

1 CD38 in the Age of COVID-19: A Medical Perspective

2 Alberto L. Horenstein^{1*}, Angelo C. Faini¹, and Fabio Malavasi^{1*}

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4 ¹Department of Medical Science, University of Turin; Centro Ricerca Medicina
5 Sperimentale (CeRMS) and Fondazione Ricerca Molinette Onlus, Turin, Italy.

6 *Corresponding authors

7
8 **A.L.H.:** email: horenstein.al@gmail.com
9 ORCID 0000-0002-0382-0595.

10 **A.C.F.:** email: angelo.faini@edu.unito.it
11 ORCID 0000-0003-2193-4577

12 **F.M.:** email: fabio.malavasi@unito.it
13 ORCID 0000-0002-1844-174X

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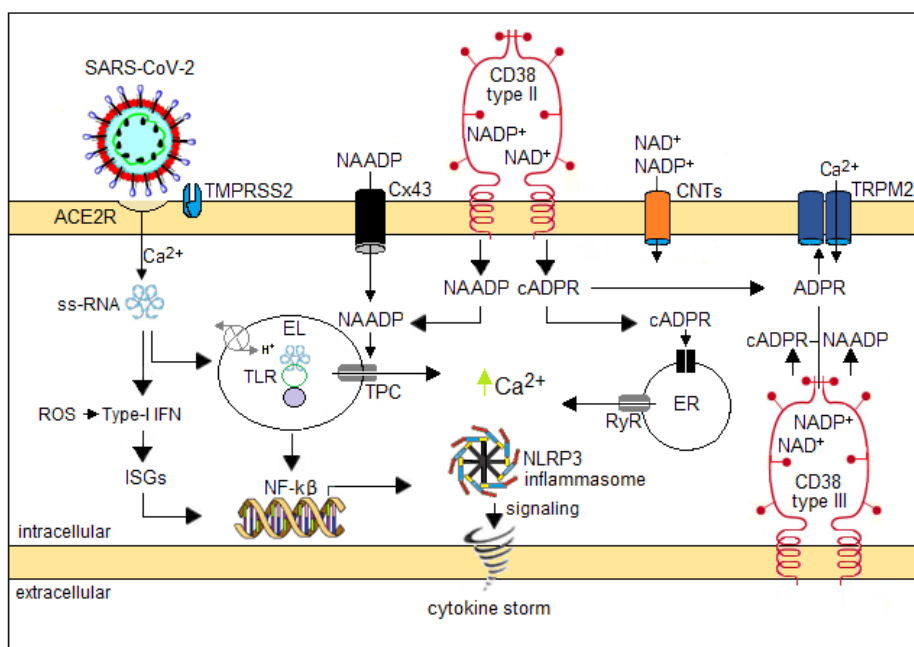
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66 **ABSTRACT** (164 words)

67 This medical review addresses the hypothesis that CD38/NADase is at the center of a functional
68 axis (i.e., intracellular Ca^{2+} mobilization/IFN γ response/ROS burst) driven by SARS-CoV-2 infection, as
69 already verified in Respiratory Syncytial Virus pathology and CD38 activity in other cellular settings. Key
70 features of the hypothesis are that: i) the substrates of CD38 (e.g., NAD^+ and NADP^+) are depleted by
71 viral-induced metabolic changes; ii) the products of the enzymatic activity of CD38 (e.g.,
72 cADPR/ADPR/NAADP) and related enzymes (e.g., PARPs, Sirtuins, ADP-ribosyl hydrolase) are
73 involved in the anti-viral and proinflammatory response that favors the onset of lung immunopathology
74 (e.g., cytokine storm and organ fibrosis); and iii) the pathological changes induced by this kinetic
75 mechanism may be reduced by distinct modulators of the CD38/ NAD^+ axis (e.g., CD38 blockers; NAD^+
76 suppliers, among others). This view is supported by arrays of associative basic and applied research
77 data which are herein discussed and integrated with conclusions reported by others in the field of
78 inflammatory, immune, tumor and viral diseases.

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80 **CALL-OUT BOX**

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.

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84 to those whose work is not cited due to space limitations.

85

86 ABBREVIATIONS

87 (Not included in the List of Commonly Accepted Abbreviations)

88 ACE: Angiotensin-Converting Enzyme

89 ADPR: Adenosine diphosphate ribose

90 ADO: Adenosine

91 ARH: ADP-ribosylhydrolase

92 ARDS: Acute Respiratory Distress Syndrome

93 AhR: Aryl hydrocarbon Receptor

94 ATRA: All-trans retinoic acid

95 8-Br-cADPR: 8-Bromo-cADPR

96 cADPR: cyclic ADPR

97 Ca²⁺: ionic calcium

98 CD38: Cluster of Differentiation 38

99 COVID-19: Coronavirus disease 2019

100 CoV: Coronavirus

101 COPD: Chronic Obstructive Pulmonary Disease

102 CSS: Cytokine Storm Syndrome

103 DAMPs: Damage-Associated Molecular Patterns

104 DCs: Dendritic cells

105 Egr-1: Early growth response-1

106 ENPP1: ectonucleotide pyrophosphatase/phosphodiesterase 1

107 e5'NT: 5'ecto-nucleotidase

108 EL: Endolysosome

109 ER: Endoplasmic Reticulum

110 GCSF: Granulocyte-Colony Stimulating Factor

111 hMDDCs: human Monocyte-Derived Dendritic Cells

112 IFN-1: type 1 interferon

113 IRF: Interferon-Responsive Element

114 ISGs: Interferon-Stimulated Genes

115 mART: (mono) ADPribosyl transferase

116 MERS-CoV: Middle East Respiratory Syndrome Coronavirus

117 MDSC: Myeloid Derived Suppressor Cell

118 NA: Nicotinic acid

119 NAADP: Nicotinic acid adenine dinucleotide phosphate

120 NAM: Nicotinamide

121 NMN: Nicotinamide mononucleotide
122 NK cell: Natural Killer cell
123 NLRP3: NLR family pyrin domain containing protein 3
124 NRF2: Nuclear factor erythroid 2-related factor 2
125 NR: Nicotinamide riboside
126 nsp: non-structural protein
127 PAMPs: Pathogen-Associated Molecular Patterns
128 PM: Plasma Membrane
129 PARP: Poly (ADP-ribose) polymerase
130 RAS: Renin-Angiotensin System
131 RyR: Ryanodine Receptor
132 RSV: Respiratory Syncytial Virus
133 SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
134 SIRT: Sirtuin
135 ss-RNA: single strand-RNA
136 TLR: Toll-like-receptor
137 TMPRSS2: Transmembrane protease serine 2
138 TPC: Two-Pore Channel
139 Trp: Tryptophan
140 Treg: T regulatory lymphocyte
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143 **I. GENERAL PREMISE**

144 **A. Starting point**

145 This perspective paper is grounded in observations from a 2018 study on the modulation of CD38
146 during Respiratory Syncytial Virus (RSV) infection in monocytes and macrophages (203). Upon
147 activation of the adaptive immune system during RSV infection, human monocyte-derived dendritic cells
148 (hMDDCs) up-regulate CD38 expression and affect the ability to activate T cell proliferation (47).
149 Similarly, during other viral infections, overexpression of CD38 by both CD4⁺ and CD8⁺ T lymphocytes,
150 results in nicotinamide adenine dinucleotide (NAD⁺) depletion (201, 242). During viral infection, the
151 infiltration of monocyte-derived macrophages is accompanied by release of high levels of reactive
152 oxygen species (ROS) and proinflammatory cytokines (164). In the case of RSV, the innate immune
153 response is initiated by recognition of single-stranded viral RNA (ssRNA) and secretion of type 1
154 interferon (IFN-1) by infected cells.

155 IFNs engage autocrine- or paracrine-specific receptors to induce expression of a set of IFN-
156 stimulated genes (ISGs), which inhibit viral replication by reprogramming the cellular metabolism.
157 Moreover, ISGs are inhibited by the anti-oxidant N-acetyl cysteine, further highlighting the role of ROS
158 in the process of anti-viral responses (46, 203). It is known that CD38 is involved in angiotensin (Ang)
159 II-induced intracellular Ca²⁺ release and ROS production (141). The ROS process in RSV-infected
160 hMDDCs is under the control of CD38 (203) and its catalytical activity is up-regulated as assessed by
161 measuring the accumulation of adenosine diphosphate-ribose (ADPR) after adding NAD⁺ as a substrate
162 (110, 203). This means that NAD⁺ consumption and generation of metabolic products by the enzymatic
163 functions of CD38 are involved in the induction of anti-viral and proinflammatory responses.

164 This paper seeks to identify the underlying basis of CD38 involvement in the response to Severe
165 Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) responsible for the coronavirus disease
166 (COVID-19) pandemic (105). It does so by examining some of the key metabolic steps controlled by
167 CD38 and its role in the immune response.

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170 (COVID-19) pandemic (105). It does so by examining some of the key metabolic steps controlled by
171 CD38 and its role in the immune response.

172 **B. The COVID-19 disease**

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

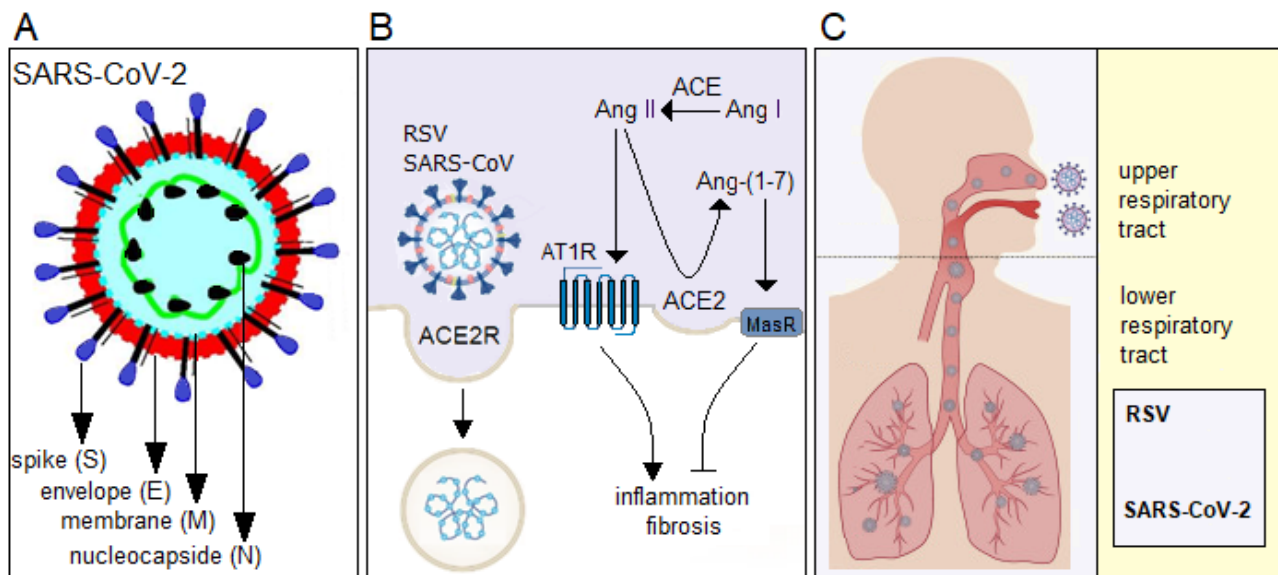
177 **C. The SARS-CoV-2 virus and cell entry**

178 Pathogenesis of SARS-CoV-2 infection (Fig. 1A-C) starts when the trimeric viral spike (S)
179 glycoprotein binds to the human cell surface type I transmembrane angiotensin-converting enzyme 2
180 receptor (ACE2R), followed by proteolytic priming of the S protein. It contains two subunits: i) S1, which
181 has two major structural elements, the receptor-binding domain (RBD) and the N-terminal domain
182 (NTD), and ii) S2, which mediates virus-cell membrane fusion after the RBD engages ACE2 (243). A
183 two-step sequential protease cleavage model has been proposed for activation of S protein priming. A
184 first cleavage between S1 and S2 activates a nick on S2' site, by host proteases: the cellular
185 transmembrane protease serine 2 (TMPRSS2) and furin, respectively (106, 118). Besides TRPRSS,
186 other proteases have also been implicated in facilitating virus entry. Indeed, the extracellular protease
187 plasmin is also able to nick the spike at the S1/S2, a furin cleavage site that increases its ability to bind
188 with ACE2R of host cells (13).

189 Once the endocytic uptake is unlocked, the viruses uncoat the genome and release the genetic
190 material, namely ss-RNA, to initiate replication. The coronavirus (CoV) genome does not encode for
191 enzymes necessary for the synthesis of proteins, amino acids, lipids or nucleotides. Therefore, SARS-
192 CoV-2 exploits the host cell for its own replication and to protect its ss-RNA from anti-viral immunity
193 (261). To ensure its integrity, viral RNA is capped and methylated at the 5' end by CoV-non-structural
194 protein (nsp) (e.g., methyltransferase, MTase) (245), thereby resembling host mRNA to promote
195 translation and to prevent its degradation. All the successive events occur in the nucleus and cytoplasm
196 (66).

197 ACE2 was originally identified as the receptor of other SARS CoVs (133) as well as of the RSV
198 (203). Of note, ACE2 is also a metalloprotease enzyme, which catalyzes the conversion of the
199 substrate angiotensin (Ang)-II to Ang-1–7 in the Renin-Angiotensin System (RAS) (75), as shown in
200 Fig.1B. Besides ACE2, it has also been suggested that CD26, the host receptor for MERS-CoV (239),
201 and CD147 (120), serve as endocytic cell entry for SARS-CoV-2.

202 The ACE2R is expressed by endothelial and epithelial cells present in different organs, such as
203 lungs, heart, gut, kidneys, brain, and placenta which are all susceptible to viral infection (226, 246, 250).
204 In the lungs, ACE2 is expressed by cells of the upper or lower respiratory tract, a critical step for initiation
205 and clinical presentation of the viral infection. Both SARS-CoV-2 and RSV mainly affect the lower
206 respiratory tract (Fig.1C). Pathognomonic signs generally found in human diseases and caused by
207 respiratory virus (e.g., RSV and SARS-CoV-2), are involved in an hyperimmune response causing lung
208 pathology (203, 250).



