can adenosine fight COVID-19 acute respiratory distress syndrome? J Clin Med 9: 3045, 2020. doi:10.3390/jcm9093045.

207. Bamba C, Singh SP, Choudhury S. Can mesenchymal stem cell therapy be the interim management of COVID-19? Drug Discov Ther 14: 139–142, 2020. doi:10.5582/ddt.2020.03032.

208. Horenstein AL, Chillemi A, Zini R, Quarona V, Bianchi N, Manfredini R, Gambari R, Malavasi F, Ferrari D. Cytokine-induced killer cells express CD39, CD38, and CD203a. J Immunol 207: 850–863, 2020. doi:10.4049/jimmunol.20190733.

209. Ohradanova-Repic A, Machacek C, Charvet C, Lager F, Le RD, Platzer R, Leksia V, Mitulovic G, Burkard TR, Zlabinger GJ, Fischer MB, Feuillet V, Renault G, Blouin S, Benko M, Suchanek M, Huppa JB, Matsuyama T, Cavaco-Paulo A, Bismuth G, Stockinger H. Extracellular purine metabolism is the switchboard of immunosuppressive macrophages and a novel target to treat diseases with macrophage imbalances. Front Immunol 9: 852, 2018. doi:10.3389/fimmu.2018.00852.

210. Ghobrial I, Cruz CH, Garfall A, Shah N, Munshi N, Kaufman J, Boise Barnes PJ. Regulation of the cd38 promoter in human airway smooth muscle cells by TNF-α and dexamethasone. Respir Res 9: 26, 2008. doi:10.1186/1465-9921-9-26.

211. Tirumurugaan KG, Kang BN, Panettieri RA, Foster DN, Walseth TF, Komaravelli N, Tian B, Ivanciuc T, Mautemps N, Brasier AR, Garofalo Yabluchanskiy A, Csipo T, Lipecz A, Reglodi D, Zlabinger GJ, Fischer E, Csiszár A, Ungvari Z. Nicotinamide mononucleotide (NNM) treatment attenuates oxidative stress and rescues angiogenic capacity in aged cerebromicrovascular endothelial cells: a potential mechanism for the prevention of vascular cognitive impairment. GeroScience 41: 619–630, 2019. doi:10.1007/s11357-019-00074-2.

212. Kiss T, Balasubramanian P, Valcarcel-Ares MN, Tarantini S, Yabluchansky A, Csipo T, Lpez A, Reglodi D, Zhang XA, Bari F, Farkas E, Csizsár A, Ungvari Z. Nicotinamide mononucleotide (NNM) treatment attenuates oxidative stress and rescues angiogenic capacity in aged cerebromicrovascular endothelial cells: a potential mechanism for the prevention of vascular cognitive impairment. GeroScience 41: 619–630, 2019. doi:10.1007/s11357-019-00074-2.

213. Saso L, Gurer-Orhan H, Stepaníč V. Modulators of oxidative stress: chemical and pharmacological aspects. Antioxidants 9: 657, 2020. doi:10.3390/antiox9080657.

214. Silva-Palacios A, Kögling M, Zazueta C, Nr2 signaling and redox homeostasis in the aging heart: A potential target to prevent cardiovascular diseases? Ageing Res Rev 26: 81–95, 2016. doi:10.1016/j.arr.2015.12.005.

215. Fulop GA, Kiss T, Tarantini S, Balasubramanian P, Yabluchansky A, Farkas E, Bari F, Ungvari Z, Csizsár A. Nr2 deficiency in aged mice exacerbates cellular senescence promoting cerebrovascular inflammation. GeroScience 40: 513–521, 2018. doi:10.1007/s11357-018-0047-6.

216. Komaravelli N, Tian B, Ivanciuc T, Mautemps N, Brasier AR, Garofalo Sasso L, Gurer-Orhan H, Stepaníč V. Modulators of oxidative stress: chemical and pharmacological aspects. Antioxidants 9: 657, 2020. doi:10.3390/antiox9080657.

217. Ferrari D, Speciale A, Cristiani M, Fratantonio D, Molonia MS, Ranaldi G, Saija A, Cimino F. Cytidin-3′-O-glucoside inhibits NF-κB expression by triggering deacetylation-proteasomal degradation of Nr2. free Radic Biol Med 58: 391–403, 2015. doi:10.1016/j.freeradbiomed.2015.05.043.

218. Ferrari D, Speciale A, Cristiani M, Fratantonio D, Molonia MS, Ranaldi G, Saija A, Cimino F. Cytidin-3′-O-glucoside inhibits NF-κB expression by triggering deacetylation-proteasomal degradation of Nr2. free Radic Biol Med 58: 391–403, 2015. doi:10.1016/j.freeradbiomed.2015.05.043.

219. Schultz MB, Sinclair DA. Why NAD+ declines during aging: it’s destroyed. Cell Metabolism 23: 965–966, 2016. doi:10.1016/j.cmet.2016.05.022.