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Figure 1. Schematic illustration of the SARS-CoV-2 molecular structure and essential mechanisms of viral infection and outcomes. A) The SARS-CoV-2 genome encodes non-structural proteins (nsp1-nsp16) (not shown) and four structural proteins: spike (S) glycoprotein, envelope, membrane, and nucleocapsid phosphoprotein, which together ensure replication of the virus in the host cell. B) The octapeptide Ang II is originated from the decapeptide Ang I by soluble ACE2 enzymatic activity. Ang II acts via AT1Rs while Ang (1–7), generated from Ang II by ACE2 carboxypeptidase, acts via the Mas receptor (MasR). SARS-CoV-2 binding to the ACE2 catalytic receptor (ACE2R) enhances lung inflammation by reducing ACE2 activity and increasing Ang II. Depletion of ACE2 activity decreases the production of Ang 1-7, which has an anti-inflammatory and anti-fibrotic activity. C) SARS-CoV-2 and RSV preferentially bind to the ACE2R expressed by alveolar epithelial cells and macrophages in the lower human respiratory tract.

222 II. CD38 CHARACTERISTICS AND FUNCTIONS POTENTIALLY LINKED TO THE HOST 223 RESPONSE TO SARS-CoV-2 INFECTION.

224 A. CD38

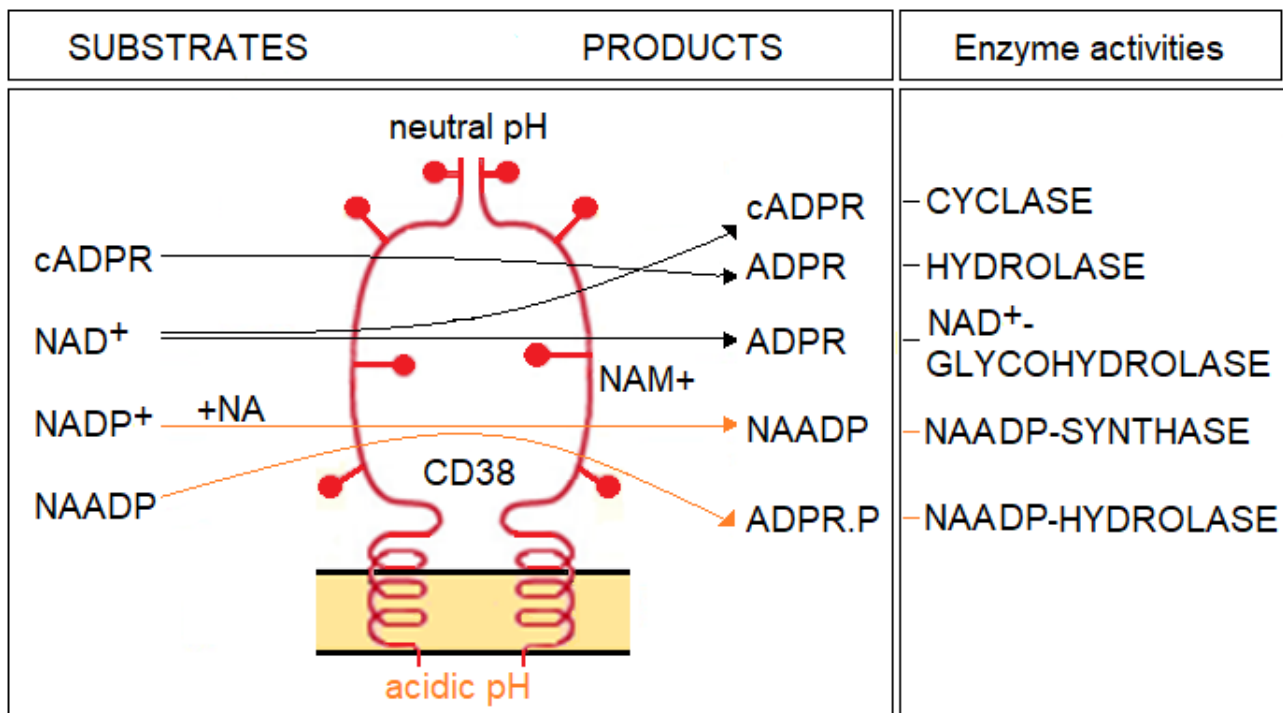
225 CD38 is a multifunctional cell protein endowed with signaling receptor and enzymatic features
226 and was initially identified as a lymphocyte antigen by monoclonal antibody typing (195). CD38, present
227 outside of the cell (45) and also intracellularly in the nucleus and organelles (1), is associated with
228 important diseases, such as AIDS, autism, diabetes, chronic lymphocytic leukemia, and multiple
229 myeloma (Table 1). These characteristics of CD38 have been comprehensively reviewed (158).

230 1. CD38 as an enzyme

231 CD38 is a 43.7-kDa transmembrane glycoprotein, which also exists in a 39-kDa soluble form
232 that retains its biochemical features in both normal and pathological fluids (80, 146). Recognition of
233 structural and functional similarities between human CD38 and the enzyme ADP-ribosyl cyclase,
234 purified from the sea mollusk *Aplysia*, allowed attribution of enzymatic activities to CD38 (137). Indeed,
235 at physiological pH, CD38 catalyzes several enzymatic reactions: i) the conversion of nicotinamide
236 adenine dinucleotide (NAD⁺) to adenosine diphosphate ribose (ADPR) (NAD⁺- glycohydrolase activity);

237 ii) the conversion of NAD^+ to cyclic ADPR (cADPR) (cyclase activity), and iii) the hydrolysis of cADPR
 238 to ADPR (hydrolase activity). At acidic pH, CD38 runs iv) the conversion of NADP^+ , the phosphorylated
 239 equivalent of NAD^+ , to nicotinic acid adenine dinucleotide phosphate (NAADP) (NAADP-synthase
 240 activity) in the presence of nicotinic acid (NA) and the degradation of NAADP to ADPR.P (NAADP-
 241 hydrolase activity) (Fig. 2). All of the reaction products are second messengers involved in the regulation
 242 of cytoplasmic Ca^{2+} fluxes (139). NAD^+ -glycohydrolase, the main enzymatic activity of CD38, is not
 243 modified in the presence of anti-CD38 human or murine antibodies. On the contrary, cyclase activity is
 244 highly inhibited, while hydrolase activity is mildly activated (11, 112, 113). This data provides further
 245 support for considering extracellular CD38 primarily as a NAD^+ -glycohydrolase (107). CD38 is also able
 246 to catalyze the degradation of intracellular NAD^+ precursors [(e.g., nicotinamide mononucleotide (NMN)
 247 and nicotinamide (NAM)] (32, 109).

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Figure 2. CD38 enzymatic activities. CD38 catalyzes several enzymatic reactions: at neutral pH i) the conversion of nicotinamide adenine dinucleotide (NAD^+) into adenosine diphosphate ribose (ADPR) (NAD^+ -glycohydrolase activity); ii) the conversion of NAD^+ into cyclic ADPR (cADPR) (cyclase activity); iii) the hydrolysis of cADPR into ADPR (hydrolase activity). At acidic pH, iv) the conversion of NADP^+ , the phosphorylated equivalent of NAD^+ , into nicotinic acid adenine dinucleotide phosphate (NAADP) (NAADP-synthase activity) in the presence of nicotinic acid (NA) and the degradation of NAADP into ADPR.P (NAADP-hydrolase activity). All of the reaction products are second messengers involved in the regulation of cytoplasmic Ca^{2+} fluxes and the generation of immunosuppressive adenosine (see text and Fig. 3)

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

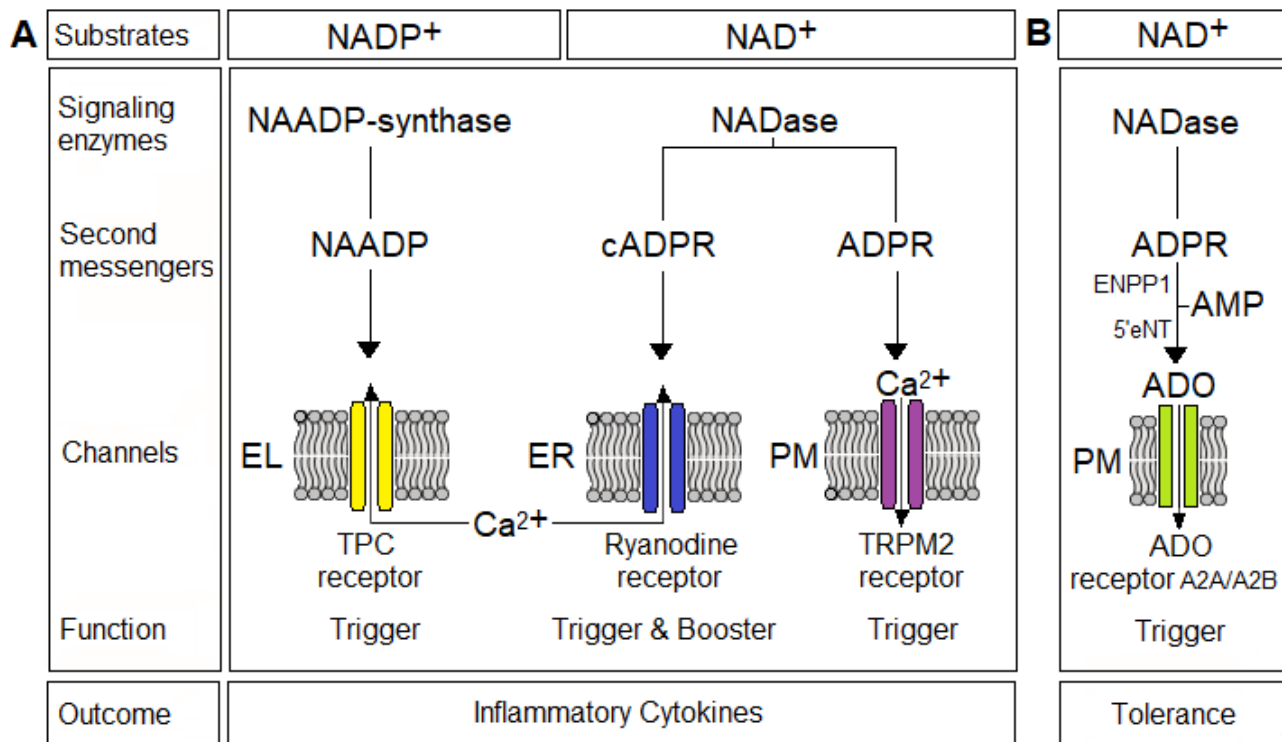
262 abrogated when the *CD38* gene is deleted, indicating that CD38 is the dominant enzyme responsible
263 for their synthesis (139). The nucleotide messengers regulate diverse cell functions by mobilizing
264 intracellular Ca^{2+} stores: i) NAADP-elicited Ca^{2+} release, important for SARS-CoV-2 entry into cells
265 (189), from the two-pore channels (TPCs), situated in acidic endolysosomes (EL) (24); ii) cADPR
266 enhances Ca^{2+} release via the activation of the ryanodine receptor (RyR) (158) situated in the membrane
267 of the endoplasmic reticulum (ER). cADPR can also activate the Ca^{2+} influx channel Transient Receptor
268 Potential Melastatin 2 (TRPM2) at the cell plasma membrane (PM), in synergy with ADPR (135) (Fig.
269 3). Although physically separated, the Ca^{2+} stores in the ER and the EL can interact: in fact, Ca^{2+}
270 released from the EL stores can be sequestered by the ER stores, boosting the latter for enhanced
271 release of Ca^{2+} through RyRs by cADPR (Fig. 3).

272 Further evidence for this view is that stimulation of the T cell receptor-CD3 complex results in
273 rapid NAADP formation in response to a stimulus. By contrast, an increase in cADPR concentration is
274 delayed, which indicates that NAADP serves as a second messenger initiating role in T cell Ca^{2+}
275 signaling (35, 100).

276 It was initially thought that CD38 operated exclusively in the extracellular compartment
277 containing the physiological substrates, with the products of the catalytic reaction being used inside the
278 cell, creating a sort of topological paradox. Most immune and non-immune cells express CD38 on the
279 surface, with the catalytic domain exposed to the outside. These are referred to as type II CD38.
280 Extracellular NAD^+ and NADP^+ substrates are metabolized by type II CD38 into cADPR/ADPR and
281 NAADP, respectively, acting in an autocrine mode for signaling (45). Substrates share the mechanism
282 for extrusion either by cell lysis under pathological conditions (e.g., inflammation or oncogenesis) or by
283 transportation through the connexin 43 (Cx43) hemichannels (21). Extracellular metabolites are able to
284 reenter the cell using concentrative nucleoside transporters (CNTs), where they can also acts in a
285 paracrine mode on neighboring cells (76). Type II CD38 is also compartmentalized in the EL/RE
286 organelles (251). Accordingly, the intracellular exploitation of type II CD38 metabolites targeting
287 intracellular Ca^{2+} release machineries, give rise to this topological enigma, only recently partially
288 disentangle (140).

289 These studies demonstrated the existence of a CD38 protein (referred to as type III CD38),
290 whose catalytic domain faces the intracellular compartment. This functionally-active molecule is
291 expressed on the inner cell membrane and in the ER and produces intracellular cADPR with high
292 efficiency (145). Type III CD38 is a non-glycosylated protein and thus devoid - in contrast to type II-
293 CD38 - of disulfide bridges (140), but whose formation during folding allows cADPR generation. The
294 autocrine/paracrine mechanisms of type II- and type III-CD38 work in concert to harmonize the
295 paradoxical regulatory issue. In mechanistic terms, and in line with previous observations on the pH
296 dependency of CD38, the resulting cADPR and ADPR products are synthesized at neutral pH, while

297 NAADP is synthesized at acidic pH (100, 138). The EL is highly acidic – and therefore not favorable for
 298 the cyclase activity of CD38 – thus pointing to EL the cellular compartment for the biogenesis of NAADP
 299 (Fig. 3). Extracellular NAADP can also be transported into the cell cytoplasm, where NAADP, either
 300 from inflow or *in situ* generated, is delivered to the EL to induce Ca^{2+} release from stores in response to
 301 various physiological stimuli (81). Additional findings were that cells expressing type III CD38 had the
 302 highest cADPR levels after induction by cytokines, and thus may be directly responsible for producing
 303 intracellular cADPR (258), targeting RyRs in the ER (Fig. 3).
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305

306 **Figure 3. Schematic illustration of intracellular signaling mediated by the CD38/NAD⁺ axis. A)**
 307 The NADPase and NADase enzymes are responsible for the formation of the Ca^{2+} -releasing
 308 messengers through the use of phosphorylated (NADP⁺) or non-phosphorylated NAD⁺, respectively.
 309 Second messengers generated as products are: NAADP, cADPR, and ADPR. NAADP-elicited Ca^{2+} is
 310 released from the two-pore channel (TPC) receptor situated in acidic endolysosomes (EL), and cADPR
 311 serves as the trigger and booster for Ca^{2+} release via the activation of the ryanodine receptor (RyR),
 312 situated in the endoplasmic reticulum (ER). ADPR elicits Ca^{2+} influx through the transient receptor
 313 melastatin 2 (TRPM2) situated in the plasma membrane (PM). **B)** ADPR can also be sequentially
 314 metabolized by ectonucleotidases (CD203a/ectonucleotide pyrophosphatase/phosphodiesterase 1
 315 (ENPP1) and CD73/5'-ectonucleotidase (5'eNT) for the formation of extracellular adenosine (ADO).
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317 2. CD38 as a receptor

318 Functional and structural data indicate that the promoter region of the human *CD38* gene,
 319 located at chromosome 4, is regulated by several nuclear factors including RAR α (retinoic acid
 320 receptor), RARE (retinoic acid-responsive element), GREs (glucocorticoid-responsive element), IRF

321 (interferon-responsive element) and NF- κ B (72). Further, CD38 expression is induced and regulated by
322 several soluble factors including cytokines and chemokines (5). The role of CD38 as a receptor was
323 confirmed by co-modulation experiments, indicating that the molecule displays lateral associations with
324 other molecules sharing signal pathways. In this way, CD38 overcomes the steric hindrance of its very
325 short cytoplasmic tail by interacting symbiotically with skilled receptors on different immune cells (e.g.,
326 T lymphocytes, NK cells and monocytes) (158). The CD38 protein, assembled as a transmembrane
327 receptor, influences both innate and adaptive immune responses by regulating the trafficking of cells
328 (e.g., macrophages, dendritic cells, lymphocytes, and neutrophils) to the sites of inflammation (77). For
329 migration purposes, CD38 expresses two hyaluronate-binding sites in the extracellular domain (183)
330 and thus interacts with its counterreceptor CD31 (PECAM, platelet/endothelial cell adhesion molecule-
331 1) (48, 180). CD38 is also related to T helper type 1 polarization and dendritic cells (DCs) chemotaxis
332 (77, 190).

333 **B. The CD38 catalytic receptor and inflammation**

334 In addition to being a surface cell differentiation and activation marker, it was later observed that
335 CD38 can induce the release of different cytokines after specific agonistic monoclonal antibody (mAb)
336 ligation (5). Conversely, it was observed that IFN- γ alone induces CD38 in human
337 macrophage/monocytes (177) and that Vitamin D causes myeloid cells to express surface markers of
338 monocytic cell differentiation (e.g., CD38, CD14, CD11b), converting macrophages into potent
339 immunosuppressive cells (191). CD38 activity in human macrophages is prevalently detected
340 intracellularly, with its primary function being i) the performance of cADPR and NAADP for Ca²⁺
341 regulation; ii) the contribution to inflammatory cytokine secretion, and iii) cooperation in reprogrammed
342 metabolic adaptations (e.g., increased glycolytic activity). Taken together, these data are consistent with
343 the role of inflammatory marker for human macrophage/monocyte CD38 in inflammatory processes (3).

344 Type 1 interferons (IFN α /IFN β) as well as other factors such as the RAS component Ang II (via
345 activation of NF- κ B) up-regulate CD38 expression (28, 162) in pro-inflammatory cytotoxic human M1
346 polarized macrophages, but not anti-inflammatory M2 (41, 117, 214). In turn, signaling through NF- κ B,
347 likely the primary transcription factor involved in the appearance of most of the proinflammatory genes,
348 is amplified by CD38 (122). Further, CD38 overexpression promotes a glycolytic adaptation in human
349 macrophages (117).

350 Related to this metabolic event, nucleotides (such as NAD⁺ and ATP) are released during the
351 early phase of viral inflammation, acting as danger signals that alert the immune system through binding
352 to P2 type of purinergic receptors (P2Rs) (22, 115). Consumed nucleotides are re-built by enzymatic
353 salvage pathways to restore extracellular homeostasis. As shown in Fig. 4, NAD⁺ scavengers are
354 nucleotide-catabolizing ectoenzymes (e.g., CD38/NADase, ectonucleoside pyrophosphatase
355 phosphorylase, ENPP1/CD203a, and 5'-ectonucleotidase, 5'eNT/CD73) that generate adenosine

356 (ADO) as end product, which can re-enter the cell to reconstitute the pool of purine nucleotides (110,
357 158). Alternatively, extracellular ADO, and probably inosine (INO), activates purinergic P1 receptors
358 (P1Rs) to dampen excessive inflammation, thus opposing inflammatory functions of P2R signaling (186).

359 Nucleotides released during viral inflammation also exert immunoregulatory roles *in vivo* (32,
360 203). For instance, macrophages not only express ACE2, but also high levels of CD38, the main
361 consumer of human NAD⁺. A reasonable model is that in hyperstimulated macrophages, the NLR family
362 pyrin domain containing protein 3 (NLRP3) inflammasome can be directly activated by SARS-CoV-2 via
363 a CD38-mediated Ca²⁺-dependent mechanism. This was posited during 2015 SARS epidemic (181).

364 A preliminary conclusion is that CD38 is involved in specific steps of viral inflammation by
365 modulating immune response and by regulating Ca²⁺ signaling in different cell populations and tissues.

366 **C. The CD38 catalytic receptor and immune response**

367 The immune system exploits cell and humoral responses to attack viruses. Of all the various
368 steps in COVID-19 immunity (237), here we analyze those potentially linked to CD38.

369 In SARS-CoV-2, innate immune response is activated when macrophages encounter viral
370 pathogen-associated molecular patterns (PAMPs) from invading SARS-CoV-2 ss-RNA. PAMPs up-
371 regulates CD38 and activates innate immune pathways through Toll-like receptors (TLRs) and NLRP3
372 inflammasome activation (240). Downstream signaling drives the secretion of a range of
373 proinflammatory cytokines, including IL1- β , IL1RA, IL-6, IL-7, IL-18, IL-10, IFN γ , and TNF α (61). This
374 leads to rapid recruitment of monocyte/macrophages to the lung in early phases of infection. The
375 successive production of IFN α /IFN β limits propagation of the virus (142). At the same time, IFNs
376 modulate the adaptive immune responses by increasing the expression of anti-viral specific genes
377 (ISGs) in neighboring cells (198).

378 For their part, CoVs escape immune responses by provoking a disbalance between anti-viral
379 and proinflammatory responses. It is hypothesized that SARS-CoV-2 exploit the up-regulation of host
380 ACE2R, by increased expression of ISGs and CD38 in human lung epithelial cells, to enhance viral
381 infection (141, 260). Other steps facilitating SARS-CoV-2 infection involve the suppression of IFN
382 expression by inhibiting the host sensor machinery or its downstream signaling (240). Other cell types,
383 including endothelial cells, are indirectly activated by circulating IL-6 and soluble IL-6 receptor
384 complexes, with massive cytokine production and cell apoptosis (227). Apoptotic infected endothelial
385 and epithelial cells contribute to tissue inflammation by releasing damage-associated molecular patterns
386 (DAMPs) into the extracellular environment and IL-1 β upon NLRP3 inflammasome activation. The
387 overproduction of IL-1 β then activates macrophages, NK and T cells, amplifying inflammation and
388 facilitating tissue infiltration through the up-regulation of adhesion molecules by lung endothelial cells.
389 Indeed, IL-1 β increases hyaluronan synthetase levels, and consequently matrix hyaluronate (12), which
390 is reported as an adhesive ligand of CD38 (183).

391 **D. The CD38 catalytic receptor in cell adhesion and thrombosis**

392 Up-regulation of molecules involved in cell adhesion (i.e., CD38 and CD31) has two-fold
393 consequences: lymphopenia and thrombosis, which are both predictors of COVID-19 disease severity
394 (224, 230).

395 Viral infection inducing excessive antigenic stimulation may cause a drastic decay in circulating
396 immune cells with progressive T cell anergy or exhaustion (50, 143). Mechanisms leading to
397 lymphopenia can be due to (i) a direct effect on lymphocytes or indirect action destroying lymphatic
398 organs; or (ii) a disordered inflammatory cytokine reaction leading to lymphocyte apoptosis (144).
399 CD38/NADase might be directly involved in these events. Indeed, CD38 activation by increased Ang II
400 levels may intensify NAD⁺ depletion. In turn, this condition affects NAD⁺-dependent enzymes (e.g.,
401 Sirtuins and PARPs), which are known regulators of cell viability and death (107).

402 CD38 express by immune cells is reported as interacting with extracellular matrix hyaluronate
403 and with CD31 (48). The balance between dissemination of immune cells (CD38^{high+} cells) to peripheral
404 blood and tissue retention in the respiratory tract is the result of the interplay between these molecules.
405 Indeed, CD38^{high+} promotes cell attachment to hyaluronate, whereas the interaction of CD38 with CD31
406 on endothelial cells results in retention prevalently in tissues (in the lungs) and a weaker egress of
407 immune cells to the peripheral blood, as has been shown in a leukemia model (82). Therefore, the
408 trapping of exhausted T lymphocytes in the lungs may contribute to lymphopenia. Lastly, lymphocyte
409 functions may be impaired by products derived from metabolic disorders, such as lactic acidemia (121)
410 (vide infra).

411 COVID-19 comorbidities feature elevated levels of the extracellular plasmin, a protease involved
412 in degradation of the fibrin matrix formed by the activity of thrombin during the process of thrombosis
413 (119, 224). Further, dysregulated Ang II due to loss of ACE2R by SARS-CoV-2, results in increased
414 signaling through i) purinergic P2R(s), and by ii) the serine protease thrombin, leading both to platelet
415 activation and thrombosis, emerging features of COVID-19 (224). Thrombin induces platelets activation
416 via mobilization of intracellular Ca²⁺, a process mediated by CD38 metabolic products, cADPR and
417 NAADP (176). Moreover, as a platelet agonist, thrombin stimulates the association of CD38 enzymatic
418 activities with the platelet cytoskeleton (236). As said, inflammatory conditions observed in COVID-19
419 are associated with the extracellular release of nucleotides, acting as ligands of purinergic receptors
420 (224). P2Rs signaling is a key mechanism for platelet activation, which contributes to
421 thromboinflammation and fibrosis (68). Indeed, an inflammatory P2R-associated release of IL-8 and
422 elastase from neutrophils contributes to the pathogenesis of chronic obstructive pulmonary lung disease
423 (COPD) (115). This finding suggest that nucleotide-activation of P2Rs can lead to inflammation, tissue
424 fibrosis, as well as to a NAD⁺-dependent Sirtuins inhibition associated to ROS production (68).
425 Purinergic and thrombotic-mechanisms can synergistically be activated during thrombosis (60).

426 Therefore, antagonistic drugs that target thrombin or P2Rs, may provide a useful therapy to blunt
427 inflammatory diseases, such as COPD and COVID-19 (224). Similarly, catalyzing the conversion of
428 ATP/NAD⁺ to ADO, thus terminating P2R effects, are already exploited in the treatment of inflammatory
429 conditions in human patients (169).

430 Consequently, CD38 may serve as a molecular target for i) immune cell trapping in the lungs
431 and ii) monitoring a down-modulation of macrophages during viral respiratory diseases (203). Further,
432 it may help track iii) lymphopenia and thrombosis resulting from uncontrolled activation of immune cells.

433 **E. The CD38 catalytic receptor and immuno-metabolic adaptations**

434 *1. The NAD⁺ metabolome*

435 The metabolism of NAD⁺ (NAD⁺ metabolome) is involved in a variety of normal biological
436 processes (182). As a tunable component of innate immunity, the NAD⁺ metabolome has become a
437 target for therapeutic modulation of the NAD⁺ status, which potentially curbs viral infection (131).
438 Observations support the view that the immune response to viral infections is linked to the NAD⁺
439 metabolome of the infected cells, as reported in Herpes virus and HIV-1 (93, 175).

440 NAD⁺ operates both intra-and extracellularly (Fig. 4). Extracellularly, NAD⁺ elicits signals acting
441 as a cytokine or serves as the substrate for a chain of nucleotidases led by CD38 to convert it to ADO,
442 a nucleoside involved in the control of inflammation and immune responses (110, 168). The extracellular
443 conversion of NAD⁺ varies significantly according to the tissue environment or health conditions. Indeed,
444 pathological settings are characterized by the NAD⁺ metabolome acting as a target of multiple
445 immunometabolic adaptations, as confirmed by a dysregulated NAD⁺ gene system upon *in vivo* SARS-
446 CoV-2 infection (103). Analyses of RNAseq data involved comparison with a gene set representative of
447 the NAD⁺ transcriptome coding for the enzymes responsible for i) NAD⁺ biosynthesis; ii) NAD⁺
448 phosphorylation to NADP⁺ and, iii) NAD⁺ consumption. First, primary cells infected by SARS-CoV-2
449 feature >3-fold depression of cellular NAD⁺ and NADP⁺, as compared to control cells. CD38 (and its
450 paralogue CD157) (158) are overexpressed (>2.5- and >1.5-fold, respectively) by infected human lung.
451 CD38 up-regulation and NAD⁺ depletion are paralleled by activation of the IFN-induced
452 mARTtransferase (mART) (65). The SARS-CoV-2 genome encodes for nsp (245): among them, an ADP-
453 ribosylhydrolase (ARH), an enzyme required for virulence that removes ADPR from proteins ribosylated
454 by mART (Fig.4). (2, 128).

455 The NAD⁺ metabolome is linked to the RAS/ACE2 system. On one side, NAD⁺ biosynthesis is
456 regulated by the nutritional supply of NAD⁺ precursors through *de novo* pathway, which uses tryptophan
457 (Trp), and the salvage pathway, which uses NAM/NA/NR (all referred to as vitamin B3), as primary
458 sources (Fig. 4) (109). Trp catabolism in chronic viral infections reduces circulating levels of NAD⁺,
459 resulting in exacerbated inflammation and low CD4⁺ T-cell recovery (163). On the other, the RAS system
460 exerts a protective role in acute lung injury via ACE2 and by modulating Trp levels in peripheral blood

461 (133). Indeed, in aminoacidic malnutrition, increasing Trp and vitamin B3 sources restores ACE2 activity
462 and prevents worsening of inflammation (102). In conclusion, epigenetic and pharmacological evidence
463 link the NAD⁺ metabolome to the RAS/ACE2 system. CD38 is activated by Ang II after ACE2 viral
464 blocking (Fig. 1B) and once the human lungs are infected, the virus may even try to suppress NAD⁺
465 production by the cells (16). NAD⁺ depletion leads suppression of both mitochondrial NAD⁺-dependent
466 signaling and resolution of inflammation (165).