220. Malavasi F, Deaglio S, Ferrero E, Funaro A, Sancho J, Ausiello CM, Ortolan E, Vaisitti T, Zubiaur M, Fedele G, Aydin S, Tibaldi EV, Durelli L, Gusso R, Cozno F, Horenstein AL. CD38 and CD157 as receptors of the immune system: a bridge between innate and adaptive immunity. GeroScience 40: 513–521, 2018. doi:10.1007/s11357-018-0047-6.
adaptive immunity. Mol Med 12: 334–341, 2006. doi:10.2119/2006-00094.Malavasi.

231. Fang EF, Bohr VA. NAD+: The convergence of DNA repair and mitophagy. Autophagy 13: 442–443, 2017. doi:10.1080/15548627.2016.1257467.

232. Gomes AP, Price NL, Ling AJ, Moslehi JJ, Montgomery MK, Rajman L, White JP, Teodorou JS, Wrann CD, Hubbard BP, Mercklen EM, Palmeira CM, de cabo R, Rolop AP, Turner N, Bell EL, Sinclair DA. Declining NAD+ induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell 155: 1624–1638, 2013. doi:10.1016/j.cell.2013.11.037.

233. Loring HS, Icsó JD, Nemmara VV, Thompson PR. Initial kinetic characterization of sterile alpha and toll/interleukin receptor motif-containing protein 1. Biochemistry 59: 933–942, 2020. doi:10.1021/acs.biochem.9b01078.

234. Wu S, Zhang R. CD38-expressing macrophages drive age-related NAD+ decline. Nat Metab 2: 1186–1187, 2020. doi:10.1038/s42255-020-00292-5.

235. Schafef MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ, Oberg AL, Birch J, Salomonovich H, Zhu Y, Mazula DL, Brooks RW, Fuhrmann-Stroissnigg H, Pirtskhalava T, Prakash YS, Robbins PD, Aubry MC, Passos JS, Kirkland JL. Characterization and phylogenetic epitope mapping of the CD38 world: the importance of SIRT1 and NAMPT-mediated NAD biosynthesis. Nat Commun 8: 14532, 2017. doi:10.1038/ncomms14532.

236. Basisty N, Kale A, Jeon OH, Kuehnemann C, Payne T, Rao C, Holtz A, Shah S, Sharma V, Ferrucci L, Campisi J. A proteomic atlas of senescence-associated secretomes for aging biomarker development. PLoS Biol 18: e3000599, 2020. doi:10.1371/journal.pbio.3000599.

237. Clarke NE, Belyaev ND, Lambert DW, Turner AJ. Epigenetic regulation of angiotensin-converting enzyme 2 (ACE2) by SIRT1 under conditions of cell energy stress. Clin Sci (Lond) 126: 507–516, 2014. doi:10.1042/CS20130291.

238. Imai S. Dissecting systemic control of metabolism and aging in the NAD World: the importance of SIRT1 and NAMPT-mediated NAD biosynthesis. FEBS Lett 585: 1657–1662, 2011. doi:10.1016/j.febslet.2011.04.060.

239. Liu T, Rinke AE, Wang J, Phan SH. Cellular NAD+, fibroblast senescence and pulmonary fibrosis. FASEB J 34: 1, 2020. doi:10.1096/fasebj.2020.34.s1.02280.

240. Bian C, Zhang C, Luo T, Vyas A, Chen SH, Liu C, Kassab MA, Yang Y, Kong M, Yu X. NADP+ is an endogenous PARP inhibitor in DNA damage response and tumor suppression. Nat Commun 10: 693, 2019. doi:10.1038/s41467-019-08530-5.

241. Shi B, Bhattacharyya S, Korman B, Marangoni RG, Camp D, Cheres L, De Oliveira G, Chen E, Varga J. Targeting dysregulated CD38/NAD+ homeostasis mitigates multiple organ fibrosis: ACR Meeting (Abstract) [Online]. Arthritis Rheumatol 70, 2020. https://acrabstracts.org/abstract/targeting-dysregulated-cd38-nad-homeostasis-mitigates-multiple-organ-fibrosis/ [2020 Oct 26].

242. Vaninov N. In the eye of the COVID-19 cytokine storm. Nat Rev Immunol 20: 277–277, 2020. doi:10.1038/s41577-020-0305-6.

243. Kumar V, Agrawal R, Pandey A, Kopf S, Hoffgen M, Kaymak S, Bandapalli OR, Gorbunova V, Seluanov A, Mall MA, Herzog S, Nawroth PP. Compromised DNA repair is responsible for diabetes-associated fibrosis. EMBO J 39, 2020. doi:10.15252/embj.2019fi03477.