467 Metabolomic studies indicate that under non-redox conditions NAD⁺ is mainly consumed by
468 CD38/NAD⁺-glycohydrolase, NAD⁺-dependent Sirtuins and -PARPs (Fig. 4) (182). Because of such
469 continuous NAD⁺ enzymatic degradation, its metabolite NAM and the other amidated and deamidated
470 NAD⁺ sources (e.g., NR, NMN, NA) needed for resynthesis of NAD⁺ are perforce scavenged (107). In
471 fact, the anti-viral host defenses mounted by NAD⁺-dependent-PARPs and -Sirtuins are removed by
472 depleting the cell of NAD⁺ (107, 203). This is supported by mice models showing that increased NAD⁺
473 levels augment the enzymatic activity of PARPs and Sirtuins, hindering CoV from hijacking the host
474 cellular machinery for replication (67).

475 CD38 is a crucial regulator of Sirtuins which modulate normal and pathological energy
476 metabolism (124). Sirtuins are dependent on NAD⁺ biogenesis, and thus regulated by Trp or by
477 nicotinamide phosphatidyltransferase (NAMPT), the rate-limiting enzyme that converts NAM into NAD⁺
478 (Fig. 4). Sirtuins and NAMPT participate in macrophage antiviral activity (43). In addition, CD38 activates
479 the Sirtuin/NFκB pathway in a NAD⁺-dependent manner, since CD38 blocking increases NAD⁺ levels
480 and Sirtuin-1 activity in the nuclear, cytoplasmic and mitochondrial compartments (1, 34). The
481 pharmacological inhibition of NAMPT and Sirtuins, components of the macrophage IFN anti-viral
482 cascade, promotes growth of cytomegalovirus in both fibroblasts and macrophages (43). The central
483 role of the NAD⁺ metabolome in these cells is further supported by the notion that extracellular NAMPT
484 behaves as a DAMP (159), which is elevated in COVID-19 patients with comorbidities (213).

485 The NAD⁺-consuming enzyme PARPs and the aryl hydrocarbon receptor (AhR) are
486 overexpressed in COVID-19 pathophysiology, and in other lung conditions (RSV and COPD) (17, 96).
487 Endogenous AhR ligands include Trp metabolite quinolinic acid in the *de novo* pathway and NA and
488 NAM in the salvage pathway of NAD⁺ biogenesis (Fig. 4). As a transcription factor, AhR is involved in
489 microbial defense, cell proliferation, immunity and NAD⁺ metabolism (17). AhR targets NAD⁺
490 metabolome functional elements such as CD38 and PARPs that are regulating glucose and lipid
491 metabolism via Sirtuins. Deregulation of these pathways may facilitate COVID-19 and age-dependent
492 pathologies (87). Indeed, a proinflammatory milieu leads to up-regulation of the AhR which in turn
493 activates PARPs. Mucin overproduction by lung epithelial cells triggered by IFN-signaling thickens the
494 blood-air barrier and leads to hypoxia (150). Because mucin up-regulation is driven by AhR, this factor

495 involved in NAD⁺ homeostasis in cooperation with CD38, PARPs and Sirtuins, is a potential target for
496 the treatment of hypoxia in COVID-19 patients (114).

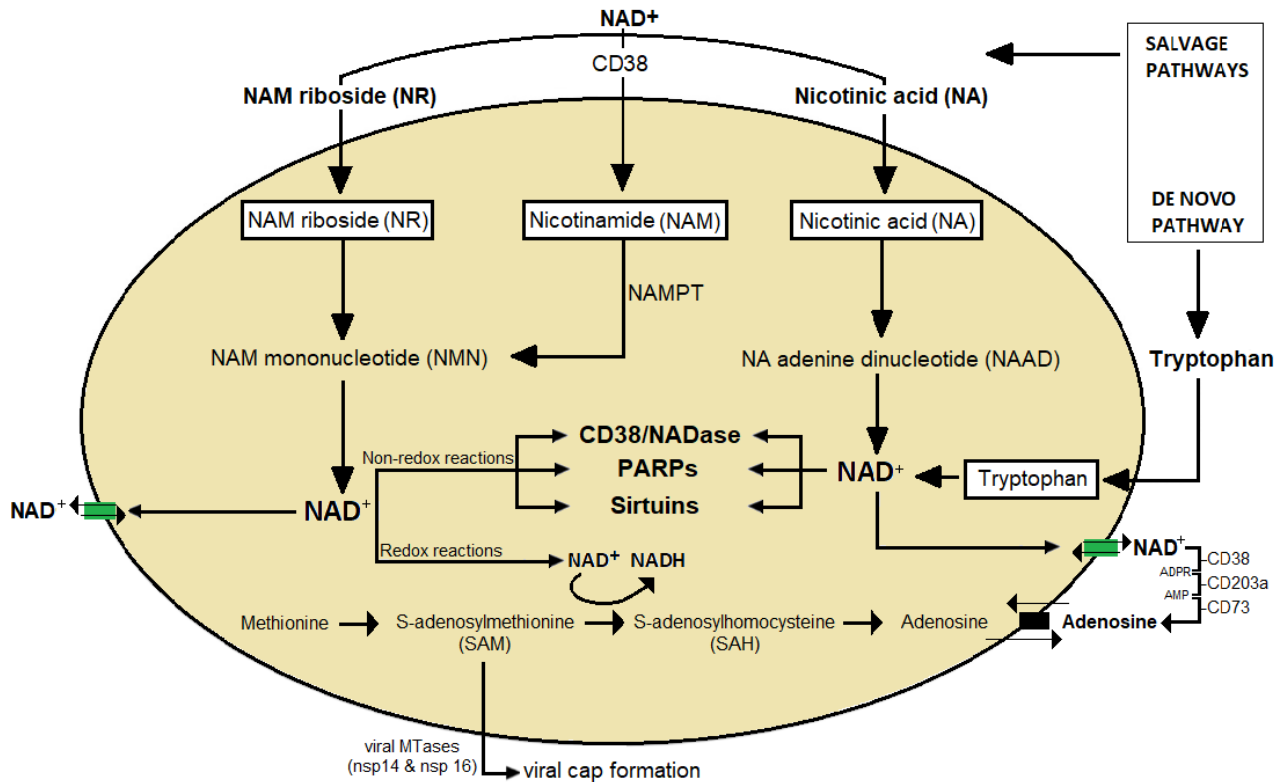
497 Overexpression of CD38 and PARPs in COVID-19 causes cell death mainly by depletion of NAD⁺
498 (6). NAD⁺ boost improves blood flow and vascular vitality by promoting Sirtuins dependent increase of
499 the levels of hydrogen sulfide (H₂S), an endothelial signal regulator of NAD⁺ levels (44, 252). Since H₂S
500 intracellular activity ensures vascular repair after injury, the relevance of the integrity of the NAD⁺
501 metabolome should be considered in an eventual SARS-CoV-2 infection of endothelial cells, known to
502 express ACE2 receptors (70).

503 Oral administration of amidated NAD⁺ precursors (NR, NAM, and NMN) has been demonstrated
504 to be the most effective approach to replenishing NAD⁺ levels *in vivo*. Of these NAD⁺ precursors, NR
505 has been shown to have anti-inflammatory effects in different disease conditions in both preclinical and
506 clinical settings (55). Currently, a clinical trial of NR as a therapeutic option in COVID-19 patients is
507 ongoing (248).

508 NAM is a potent PARPs inhibitor that boost NAD⁺/NADP⁺ synthesis. Hence NAM reverses lung
509 injury caused by ischaemia, inhibits proinflammatory cytokines and is effective against HIV-1 infection
510 (87, 213). Another aspect of NAM effects that is relevant to the metabolome rewiring of NAD⁺ is their
511 contribution to maintaining homeostasis through the involvement of gut microbiota in NAD⁺ biogenesis
512 (53). NAM suppliers (such as NR and NMN) are thus potential candidates for use in COVID-19 treatment
513 by replenishing NAD⁺ levels (6, 32, 55). NMN plays an anti-inflammatory role in preclinical models
514 decreasing the levels of lactic acidosis and IL-6. By reducing IL-6, NMN improves shock-induced
515 hyperglycemia, reducing inflammation (32).

516 All of the evidence seems to confirm that key events of the biosynthesis and consumption of
517 NAD⁺ play significant roles in the anti-viral immune response. Consequently, NAD⁺ refueling by
518 modulating the biosynthetic pathways or – alternatively - by reducing NAD⁺ consumption (34) may be
519 of help in controlling the hyperimmune response to SARS-CoV-2 infection.

520



521

522 **Figure 4. Pathways for NAD⁺ biogenesis and consumption.** Intracellular NAD⁺ is synthesized either
 523 from tryptophan (*de novo* pathway) or from nicotinamide riboside (NR), nicotinamide (NAM), or nicotinic
 524 acid (NA) (salvage pathways). Once internalized, NAM and NR merge at the step of nicotinamide
 525 mononucleotide (NMN), which is converted into NAD⁺. NA is converted to NA adenine dinucleotide
 526 (NAAD), and then to NAD⁺. Depletion of NAD⁺ is associated with enzymatic reactions that take place
 527 intracellularly: CD38/NAD⁺-glycohydrolase, PARPs and Sirtuins. NAD⁺ is also used as a cofactor by S-
 528 adenosylmethionine (SAM) for i) the generation of intracellular adenosine from methionine, and ii) the
 529 activity of a viral SAM-dependent Methyl Transferase (MTase) enzyme, composed by the SARS-CoV-
 530 non-structural proteins (nsp) 14 and 16, active for viral cap formation during viral replication.
 531 Extracellular NAD⁺ is metabolized by CD38, the first enzyme within a purinergic signaling cascade that,
 532 together with CD203 and CD73, generates exogenous adenosine.

533

534 2. Alternative NAD⁺-consuming enzymes

535 CD38 consumes NAD⁺ in multiple ways, such as by i) mobilizing extracellular or intracellular
 536 NAD⁺ pools, depending on its membrane topological conformation (140), and by ii) degrading
 537 extracellular NAD⁺ to generate NAM, which can cross the plasma membrane and be converted to NMN
 538 and NAD⁺ through NAMPT and NMNAT (25, 109). Although CD38 is the major ectoenzyme responsible
 539 for NAD⁺ metabolization in mammalian tissues (158), there is evidence for cADPR and NAADP
 540 generation by other molecules. Indeed, depletion of extracellular NAD⁺ also occurs through the highly
 541 conserved CD38 homolog CD157/Bst1, a molecule which, however, exhibits very low NAD⁺-consuming
 542 activity (158). Another ectoenzyme that degrades extracellular NAD⁺ is CD73/e5'NT, which successively
 543 metabolizes NAD⁺ to NMN, and further to NR (84), to support intracellular NAD⁺ biosynthesis. In
 544 particular, the cADPR levels in the brain of CD38-KO mice are consistent (190), indicating the existence

545 of a cADPR-synthesizing enzyme. This enzyme was identified in the brain as SARM1 (sterile alpha and
546 Toll/interleukin receptor motif-containing protein 1) (59, 153), which features NAD⁺-cyclizing activity
547 much higher than CD38, already known by its low (2%) cADPR yield after NAD⁺ dismantling activity
548 (138). The SARM1 molecule has no sequence similarity, but has the same cytosolic orientation as type
549 III CD38, and is able to catalyze the same set of NAD⁺-depleting multi-reactions after being activated by
550 endogenous NMN (25, 59, 259). CD38 is the main enzyme involved in the degradation of NMN *in vivo*
551 (25). As an NMNase, CD38 controls the paracrine availability of extracellular NMN (but not NR or NA)
552 (32), and thus influences the accessibility of NMN to SARM1.

553 For extracellular signaling activities in immune cells, NAD⁺ uses purinergic P1 and P2 receptors
554 and metabolizing ectoenzymes (CD38, CD203a and CD73) (110). Notably, recent data showed that
555 CD203a/ENPP1 also metabolizes 2',3' cyclic GMP-AMP dinucleotide (cGAMP), generating AMP and
556 GMP (7), all acting as modulators of immunity (123). Indeed, DNA/RNA released in the cytoplasm during
557 viral infection activates a cyclic GMP-AMP synthase (cGAS), forming cGAMP from cAMP/cGMP.
558 Interesting, cGAMP is an activator of STING (stimulator of interferon genes), that integrates together
559 with SARM1, a subset of Toll-Interleukin receptor (TIR) domain-containing proteins. Both proteins can
560 degrade NAD⁺ by acting as NAD⁺-hydrolases producing ADPR and NAM, thus supporting TIR domain-
561 mediated sensing of innate immunity (152). Links between the cGAMP-STING pathway with CD203a
562 and NAD⁺ have emerged whereby the hydrolysis of cGAMP by CD203a attenuates cGAS-STING
563 signaling and, therefore, the depletion of NAD⁺ (187). Consequently, inhibitors of CD203a (207) could
564 help to combat viral activity by inhibiting cGAMP degradation and extracellular NAD⁺ consumption.

565 New aspects of NAADP generation were reported indicating that the CD38-base exchange
566 reaction is not the enzyme responsible for *in vivo* generation of this nucleotide in human myometrial
567 cells (219). Of note, NAADP-dependent generation and the release of Ca²⁺ was experimentally
568 evidenced at physiological pH in response to histamine and oxytocin as modulators and with the use of
569 pharmacological inhibitors. On the other hand, an insulin sensitization by NAADP was reported to be
570 produced through both CD38-dependent and CD38-independent pathways (221). CD38 is still the only
571 molecule fully characterized as consuming NAD⁺ and synthesizing messengers (cADPR, ADPR and
572 NAADP) in a variety of cells (158) (and references herein).

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

578 *3. Metabolic acidosis and adenosinergic activities*

579 Cell homeostasis depends on adenine nucleotides (e.g., $\text{NAD}^+/\text{NADP}^+$, and ATP). They produce
580 energy on the one hand, and generate anabolic products and second signal messengers (109) on the
581 other. Energy production takes place in the cytoplasm, and glucose is transformed into pyruvate. Under
582 normal oxygenation, pyruvate enters the mitochondria, where it undergoes enzymatic processes
583 generating large quantities of ATP. In hypoxic cells (e.g., inflammation, tumors), pyruvate cannot enter
584 the mitochondria, but is converted to lactic acid. This step is marked by the generation of low ATP and
585 higher production of NAD^+ . Lactic acid and NAD^+ are transported to the extracellular environment, where
586 the dinucleotide is consumed by CD38 to trigger intercellular communications and signaling mediated
587 through nucleotides (i.e., cADPR, ADPR, NAADP) and nucleosides (i.e., ADO) (108).

588 Patients with severe COVID-19 have been found to have high levels of lactic acid, leading to
589 suppressed proliferation and functions of T lymphocytes (exhaustion). The results are a paresis of
590 cellular and humoral immunities (74). Natural killer (NK) cells exposed to an acidic pH via lactic acid are
591 driven to a state of anergy (19), while acidic conditions inhibit the maturation of DCs and antigen
592 presentation (92). In contrast, myeloid-derived suppressor cells (MDSCs) and regulatory T lymphocytes
593 (Treg) are functionally active in acidic environments (91). If these conditions of the immune compartment
594 correlate *in vivo* with the viral infection, it is possible that a dysregulated inflammatory response may
595 derive from metabolic acidosis (30). Similar observations have been made in multiple myeloma and
596 severe bacterial sepsis (108, 129).

597 The dysregulated metabolic conditions observed during progression of SARS-CoV-2 infection
598 may be brought about by the decay of CD4^+ Treg cells, which influences hyperinflammation through
599 production of anti-inflammatory ADO (185). ADO has a central role in mediating the pathophysiology of
600 chronic lung diseases (257). The first evidence of a non-canonical adenosinergic pathway involving
601 CD38 activity was described in the human Jurkat T cell line (110). Recent studies have determined that
602 NAD^+ serves as a precursor to form ADO in the lungs where the dinucleotide is released from human
603 airway epithelial cells and that ectoenzymes (CD38/CD203a/CD73) present in lung cells have the ability
604 to metabolize NAD^+ to ADO (94).

605 All lung NADase activity was impaired in CD38KO mice as well as in lung membranes suggesting
606 that CD38 is the primary NADase in parenchymal lung cells, whose expression is up-regulated by $\text{TNF-}\alpha$
607 and inhibited by 78c, a pharmacologic blocker of CD38 enzymatic activity (101). The functional impact
608 of the adenosinergic pathway led by CD38 in the lungs may be greater under pathologic conditions,
609 given the overproduction of ADO and the high expression of its receptors in patients with chronic
610 obstructive pulmonary diseases (COPD) (20), confirming the potential therapeutic value of CD38 in lung
611 pathologies [(e.g., acute respiratory distress syndrome (ARDS) and COVID-19].

612 Generated via a cascade of events triggered by the metabolization of NAD^+ by CD38 or via ATP
613 degradation (73, 110), ADO regulates innate and adaptive immune responses by stimulating A2A and

614 A2B P1 purinergic receptors (22). ADO ligation to A2A leads to inhibition of the cytolytic activities of
615 effector T lymphocytes (185) and IFN- γ release by NK cells (168). Moreover, when extracellular ADO
616 levels are high, ligation of A2B (the low-affinity ADO receptor) influences the antigen-presenting activity
617 of DCs (64) and activates normal infiltrating cells that block the immune response (such as Tregs,
618 MDSCs, and macrophages). These effects lead to an established peripheral tolerance (257).
619 Accordingly, extracellular ADO may act in diseases with essential inflammatory pathognomonic
620 components (e.g., tumors, COVID-19) as a negative immune checkpoint molecule (108, 213).

621 At early stages of COVID-19, a severe hypoxia may help induce physiological tissue-protecting
622 mechanisms. If left unchecked, they may damage local host tissues. In this sort of scenario, ADO
623 accumulates in the extracellular space of tissues under hypoxic conditions and is able to inhibit the acute
624 inflammatory process via A2A and A2B ADO receptor engagement on immune cells (216, 217).
625 Downstream increase of intracellular cAMP, which in turn inhibits NF- κ B-driven inflammation, reduces
626 the damage due to an overactive immune system (186). However, SARS-CoV-2 induces a host pro-
627 inflammatory critical life-threatening response, which eventually damages lung epithelial and endothelial
628 cells, impairing the exchange of O₂ and CO₂ (114). This immune response imbalance induces ARDS,
629 which results in a massive release of inflammatory cytokines or CSS.

630 4. *Ca²⁺ mediated signals*

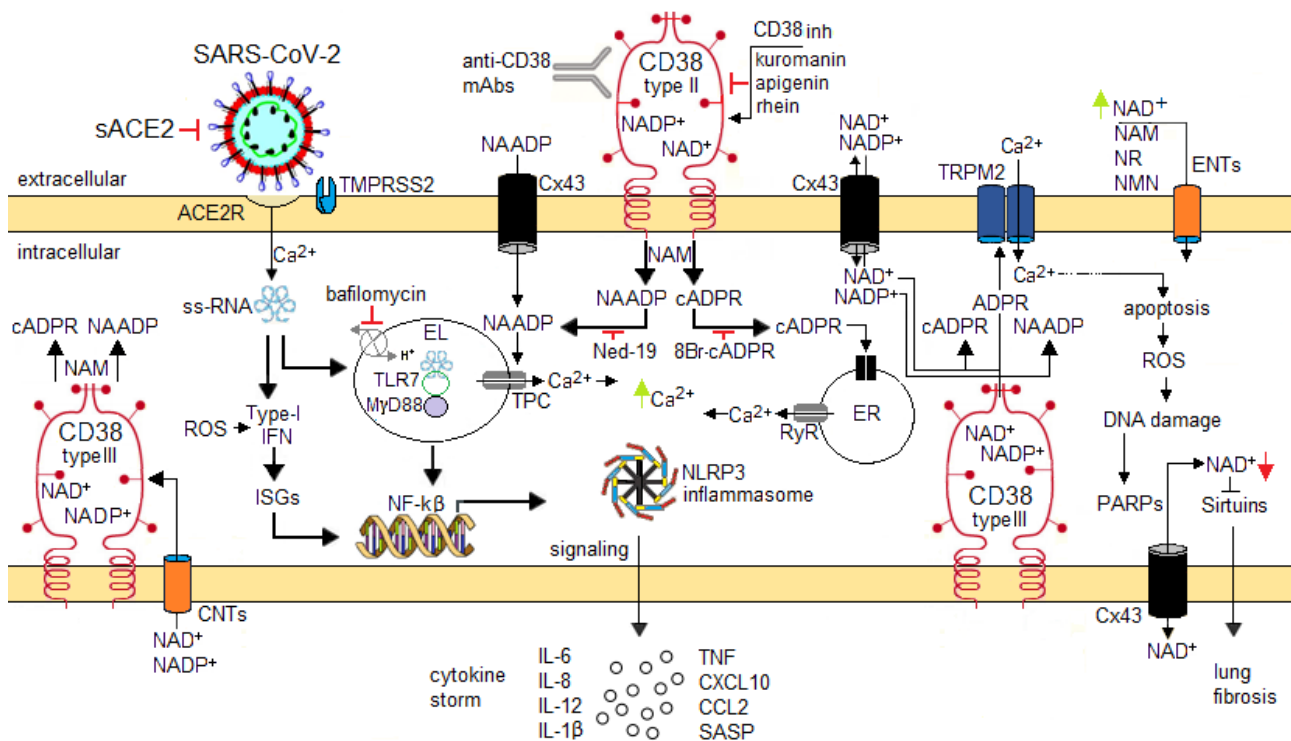
631 Mobilization of intracellular Ca²⁺ is a universal signaling mechanism to control proliferation,
632 differentiation, transcription, replication and metabolism (37).

633 The endocytic internalization of SARS-CoV-2, the delivery of the viral capsid into the cytoplasm
634 for replication, and the activity of NAD⁺-dependent enzymes, all rely upon Ca²⁺ release from intracellular
635 organelles (103, 106) (Fig. 5). After viral entry, the pathogen-associated molecular patterns (PAMPs)
636 from SARS-CoV-2 are recognized by TLRs (36). The interaction of the TLRs with NF- κ B and the adaptor
637 protein MyD88 induces a IFN-1 innate inflammatory response (4). TLRs, MyD88 and NF- κ B expression
638 are downregulated by Ang II receptor (AT1R) blockers (ARB), reducing inflammation and protecting lung
639 function (56). In this context, it has been previously established that CD38-mediated Ca²⁺ signaling that
640 contributes to Ang II-induced human hepatic fibrosis and increased lung fibrosis in animal models is
641 suppressed by ARB treatment. This adds a reasonable evidence in favor of the therapeutic use of ARB
642 in SARS-CoV-2 infection (126, 210).

643 Activation of CD38 triggers a NAADP/cADPR-Ca²⁺ signaling pathway (Fig. 5). NAADP is formed
644 by CD38 catalysis at acidic pH by the exchange of the base NAM of NADP⁺ with NA and localized in EL
645 stores (138, 139). In fact, blocking acidic EL stores by inhibiting the vacuolar H⁺-adenosine
646 triphosphatase (ATPase) with bafilomycin abrogated NAADP induced Ca²⁺ signaling (86). Downstream
647 signaling then initiates DNA transcription for activation of ISGs controlled by the NF- κ B transcription
648 factor and of the NLRP3 inflammasome (204). The CD38/NAD⁺ pathway is found at the crossroads

649 between adaptive (i.e., activation of immune cells) and innate immune (i.e., type I IFN-dependent anti-
 650 viral, the oxidative burst and the proinflammatory responses) defenses. The CD38-induced opening of
 651 intracellular Ca^{2+} channels promotes activation of inflammatory and anti-viral processes (174). However,
 652 the process of Ca^{2+} mobilization from intracellular stores is exploited by SARS-CoV-2 to trigger the
 653 production of highly inflammatory cytokines and profibrotic signals.

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



662
 663 **Figure 5. Schematic model showing the potential role of CD38-mediated Ca^{2+} signals in COVID-19 pathogenesis.** SARS-CoV-2 cell endocytosis depends on the ACE2 catalytic receptor (ACE2R) and proteolytic priming (i.e., TMPRSS2 peptidase) (shown in Fig. 1). Ang II binds to the AT1R to induce activation of either type II- or type III-CD38 catalytic receptor, which in turn stimulates Ca^{2+} release through TPCs and RYRs. Ca^{2+} influx through TRPM2 channels also cooperates to provide a high concentration of Ca^{2+} in the cytosol. The overload of cytosolic Ca^{2+} is involved in the activation of the i) ROS/IFN-type I/ISGs metabolic sequence; ii) NF- κ B via PAMPs/TLRs/MyD88-dependent pathway, and iii) NLRP3 inflammasome. This sequence of events is proposed as the likely effects in COVID-19 that culminate in a cytokine storm and multi-organ fibrosis. Pharmacological interventions to control the CD38-dependent NAD^+ metabolome are being proposed to create hurdles at different steps of SARS-CoV-2 infection. ARBs and ACEi i) block (---|) Ang II/AT1R activation, ii) increase expression of ACE2
 671
 672
 673

674 (arrested by viral binding), inducing iii) Ang (1–7) to counterbalance the deleterious pro-inflammatory
 675 effects of Ang II/AT1R (see Fig. 1B). In parallel CD38 activation by Ang II is reduced and consequently
 676 NAD⁺ levels are boosted. Similar effects might be obtained using CD38 inhibitors (CD38inh) or by means
 677 of NAD⁺ precursors supplied. The sACE2 acting as decoy-receptor blocks the viral entry. Therapeutic
 678 checkpoints are depicted as hypothesis-driven, but based on observations in other viral infections,
 679 CD38-related diseases, and preliminary data on COVID-19 (see text).

680

681 **III. CD38 AND RELATED MOLECULAR PATHWAYS MAY HELP MITIGATE COVID-19 EFFECTS.**

682 **A. Viral endocytosis and Ca²⁺ mediated signals**

683 During viral Ca²⁺-dependent endocytosis, the S protein is cleaved by TRPMSS2 and by other
 684 human enzymes at furin sites [i.e., furin (which is abundant in respiratory tract), and plasmin (involved
 685 in fibrinolysis)] to become active to bind to ACE2R. Noteworthy, comorbidities feature elevated levels of
 686 the extracellular protease plasmin (119, 224). Following this line, it has been hypothesized that a
 687 fibrinolytic inhibition may prove a promising therapeutic target for COVID-19 (119). Virus entry into cells
 688 can be also impeded by soluble human recombinant ACE2, which acts as a decoy receptor to hijack
 689 the virus from the host cellular receptor in very early stages of SARS-CoV-2 infections (167) and,
 690 downstream viral infection, by antagonists of Ca²⁺-mediated signals (174). Among these, chloroquine
 691 and hydroxychloroquine interfere with Ca²⁺ release from acidic EL (and with the terminal glycosylation
 692 of ACE2), thus impairing virus-receptor endocytosis in SARS-CoV-2 infection (106, 243, 244).

693 Cell infection generally depends on Ca²⁺ release gated by EL TPCs (29). As with MERS, NAADP-
 694 dependent Ca²⁺ signaling regulates SAR-CoV-2 translocation from the cell surface to the cytoplasm
 695 (99). After CD38 activation, TPCs activity is known to i) alter endolysosomal Ca²⁺ content and pH (24),
 696 and to ii) regulate the activity of furin required for proteolytic activation of the viral S protein, fusion
 697 activity and cytoplasmic translocation (106, 118). Therefore, direct antagonists of cADPR/NAADP would
 698 prevent viral entry in the cell. Indeed, blocking TPCs by the inhibitor tetrandrine strongly inhibited entry
 699 of SARS-CoV-2 mediated by S protein (104).

700 **B. CD38 expression and regulation of intracellular Ca²⁺ stores.**

701 Viral infection awakens different pathways that induce inflammatory conditions. One of these
 702 works by activating CD38. TPCs and RYRs are controlled by CD38, and contribute to Ca²⁺ signals
 703 responsible for inflammasome activation (24, 29). Thus, inhibition of NAD⁺ and NADP⁺ catabolism
 704 mediated by CD38 might interfere with SARS-CoV-2 infection and the inflammatory response.

705 EL is an acidic compartment ruled by a proton pump. CoV entry is blocked when the pump is
 706 inhibited (e.g., by bafilomycin) (85). Given that endosomal acidification depends on proton pump/Ca²⁺
 707 release activities, and that the entry of SARS-CoV-2 is reduced when TPCs are inhibited (104), it would
 708 be of considerable interest to know whether modulation of the NAADP-dependent Ca²⁺ signaling
 709 generated by CD38/NADase activity interferes with the SARS-CoV-2 pathological process.