244. Sumoza-Toledo A, Penner R. TRPM2: a multifunctional ion channel for calcium signalling. J Physiol 589: 1515–1525, 2011. doi:10.1113/jphysiol.2010.201855.

245. Son YM, Cho E, Park IS, Kong M, Wei X, Song Y, Lin Y, Guo X, Gao X, Che J, Takahashi Y, Fu YX, Dent AL, Kaplan MH, Taylor JJ, Cui W, Sun J. Tissue-resident CD4+ T helper cells assist the development of protective respiratory B and CD8+ T cell memory responses. Sci Immunol 6: eabb6852, 2021. doi:10.1126/sciimmunol.abb6852.

246. Morra M, Zubiaur M, Terhorst C, Sancho J, Malavasi F. CD38 is functionally dependent on the TCR/CD3 complex in human T cells. FASEB J 12: 581–592, 1998. doi:10.1096/fasebj.12.7.581.

247. Muñoz P, Mittelbrunn M, de la Fuente H, Pérez-Martínez M, García-Pérez A, Ariza-Veguillas A, Malavasi F, Zubiaur M, Sánchez-Madrid F, Sancho J. Antigen-induced clustering of surface CD38 and recruitment of intracellular CD38 to the immunologic synapse. Blood 111: 3653–3664, 2008. doi:10.1182/blood-2007-07-101600.

248. Morena M, Marimpietri D, Horenstein AL, Bolzoni M, Pistoia V, Costacou T, Costa F, Castella B, Faini AC, Massaia M, Pecotich A, Giuliani N, Malavasi F. Microvesicles released from multiple myeloma cells are equipped with ectoenzymes belonging to canonical and non-canonical adenosinergic pathways and produce adenosine from ATP and NAD. Oncoimmunology 7: e1458809, 2018. doi:10.1080/2162402X.2018.1458809.

249. Gul R, Kim UH, Affalda AA. Renin-angiotensin system at the interface of COVID-19 infection. Eur J Pharmacol 890: 173656, 2021. doi:10.1016/j.ejphar.2021.173656.

250. Tay MZ, Poh CM, Reina L, Macay PA, Ng LF. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 20: 363–374, 2020. doi:10.1038/s41577-020-0311-8.

251. Wax RS, Christian MD. Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Can J Anaesth 67: 568–576, 2020. doi:10.1007/s12630-020-01591-x.

252. Sitkovsky MV, Ohta A. The “danger” sensors that STOP the immune response: the A2 adenosine receptors? Trends Immunol 26: 299–304, 2005. doi:10.1016/j.it.2005.04.004.

253. Mutti L, Pentimalli F, Baglio G, Maiorano P, Saladino RE, Correale P, Giordano A, Coronavirus disease (Covid-19): what are we learning in a country with high mortality rate? Front Immunol 11: 1208, 2020. doi:10.3389/fimmu.2020.01208.

254. Thiel M, Troulopou M, Ohta A, Jackson E, Caldwell C, Smith P, Lukashov D, Bittmann I, Sitkovsky MV. Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury. PLoS Biol 3: e174, 2005. doi:10.1371/journal.pbio.0030174.

255. Liu Y, Clement J, Grant R, Sachdev P, Braidy N. Quantification of NAD+: why do we need to measure it? Biochim Biophys Acta 1862: 2527–2532, 2018. doi:10.1016/j.bbamag.2018.07.023.

256. Enkirch T, von Messling V, Ferret models of viral pathogenesis. Virology 479: 259–270, 2015. doi:10.1016/j.virol.2015.03.017.

257. Rogers TF, Zhao F, Huang D, Beutler N, Burns A, He WT, et al. Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model. Science 369: 956–963, 2020. doi:10.1126/science.abc7520.

258. Ferrero E, Orciani M, Vacca P, Ortolan E, Crovella S, Titti F, Saccucci F, Malavasi F. Characterization and phylogenetic epitope mapping
of CD38 ADPR cyclase in the cynomolgus macaque. BMC Immunol 5: 21, 2004. doi:10.1186/1471-2172-5-21.

259. Munster VJ, Feldmann F, Williamson BN, van Doremalen N, Pérez-Pérez L, Schulz J, Meade-White K, Okumura A, Callison J, Brumbaugh B, Avanzato VA, Rosenke R, Hanley PW, Saturday G, Scott D, Fischer ER, de Wit E. Respiratory disease and virus shedding in rhesus macaques inoculated with SARS-CoV-2. Nature 585: 268–272, 2020. doi:10.1038/s41586-020-2324-7.

260. Yu P, Qi F, Xu Y, Li F, Liu P, Liu J, et al. Age-related rhesus macaque models of COVID-19. Animal Model Exp Med 3: 93–97, 2020. doi:10.1002/ame2.12108.

261. Si L, Bai H, Rodas M, Cao W, Oh CY, Jiang A, et al. A human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics. Nat Biomed Eng. In press. doi:10.1038/s41551-021-00718-9.