710 The inflammatory conditions and the status of macrophages has been monitored using two types
711 of CD38 inhibitor molecules. The first (kuromanin, apigenin and rhein) originates from the flavonoid and
712 anthraquinone families (58, 229), while the second (LX102) is a specifically designed chemical
713 compound (254). When applied to explore the functional role of CD38 in macrophages, these treatments
714 suppressed the IL-6 and IL-12 molecules, as well as pathways such as NF- κ B, P2Rs, caspase-1 and
715 ERK1/2, all of which are involved in the promotion of inflammation by CD38 (162, 211). Inhibition of
716 CD38 may therefore increase NAD⁺ levels and reduce proinflammatory macrophage polarization, thus
717 improving related pathologies (33, 255).

718 cADPR, ISGs and production of IFN- β are greatly reduced by 8-Bromo-cADPR, a cADPR
719 antagonist, and by kuromanin (58, 203). Both drugs block the release of intracellular Ca²⁺ mediated by
720 the CD38/NAD⁺ axis, thus preventing the onset of a hyperinflammatory condition. Further, kuromanin
721 has an antioxidant function. The anti-oxidative effects of scavenging free radicals may also contribute
722 to warding off inflammation. Inhibition of the enzymatic activities of CD38 may therefore be useful in the
723 design of COVID-19 therapeutics.

724 Severe lung fibrosis in viral respiratory pathologies might be secondary to high expression of
725 CD38 by endothelial cells. On this line, CD38 has been identified as a key regulator of hepatic stellate
726 cells (HSC) activation and reported to increase following the progression of hepatic fibrosis produced
727 as a result of viral infections (161). The fibrotic process in HSC is activated by Ang II and attenuated by
728 AT1R (angiotensin II receptor type 1) blockers (so-called ARB) (224), premises suggestive that the RAS
729 system plays a major role in multi-organ fibrosis (209). The intracellular Ca²⁺ release-dependent pro-
730 fibrogenic effects of Ang II/CD38, are further supported by the findings of i) association with increased
731 concentration of TGF- β 1 (95) and ii) Ang II-induced overproduction of extracellular matrix proteins (e.g.,
732 hyaluronate). The effects on Ca²⁺ elicited by Ang II can be reduced by inhibiting CD38 with 8-Br-cADPR
733 or NAM (both cADPR antagonists) or with Ned-19 or dipyridamole (both NAADP competitive
734 antagonists) (126, 148).

735 Furthermore, Ang II-induced Ca²⁺ release is inhibited by staurosporine (a protein kinase C
736 inhibitor) and by scavengers of ROS (179). In addition, NAM prevents tissue damage in animal models
737 with induced lung injury. Indeed, NAM inhibition of CD38 cyclase could attenuate tissue damage induced
738 by Ca²⁺ signaling (18). In fact, NAM is now included among the treatments against COVID-19 (213,
739 222).

740 Lung fibrosis secondary to the SARS-CoV-2 virus is reminiscent of the macrophage activation
741 syndrome (MAS) (42) observed in autoimmune diseases. Examples include systemic lupus
742 erythematosus (SLE) and rheumatoid arthritis (RA), where CD38^{high+} plasma cells play a key role (188).
743 Anti-CD38 mAbs are currently used in the treatment of multiple myeloma (MM), a cancer of the plasma
744 cells, and other hematologic malignancies (156, 160). The results obtained indicate that antibodies also

745 modulate immune cells, including inflammatory monocytes and macrophages. The effects mediated by
746 reacting the catalytic functions and intracellular Ca^{2+} release with CD38 antibodies, still need to be
747 evaluated in COVID-19 patients.

748 In a variety of cell types, Ca^{2+} homeostasis is regulated by the transcription factor early growth
749 response-1 (Egr-1), which promotes Ca^{2+} entry across the PM upon ER- Ca^{2+} store depletion (233).
750 Activation of Egr-1, mediated by inhibition of NAD^+ dependent Sirtuins, is critical for the replication of
751 CoV (23). The uptick in the activity of acetylated Egr-1 seen in proinflammatory hyperglycemic
752 atherosclerosis (241) highlights an eventual association between the comorbidities and Ca^{2+} -dependent
753 mechanisms of SARS-CoV-2 infection in determining the aggressiveness of COVID-19 disease.

754 **C. CD38 and pregnancy-associated immunosuppression in COVID-19**

755 Pregnant women are more susceptible to respiratory pathogens and severe pneumonia because
756 of the conditions of tolerance established between the immune system of mother and embryo (246). In
757 addition to immunogenetic factors, the ectoenzymatic adenosinergic networks operating in closed
758 environments metabolizes nucleotides (ATP, NAD^+), providing nucleosides (ADO, INO) with
759 immunosuppressive potential (110, 206). The existence of these networks and the contribution of ADO-
760 producing ectoenzymes at the maternal/fetal interface has already been highlighted (27). Accordingly,
761 the impact of COVID-19 infection on pregnant women appears to be less severe or similar to that
762 reported for non-pregnant patients who developed COVID-19 pneumonia (253), due to protection of the
763 lungs from CSS brought about by the immune system. Indeed, ADO, acting through the low affinity A2B
764 ADO receptor, stimulates IL-6 and acute-phase inflammatory proteins, such as C-Reactive Protein
765 (CRP) production in macrophages and endothelial cells (154). In fact, reported data show that the
766 majority of viral infected pregnant patients had increased IL-6 and CRP (253). Similar trend was reported
767 during the development and progression of MM, where metabolic reprogramming contributes to
768 increasing levels of immunosuppressive ADO (113). This experimental data makes it reasonable to
769 speculate that the induction of ADO within the close placental compartment in gestational patients (27)
770 helps mitigate COVID-19 related pneumonia during pregnancy.

771 **D. CD38 connections and pharmacological control of COVID-19**

772 Promising therapeutic options include neutralizing antibodies, vaccines, antibody transfer from
773 convalescent-phase plasma, anti-viral proteases, receptor-blocker inhibitors, and drug repurposing
774 (192). Potential therapies (Table 2) include i) small-molecules and drugs as modulators of the
775 CD38/ NAD^+ axis (e.g., CD38 inhibitors, NAM, dexamethasone), ii) soluble factors such as ADO
776 modulators (184) , iii) immunomodulators of CD38 expression (88), as well as iv) immunosuppressive
777 cells (e.g., cytokine-induced killer cells and mesenchymal stem cells) (8, 111).

778 As previously mentioned, viral infection causes the blocking of surface ACE2 (ACE2R) facilitating
779 the actions of Ang II, thus contributing to COVID-19 pathology (75). It was therefore suggested (225)

780 that an imbalance in the action of ACE1 (that catalyzes Ang II from Ang I) and ACE2 (that catalyzes Ang
781 1-7 from Ang II) may act as primary driver of COVID-19 pathobiology (Fig. 1B). The ACE1/ACE2
782 imbalance occurs due to the viral interference in the ACE2 enzymatic activity, thus i) it enhances Ang II
783 signaling through AT1R associated to harmful effects (vascular and pulmonar tissue injuries), and ii) it
784 reduces Ang 1-7 signaling through its protective MasR (anti-inflammatory, anti-fibrogenic and anti-
785 oxidative). Several approaches have been proposed to treat COVID-19 by restoring ACE1/ACE2
786 steady-state: among these, (i) AT1R antagonists/blockers (ARBs); (ii) ACE1 inhibitors; (iii) agonists of
787 MasR; (iv) recombinant human ACE2 as decoy receptor for the virus, and (v) the development of drugs
788 enhancing ACE2 activity. Reducing ACE1/ACE2 imbalance is predicted to blunt COVID-19-associated
789 morbidity and mortality, especially in elderly and vulnerable patients. Importantly, approved direct ARBs
790 (AT1R antagonists) and ACE1 inhibitors (that block the synthesis of Ang II) can be repurposed to test
791 their efficacy in treating COVID-19 (223). Related to this, it was reported that Ang II induces
792 NAADP/cADPR production via CD38, both essential for the entire Ang II-mediated Ca^{2+} signaling.
793 Indeed, 8-Br-cADPR antagonizes NAADP production, which was partially blocked by pretreatment with
794 Ned19, a NAADP receptor blocker. Notably, anti-hypertensive ARB-drugs (i.e., losartan) abolished both
795 Ang II-induced NAADP/cADPR production and Ca^{2+} increase (194).

796 The raw material for NAD^+ biosynthesis, Trp, decreases as a consequence of health disorders
797 (infection, inflammation), thus leading to reduce NAD^+ . Such COVID-19-associated conditions were
798 corrected by prescription of NAD^+ and/or its precursors (e.g., Trp, NAM, NR, NMN) together with CD38
799 inhibitor (34). Moreover, clinical trials with ARDS patients, show indeed that NR depresses levels of IL-
800 6, IL-5, IL-2 and TNF- α (55), supporting the view that NAD^+ boosters might be tested for controlling CSS
801 in COVID-19 patients.

802 In the human respiratory tract, CD38 expression is regulated by TNF- α , an inflammatory cytokine
803 requiring NF- κ B activation, resulting in increased Ca^{2+} responses to agonist corticosteroids (9). Among
804 them, glucocorticoids are used in the management of airway hyperresponsiveness as a result of the
805 negative regulation of genes that promote inflammation or the induction of genes that inhibit
806 inflammation in lung cells (235). The *CD38* promoter region includes NF- κ B and glucocorticoid response
807 element (GRE) motifs (158). Thus, CD38 increased expression is down-regulated by dexamethasone
808 through inhibition of NF- κ B and its use in COVID-19 has been proposed (136).

809 The *CD38* gene promoter is also sensitive to vitamins, hormones, cytokines, and different
810 retinoids (158). All-trans retinoic acid (ATRA) is a highly specific inducer of CD38 expression in human
811 myeloid cells mediated through RAR α (54). CD38 expressed by immune cells has been induced by
812 ATRA, which promotes adhesion of cells to endothelium, a feature which is responsible for respiratory
813 distress caused by pulmonary interstitial cell infiltration (the so-called RA syndrome) (83). This event
814 could be the first step towards CSS, which is characteristic of the late phases of COVID-19. In line with

815 this observation, anti-CD38 mAbs specifically block binding of ATRA-treated CD4⁺CD45 T-cells to
816 endothelium (49), mediated by CD38 interactions between leukocytes and the CD31 antigen present on
817 the surface of lung endothelial cells.

818 Extracellular ADO levels governs the switch from the proinflammatory to the suppressive
819 macrophage phenotype (184). This mechanism provides a rationale for targeting the purine metabolism
820 by methotrexate, in order to boost ADO production and reduce the dominance of proinflammatory
821 macrophages. This happens in rheumatic diseases and, potentially, in COVID-19 patients (196, 213).

822 SARS-CoV-2 grows in the cell, where its ss-RNA is protected from the host's cellular innate
823 immunity (261). To ensure ss-RNA integrity, the viral nsp 10, 14, and 16 are involved in a cap formation
824 (by methylation of the ss-RNA molecule), a process essential for viral replication in host cells (245). Both
825 nsp14 and nsp16 are methylated by S-adenosylmethionine (SAM)-dependent methyltransferase
826 (MTase) enzymes (Fig. 4). As a potential target for antiviral therapy, a complex between SARS-CoV-2
827 nsp10-nsp16 and a purine adenine (sinefungin) becomes a promising therapeutic approach as a pan-
828 MTase inhibitor (132).

829

830 **IV. CD38 IMPACTS BIOLOGICAL MECHANISM(S) THROUGH WHICH SARS-CoV-2 TARGETS** 831 **ELDERLY PATIENTS WITH ACUTE DISEASE**

832 COVID-19 is a biphasic illness with an innate immune response that transitions into an adaptive
833 immune response except in many elderly patients, who develop severe disease with diffuse lung
834 damage (61). Consequently, the high morbidity in the elderly is a striking feature of COVID-19 (166).

835 **A. SARS-CoV-2 cell receptors and senescence**

836 Along with ACE-2, CD26 was also proposed as an endocytic cell receptor for SARS-CoV-2,
837 interacting with the S-protein (239). Both ACE2 and CD26 are associated to senescence: ACE-2 is a
838 known inhibitor of cell proliferation and the RAS system is up-regulated in senescence (125). CD26 is
839 known to be a *bona fide* cell surface marker of senescent cells (155). Similarly, myofibroblasts (which
840 are considered to be senescent and pro-fibrotic cells) also overexpress ACE-2 and CD26 (120, 199).
841 Thus, increased mortality in elderly COVID-19 patients may be related to an increased number of
842 senescent lung cells, which are the main host target for COVID-19 viral infection (26).

843 **B. Host defense and maintenance of a balanced inflammatory response in aging**

844 Aging may contribute to the disease scenario through general dysregulation of the immune
845 system, as evinced by increased levels of inflammatory cytokines. Aging is also characterized by
846 increased expression of CD38 in immune cells, resulting in high consumption of the NAD⁺ substrate (31,
847 255). The consequence is that NAD⁺ depletion may exacerbate the cytokine storm and lead to fatal
848 ARDS, which is most common in older COVID-19 patients (131).

849 Besides NAD⁺ depletion, ROS detected during hypertension-induced vascular organ damage is
850 also associated to aging endothelial cells and fibroblasts (127). This ROS-dependent cell weakness
851 increases with age, and the same is true in older COVID-19 patients (166). ROS damage means that
852 aging cells are unable to express pro-survival antioxidants and anti-inflammatory genes due to
853 dysregulation of the nuclear factor erythroid 2-related factor 2 (NRF2) signaling transcription factor (200,
854 215). In addition, silencing of the antioxidant *NRF2* gene results in an increased secretion of
855 proinflammatory cytokines, which mediate CoV-induced CSS (79). Moreover, the cellular levels of the
856 NRF2 protein are down-regulated during RSV infection, promoting ROS damage by triggering NAD⁺-
857 dependent Sirtuins deacetylation of NRF2 (130). NRF-2 pathway activation is reduced by the CD38
858 inhibitor kuromanin, which supports the hypothesis of an involvement of the NAD⁺ metabolome during
859 viral infections (69).

860 **C. The NAD⁺ metabolome in the elderly**

861 The question remains as to why NAD⁺ declines during innate aging and premature aging
862 syndromes (25, 78, 231). The main culprit is CD38, whose expression is physiologically up-regulated
863 during aging (34, 205), particularly in cells targeted by SARS-CoV-2 and expressing high levels of CD38
864 either at protein or mRNA contents (Fig. 6). These considerations provide support to the
865 pharmacological strategies for reversal of physiological- and pathological-related NAD⁺ depletion and
866 subsequent metabolic dysfunctions (34).

867 CD38 regulates NAD⁺ homeostasis along with other normal and pathological NAD⁺-dependent
868 cellular processes (1, 159). Among these, CD38 expression is elevated in tissue repair and in fibrotic
869 processes in different organs (209) in a way similar to CD38 up-regulation and NAD⁺ depletion seen in
870 aging. This may suggest intriguing parallels between the biology of aging and fibrogenesis traceable
871 to Ang II/CD38-dependent dysregulation of NAD⁺ homeostasis (126).

872 Mitochondrial dysfunction occurs during aging due to reduced synthesis of NAD⁺ (25, 63, 90),
873 which could impact macrophage function (165). Interestingly, CD38 is highly expressed in pro-
874 inflammatory macrophages (3), and genetic ablation or pharmacological inhibition of CD38 can reverse
875 mitochondrial dysfunction and reduce inflammatory cytokines in human monocyte/macrophages and in
876 mice (165, 231). Therefore, it is possible that increased circulating levels of inflammatory factors in an
877 imbalanced metabolic cell microenvironment (e.g., in aging, oncogenesis, viral infection) induces CD38
878 expression, contributing to metabolic dysregulation and in turn promoting the inflammatory function of
879 macrophages in the elderly.

880 NAD⁺ depletion, and the deriving metabolic imbalance (e.g., hypoxia, glycolytic metabolism, and
881 increased levels of lactic acid linked to a dysregulation of the immune system) driven by CD38 is
882 believed to play a key role in cellular senescence (107). In senescent cells, DNA fragments of nuclear
883 origin accumulated in the cytoplasm induce activation of the cGAS-STING cytoplasmic DNA-sensing

884 machinery (151), with the acquisition of a senescence-associated secretory phenotype (SASP). SASP
885 induces an increase of CD38 expression and subsequent NAD⁺ consumption (31, 32). These SASP⁺-
886 senile cells do accumulate in different organs (liver and white adipose tissue) and produce pro-
887 inflammatory cytokines that promote chronic inflammation and fibrosis (32). The senescent SASP cell
888 is reported to up-regulate CD38 expressed in peripheral macrophages (41); it is thus hypothesized that
889 the accumulation of senescent cells releasing SASP factors increases the activity of CD38, with
890 amplification of cytokine release and NAD⁺ depletion (31, 249).

891 The senescence/age-related NAD⁺ decline/COVID-19 link may appear paradoxical, since
892 senescent cells do not themselves express high levels of CD38. It may be that the SASP factors up-
893 regulate CD38 expression in non-senescent cells (for instance, endothelial cells or M1-macrophages).
894 The SASP circuit might support the relation among cellular senescence, NAD⁺ decline and
895 hyperinflammation, with disruption of cellular NAD⁺ homeostasis and promotion of tissue deterioration
896 (202). In the latter case, senescent cells also secrete proteases, growth factors, and extracellular matrix
897 modifiers, which promote chronic inflammation and fibrosis.

898 A proteomic database has been compiled of senescence-associated secretomes for aging and
899 several diseases and provides a link between the accumulation of senescent cells and pathological
900 process (10). This data base is expected to shed light on the lesser known aspects of SASP in elderly
901 COVID-19 affected patients and, at the same time, to help disentangle the CD38-dependent
902 mechanisms driving inflammation during SARS-CoV-2 infection in the elderly.

903 CD38 expression is regulated by transcription factor NF- κ B (122), which plays a role in the silent
904 inflammation frequently encountered in aging. This suggests that the COVID-19 process may alter the
905 NAD⁺/CD38 axis, given that SARS-CoV-2 cell infection dysregulates the NAD⁺ gene set, that includes
906 enzymes required for the innate immune response, inducing a severe depletion of NAD⁺ by host cell
907 (103).

908 The reported NAD⁺ attack during aging and the course of COVID-19 involves i) the CD38 NAD⁺-
909 glycohydrolase (34, 131), ii) the NAD⁺-dependent Sirtuins, that suppresses both chronic inflammation
910 and, by binding to the promoter region of ACE2, viral replication (38), and iii) PARPs, whose transcription
911 is increased in individuals infected with SARS-CoV-2 (103). Other NAD⁺-dependent enzymes are iv)
912 ADP-ribosyltransferases (ARTs) and v) ADP-ribosylhydrolases (ARHs). After ARTs transfer the ADPR
913 unit from NAD⁺ onto an acceptor protein (ADPribosylation), ARHs release the ADPR from the target
914 (128). SARS-CoV-2 possess an ARH involved in cell signaling, gene regulation and apoptosis (128,
915 131), which contributes to the depletion of the already low NAD⁺ levels in aged people.

916 Among other mechanisms involved in age-related declines in NAD⁺ levels, one is the depletion
917 of NAD⁺ precursors (e.g., NMN and NR). Indeed, NAMPT levels also reportedly declining during aging
918 (116). Interestingly, it has been reported that NAMPT and NAD⁺ levels are significantly reduced by TNF-

919 α and ROS, impairing the activity of the senescence suppressor Sirtuin1 deacetylase and, therefore,
920 contributing to the development of aging-related illnesses and chronic inflammation. Hence, strategies
921 to sustain NAD⁺ biosynthesis might be effective in suppressing physiological and pathological
922 inflammation (33, 34). NAD⁺ boosting via dietary NR supplementation (Fig. 4) was shown to improve
923 hepatic fibrosis, while NMN supplementation was shown to reduce pulmonary fibrosis (147). Moreover,
924 78c, a thiazoloquin(az)olin(on)e specific CD38 inhibitor, reversed NAD⁺ depletion and reduced the
925 accumulation of inflammatory cells, with a substantial regression of pathological alterations (e.g., fibrotic
926 and inflammatory changes) (101, 231) with therapeutic implications. Indeed, pharmacological
927 approaches to boosting NAD⁺ by inhibiting CD38 activity, by NAD⁺ precursor supplementation or by a
928 combination of both, represent potential therapeutic strategies for reversing the consequences of SARS-
929 CoV-2 infection.

930 The main advantages provided by the supply of NAM/NR/NMN regarding NAD⁺ depletion are
931 that: (i) NAM inhibits PARP activity by competing with NAD⁺ for the CD38 active site, thus boosting
932 NAD⁺ homeostatic levels; ii) the increased concentration of NAD⁺ provides the substrate for NAD⁺
933 kinase, leading to production of NADP⁺, which is a stronger PARP inhibitor (14); (iii) NAM is also able
934 to inhibit Sirtuins (15), thereby replenishing NAD⁺ levels. Overall, the effects of amidated sources for
935 NAD⁺ biogenesis support its use in COVID-19 therapy.

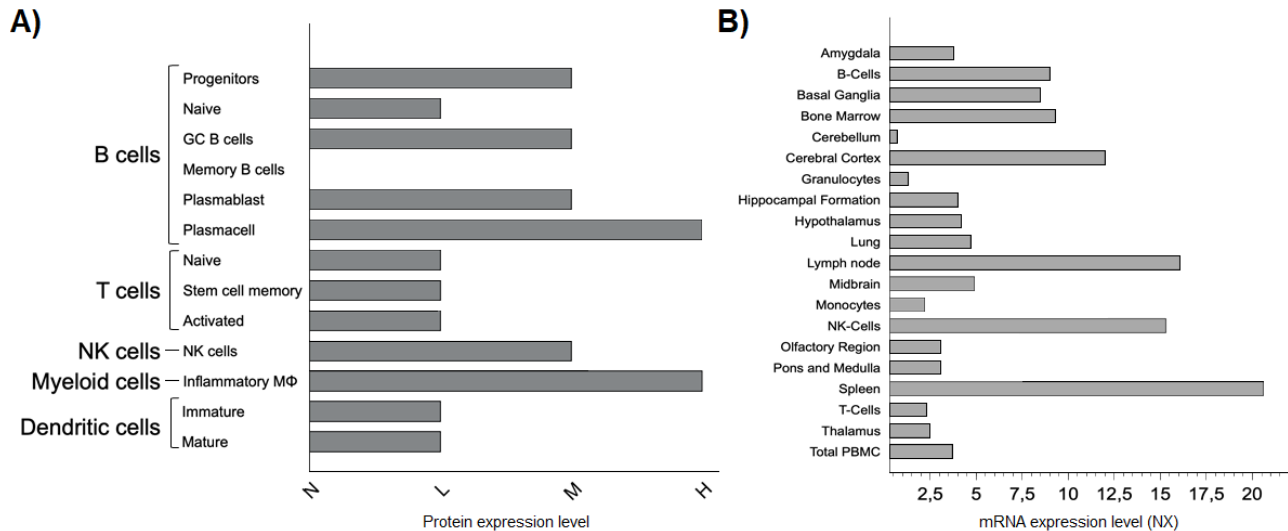
936 Fibrosis is frequently seen in SARS-CoV-2 inflammation in elderly patients (208, 238). Fibrosis
937 on the basis of persistent DNA damage signaling is reported in SARS-CoV-2 infection (134). Damaged
938 DNA induced PARPs to accumulate free ADPR. Concurrently, NAD⁺ consumption by CD38 generates
939 ADPR that binds to the TRPM2 channel, causing a Ca²⁺ influx across the plasma membrane (228). On
940 the other hand, TPC and RyR, respectively gated by NAADP and cADPR, release intracellular Ca²⁺
941 from the EL and ER organelles to provide high concentration of Ca²⁺ in the cytosol. The overload of
942 cytosolic Ca²⁺ initiates cell apoptosis along with a cytokine hyperinflammation, potentially causing
943 severe lung failure in COVID-19 patients (Fig. 5). Indeed, the high number of fatalities in elderly COVID-
944 19 patients is due to the macrophage overactivation, which leads to a CSS and to lung fibrosis (238).

945 Also relevant to the present topic is the recent observation that CD8⁺ tissue-resident memory T
946 cells (Trm) in murine models drive age-associated chronic lung sequelae after viral pneumonia (220).
947 The authors found that chronic non-resolving lung pathologies in mice are associated with an
948 accumulation of Trm. However, Trm cells isolated from aged mice display reduced effector functions.
949 The authors demonstrated this is a secondary effect of the lack of a subpopulation expressing molecules
950 involved in TCR signaling. It is reasonable to anticipate that CD38 plays a role in this process. Firstly,
951 the enzymatic roles played by the molecule and derived products may contribute to the effects observed
952 (209). Secondly, CD38 is reported as being associated to the TCR/CD3 complex and functionally
953 dependent on it, at least in human models (171, 172). Finally, it would be of interest to investigate the

954 presence of CD203a in the context of the lung environment, before and after viral infection, as a potential
 955 source of immunosuppressive ADO (108).

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959 **Figure 6. A.** Expression level of CD38 in the principal hematological cell subsets involved in the immune
 960 response against viral infections and other diseases. Data were obtained from literature (157, 158), and
 961 are a knowledge-based best estimate of the protein expression resulting from evaluation of
 962 immunohistochemical staining RNA data and available protein/gene characterization data (N=not
 963 detected, L=low expression, M=medium expression, H=high expression). **B.** CD38 mRNA expression
 964 levels in hematological tissues and in tissues/organs primarily interested by viral infections and other
 965 diseases. Data were obtained from the Human Protein Atlas and are expressed as Consensus
 966 Normalized eXpression (NX), created by combining the data from the three transcriptomics datasets
 967 (HPA, GTEx and FANTOM5) using the internal normalization pipeline.

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969 V. IMPLICATIONS OF CD38 FOR COVID-19 THERAPY

970 Despite the well-known multi-faceted biology behind CD38 functions, so far clinical applications
 971 in viral infections stay back and still need to be addressed. Moreover, to date no specific drugs and
 972 therapeutics are approved by any Regulatory Agencies to prevent or treat SARS-CoV-2 infection.
 973 However, the strong groundwork on CD38 provided by theragnostic studies in multiple myeloma and
 974 other diseases (Table 1), leave footprints for future research requiring further experimental and
 975 preclinical studies (170).

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CD38 IN DISEASE	
DISEASE	POTENTIAL AND THERAPEUTIC APPROACHES
Multiple Myeloma	Elimination of plasma cells through therapeutic anti-CD38 antibodies (ADCC, ADCP, CDC, induction of apoptosis) (52)
Amyloidosis	Elimination of plasma cells (89)
Systemic Lupus Erythematosus (SLE)	Elimination of plasma cells and NK cells (188)
Rheumatoid Arthritis (RA)	Elimination of plasma cells (39)
Systemic Sclerosis (SS)	Mitigation of fibrosis by CD38-targeting of NAD ⁺ metabolism (209)
Chronic active antibody-mediated kidney allograft rejection	Elimination of plasma cells (51)
Neurodegeneration	Age-related modulation of NAD ⁺ metabolism (25)
Eye	Interaction of neuronal CD38 with the soluble CD31 ligand (97)
Olfactory	Interactions among genes for oxytocin release, oxytocin receptor and CD38 (193)

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Table 1: Potential and therapeutic approaches involving CD38 in diseases. For each disease or organ involved, a potential mechanism of action is suggested. References are included in brackets.

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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⁺-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 (98). 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

998 therapy, a clinical trial has been recently launched recently to test whether (or not) ARBs reduce
 999 respiratory failure in COVID-19 patients (NCT04340557).

1000

DRUGS	BIOACTIVITY
Inhibitors SARS-CoV-2 endocytosis	
rhACE2 as decoy viral receptor	Blockage of SARS-CoV-2 cell entry (167)
Bafilomycin	Inhibition of Ca ²⁺ release (85)
PanMTase inhibitor Sinefungin	Purine adenine metabolism (132)
Repurposed drugs (HCQ, CQ)	Ca ²⁺ metabolism (244)
Modulators of the RAS system	
AT1R blockers (ARBs)	AT1R antagonists (56)
ACE1 inhibitors (ACEi)	Block the synthesis of Ang II (223)
Agonists of MasR	Activation of Angiotensin protective effects (225)
Drugs enhancing ACE2 Activity	Restoration of ACE1/ACE2 imbalance (223)
Modulators of the CD38/NAD⁺ axis	
Kuromanin, Apigenin, Rhein, 78c, LX102	CD38/NADase inhibitors (58, 229, 231, 254)
NAD ⁺ , NMN, Vitamin B3 (NAM, NR, NA), Tryp	Restoration of NAD ⁺ levels (15, 32, 33)
Dexamethasone	Downregulation of CD38 expression (136)
Vitamins (Retinoic Acid, D3)	Upregulation of CD38 expression (54, 191)
NAM, 8Br-cADPR	cADPR antagonists (15, 126)
Ned19, Dipyridamole	NAADP antagonists (148, 194)
Soluble Immunomodulators	
Anti-CD38 mAbs (Isatuximab, Daratumumab, MOR202, TAK-079)	Allosteric inhibition of CD38 cyclase activity, cytotoxic effects, clearance of CD38 ⁺ cells (156, 160)
Extracellular ADO	Protection of ARDS patients from hyper-oxygenation damages (40, 62)
Cellular Immunomodulators	
Cytokine-induced killer (CIK) cells	Immunosuppression (8)
Mesenchymal stem cells (MSC)	Immunosuppression (111)

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1002 **Table 2:** Summary of experimental drugs with potential use in SARS-CoV-2 infection therapy. Each drug
 1003 is flanked by its mechanism of action controlled by CD38 (details in the text). References are included
 1004 in brackets.

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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: i) active hyperoxic ventilation (supplemental oxygen), and measures to prevent infection and worsening of the pathological conditions (232, 247). Unfortunately, this means of oxygenation inhibits the local tissue hypoxia-driven ADO-A2AR-mediated anti-inflammatory protecting mechanism (218), and thereby exacerbates ARDS, a

1012 pathophysiological process that lead to the death of COVID-19 patients (178, 234). As a proof-of-
1013 principle, it was reported that a COVID-19 patient with ARDS treated with ADO in high flow 21% O₂
1014 aerosol showed an improvement in clinical conditions (62). These effects were confirmed in a pilot trial
1015 with very promising clinical outcomes. Indeed, the pharmacological compensation for the oxygenation-
1016 associated loss of the generated extracellular ADO in the lungs of COVID-19 patients was achieved
1017 through intra-tracheal injection or inhalation of synthetic ADO (40). Importantly, the resolution of
1018 respiratory failure allowed the authors to concluded that the use of ADO is a valid therapeutic option in
1019 ARDS/COVID-19.

1020 CD38 may be part of the multiple mechanisms explaining the low NAD⁺ levels observed in CD38-
1021 related diseases (Table 1). Therefore, inhibition of the CD38 enzymatic activity leading to increased
1022 NAD⁺ levels might be of interest for treatment. Unfortunately, the small-molecule inhibitors now available
1023 of CD38 enzymatic activity either have an affinity in the micromolar range (231) or trigger cell cytotoxicity
1024 like the therapeutic anti-CD38 mAbs. However, the observed immunosuppressive effects of anti-CD38
1025 mAbs on malignant plasma cells could be useful after regulation of its functional effects. The
1026 consequence of a CD38 fine-tuning on the intracellular and extracellular NAD⁺ levels and related
1027 metabolites will help understanding how to modulate CD38 to maximize efficacy and lower potential
1028 adverse events (149).

1029 To explore important aspects of COVID-19 therapeutic drugs, a number of small animal models
1030 (such as mice, hamsters, ferrets) can be used (57, 197). Non-human primate models have also been
1031 explored for COVID-19. Interesting, a characterization of CD38 from cynomolgus macaque was reported
1032 and demonstrates genetical, biochemical and immunological similarities of the primate CD38 with the
1033 human protein (71). The study opened new prospects for the pharmacological applications of this
1034 catalytic receptor. Indeed, a current study in cynomolgus macaque has focused on the effect of age on
1035 infection with SARS-CoV-2 (173, 256). To facilitate the study of SARS-CoV-2 pathogenesis, and to test
1036 candidate COVID-19 therapeutic agents and drug repurposing, micro-engineered organs-on-chips and
1037 lung organoids as models have been developed (212).

1038

1039 VI. CONCLUSIONS

1040 The aim of this perspective review is to examine the connections between CD38 and COVID-
1041 19. It provides detailed analysis of the mechanisms i) of viral invasion, ii) of viral evasion from innate
1042 and adaptive immune responses, iii) of hyperinflammation associated to metabolic conditions; and
1043 examines the iv) protected immune status during pregnancy and vi) clinical fragility of elderly patients.
1044 To achieve these goals the current review re-analyses hypotheses formulated in the context of RSV
1045 infection by exploiting the results about the role of multi-faceted CD38 in other cellular systems.

1046 Associative basic and clinical research data are herein discussed and integrated with conclusions
1047 reported by others within the field.

1048 We are led to conclude that CD38/NADase is at the centre of a functional axis (i.e., intracellular
1049 Ca^{2+} mobilization/IFNs response/ROS burst) exploited by viral infections (e.g., RSV, SARS).
1050 Consequently, CD38-induced opening of intracellular Ca^{2+} channels would activate processes able to
1051 influence early steps of the disease, but whose persistence and worsening negatively affect the outcome
1052 of the COVID-19 disease.

1053 The grounds for this hypothesis are that: i) the substrates of CD38 (i.e., NAD^+ and NADP^+) are
1054 depleted by viral-induced metabolic rewiring; ii) the products of the enzymatic activities of CD38 (i.e.,
1055 cADPR/ADPR/NAADP) are involved in an anti-viral and proinflammatory response that may favor the
1056 onset of lung immunopathology (i.e., CSS and organ fibrosis). The role of the CD38/ NAD^+ axis at
1057 different stages of COVID-19 were also analyzed, along with different therapeutic possibilities. The
1058 conclusions are that pathological events of the current pandemic may be mitigated by distinct
1059 modulators of the CD38/ NAD^+ axis.

1060 There are still many open questions to be answered concerning i) the impact of the CD38/ NAD^+
1061 axis *in vivo* during SARS-CoV-2 infection; ii) certain mechanisms underlying NAD^+ involvement during
1062 SARS-CoV-2 infection, which remains unclear and requires further research for identifying the precise
1063 molecular mechanisms implicated in immunity and metabolic adaptations to SARS-CoV-2 infection, and
1064 iii) how to meet the challenge of discovering and developing new therapeutic agents, so critically in
1065 demand. However, many of today's findings echo those from past viral infections (e.g., RSV and SARS),
1066 thus providing a foothold for dealing with COVID-19.

1067 Of clinical relevance for the future in the strategy to fight COVID-19 is the identification of
1068 molecular metabolic pathways generally usurped by the viral pathogen and addressing the evaluation
1069 of the impact of agents that selectively target CD38's receptorial and catalytic activities to confirm the
1070 potential of CD38 as a novel therapeutic target.

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- 1888

1889 **FIGURE AND TABLE CAPTIONS:**

1890

1891 **Figure 1. Schematic illustration of the SARS-CoV-2 molecular structure and essential**

1892 **mechanisms of viral infection and outcomes.** A) The SARS-CoV-2 genome encodes non-structural
 1893 proteins (nsp1-nsp16) (not shown) and four structural proteins: spike (S) glycoprotein, envelope,
 1894 membrane, and nucleocapsid phosphoprotein, which together ensure replication of the virus in the host
 1895 cell. B) The octapeptide Ang II is originated from the decapeptide Ang I by soluble ACE2 enzymatic
 1896 activity. Ang II acts via AT1Rs while Ang (1–7), generated from Ang II by ACE2 carboxypeptidase, acts
 1897 via the Mas receptor (MasR). SARS-CoV-2 binding to the ACE2 catalytic receptor (ACE2R) enhances
 1898 lung inflammation by reducing ACE2 activity and increasing Ang II. Depletion of ACE2 activity decreases
 1899 the production of Ang 1-7, which has an anti-inflammatory and anti-fibrotic activity. C) SARS-CoV-2 and
 1900 RSV preferentially bind to the ACE2R expressed by alveolar epithelial cells and macrophages in the
 1901 lower human respiratory tract.

1902

1903 **Figure 2. CD38 enzymatic activities.** CD38 catalyzes several enzymatic reactions: at neutral pH i) the

1904 conversion of nicotinamide adenine dinucleotide (NAD⁺) into adenosine diphosphate ribose (ADPR)
 1905 (NAD⁺-glycohydrolase activity); ii) the conversion of NAD⁺ into cyclic ADPR (cADPR) (cyclase activity);
 1906 iii) the hydrolysis of cADPR into ADPR (hydrolase activity). At acidic pH, iv) the conversion of NADP⁺,
 1907 the phosphorylated equivalent of NAD⁺, into nicotinic acid adenine dinucleotide phosphate (NAADP)
 1908 (NAADP-synthase activity) in the presence of nicotinic acid (NA) and the degradation of NAADP into
 1909 ADPR.P (NAADP-hydrolase activity). All of the reaction products are second messengers involved in
 1910 the regulation of cytoplasmic Ca²⁺ fluxes and the generation of immunosuppressive adenosine (see text
 1911 and Fig. 3)

1912

1913 **Figure 3. Schematic illustration of intracellular signaling mediated by the CD38/NAD⁺ axis. A)**

1914 The NADPase and NADase enzymes are responsible for the formation of the Ca²⁺-releasing
 1915 messengers through the use of phosphorylated (NADP⁺) or non-phosphorylated NAD⁺, respectively.
 1916 Second messengers generated as products are: NAADP, cADPR, and ADPR. NAADP-elicited Ca²⁺
 1917 is released from the two-pore channel (TPC) receptor situated in acidic endolysosomes (EL), and cADPR
 1918 serves as the trigger and booster for Ca²⁺ release via the activation of the ryanodine receptor (RyR),
 1919 situated in the endoplasmic reticulum (ER). ADPR elicits Ca²⁺ influx through the transient receptor
 1920 melastatin 2 (TRPM2) situated in the plasma membrane (PM). **B)** ADPR can also be sequentially
 1921 metabolized by ectonucleotidases (CD203a/ectonucleotide pyrophosphatase/phosphodiesterase 1
 1922 (ENPP1) and CD73/5'-ectonucleotidase (5'eNT) for the formation of extracellular adenosine (ADO).

1923

1924 **Figure 4. Pathways for NAD⁺ biogenesis and consumption.** Intracellular NAD⁺ is synthesized either
 1925 from tryptophan (*de novo* pathway) or from nicotinamide riboside (NR), nicotinamide (NAM), or nicotinic
 1926 acid (NA) (salvage pathways). Once internalized, NAM and NR merge at the step of nicotinamide
 1927 mononucleotide (NMN), which is converted into NAD⁺. NA is converted to NA adenine dinucleotide
 1928 (NAAD), and then to NAD⁺. Depletion of NAD⁺ is associated with enzymatic reactions that take place
 1929 intracellularly: CD38/NAD⁺-glycohydrolase, PARPs and Sirtuins. NAD⁺ is also used as a cofactor by S-
 1930 adenosylmethionine (SAM) for i) the generation of intracellular adenosine from methionine, and ii) the
 1931 activity of a viral SAM-dependent Methyl Transferase (MTase) enzyme, composed by the SARS-CoV-
 1932 2 non-structural proteins (nsp) 14 and 16, active for viral cap formation during viral replication.
 1933 Extracellular NAD⁺ is metabolized by CD38, the first enzyme within a purinergic signaling cascade that,
 1934 together with CD203 and CD73, generates exogenous adenosine.

1935

1936 **Figure 5. Schematic model showing the potential role of CD38-mediated Ca²⁺ signals in COVID-
 1937 19 pathogenesis.** SARS-CoV-2 cell endocytosis depends on the ACE2 catalytic receptor (ACE2R) and
 1938 proteolytic priming (i.e., TMPRSS2 peptidase) (shown in Fig. 1). Ang II binds to the AT1R to induce
 1939 activation of either type II- or type III-CD38 catalytic receptor, which in turn stimulates Ca²⁺ release
 1940 through TPCs and RYRs. Ca²⁺ influx through TRPM2 channels also cooperates to provide a high
 1941 concentration of Ca²⁺ in the cytosol. The overload of cytosolic Ca²⁺ is involved in the activation of the i)
 1942 ROS/IFN-type I/ISGs metabolic sequence; ii) NF-κB via PAMPs/TLRs/MyD88-dependent pathway, and
 1943 iii) NLRP3 inflammasome. This sequence of events is proposed as the likely effects in COVID-19 that
 1944 culminate in a cytokine storm and multi-organ fibrosis. Pharmacological interventions to control the
 1945 CD38-dependent NAD⁺ metabolome are being proposed to create hurdles at different steps of SARS-
 1946 CoV-2 infection. ARBs and ACEi i) block (---I) Ang II/AT1R activation, ii) increase expression of ACE2
 1947 (arrested by viral binding), inducing iii) Ang (1–7) to counterbalance the deleterious pro-inflammatory
 1948 effects of Ang II/AT1R (see Fig. 1B). In parallel CD38 activation by Ang II is reduced and consequently
 1949 NAD⁺ levels are boosted. Similar effects might be obtained using CD38 inhibitors (CD38inh) or by means
 1950 of NAD⁺ precursors supplied. The sACE2 acting as decoy-receptor blocks the viral entry. Therapeutic
 1951 checkpoints are depicted as hypothesis-driven, but based on observations in other viral infections,
 1952 CD38-related diseases, and preliminary data on COVID-19 (see text).

1953

1954 **Figure 6. A.** Expression level of CD38 in the principal hematological cell subsets involved in the immune
 1955 response against viral infections and other diseases. Data were obtained from literature (157, 158), and
 1956 are a knowledge-based best estimate of the protein expression resulting from evaluation of

1957 immunohistochemical staining RNA data and available protein/gene characterization data (N=not
1958 detected, L=low expression, M=medium expression, H=high expression). **B.** CD38 mRNA expression
1959 levels in hematological tissues and in tissues/organs primarily interested by viral infections and other
1960 diseases. Data were obtained from the Human Protein Atlas and are expressed as Consensus
1961 Normalized eXpression (NX), created by combining the data from the three transcriptomics datasets
1962 (HPA, GTEx and FANTOM5) using the internal normalization pipeline.

1963

1964

1965

1966 **Table 1:** Potential and therapeutic approaches involving CD38 in diseases. For each disease or organ
1967 involved, a potential mechanism of action is suggested. References are included in brackets.

1968

1969 **Table 2:** Summary of experimental drugs with potential use in SARS-CoV-2 infection therapy. Each drug
1970 is flanked by its mechanism of action controlled by CD38 (details in the text). References are included
1971 in brackets.

1972