REVIEW ARTICLE

Beauty and the beast: host microRNA-155 versus SARS-CoV-2

K. I. Papadopoulos[1] · A. Papadopoulou[2] · T. C. Aw[3,4]

Abstract

Severe acute respiratory coronavirus 2 (SARS-CoV-2) infection in the young and healthy usually results in an asymptomatic or mild viral syndrome, possibly through an erythropoietin (EPO)-dependent, protective evolutionary landscape. In the old and in the presence of co-morbidities, however, a potentially lethal coronavirus disease 2019 (COVID-19) cytokine storm, through unrestrained renin-angiotensin aldosterone system (RAAS) hyperactivity, has been described. Multifunctional microRNA-155 (miR-155) elevation in malaria, dengue virus (DENV), the thalassemias, and SARS-CoV-1/2, plays critical antiviral and cardiovascular roles through its targeted translational repression of over 140 genes. In the present review, we propose a plausible miR-155-dependent mechanism whereby the translational repression of *AGRT1*, *Arginase-2* and *Ets-1*, reshapes RAAS towards Angiotensin II (Ang II) type 2 (AT2R)-mediated balanced, tolerable, and SARS-CoV-2-protective cardiovascular phenotypes. In addition, it enhances EPO secretion and endothelial nitric oxide synthase activation and substrate availability, and negates proinflammatory Ang II effects. Disrupted miR-155 repression of AT1R + 1166C-allele, significantly associated with adverse cardiovascular and COVID-19 outcomes, manifests its decisive role in RAAS modulation. *BACH1* and *SOCS1* repression creates an anti-inflammatory and cytoprotective milieu, robustly inducing antiviral interferons. MiR-155 dysregulation in the elderly, and in comorbidities, allows unimpeded RAAS hyperactivity to progress towards a particularly aggressive COVID-19 course. Elevated miR-155 in thalassemia plausibly engenders a favorable cardiovascular profile and protection against malaria, DENV, and SARS-CoV-2. MiR-155 modulating pharmaceutical approaches could offer novel therapeutic options in COVID-19.

Keywords MicroRNA-155 · Severe acute respiratory coronavirus 2 · Renin-angiotensin aldosterone system · Angiotensin-converting enzyme 1 · Angiotensin-converting enzyme 2 · Erythropoietin

Introduction

Severe acute respiratory coronavirus 2 (SARS-CoV-2) infection causing coronavirus disease 2019 (COVID-19) emerged in the markets of Wuhan, People's Republic of China in late 2019, and has since had the world in its grip in an unprecedented pandemic, challenging human health and economies [1]. COVID-19 demonstrates a highly variable and unpredictable course; asymptomatic or subclinical in some, inexplicably culminating into a catastrophic hyperinflammation and rapidly progressing to a potentially lethal cytokine storm in others, demanding sophisticated resources from strained health care systems [2]. Co-morbidities associated with chronic inflammatory states such as old age, smoking, hypertension, obesity, diabetes mellitus (DM), and cardiovascular disease (CVD), along with male gender, perilously predispose towards such unfortunate progression [2, 3]. Certain host attributes predict a severe course and impending

✉ K. I. Papadopoulos
kostas@thaistemlife.co.th

A. Papadopoulou
Alexandra.Papadopoulou3@gmail.com

T. C. Aw
tarchoon@gmail.com

1   THAI StemLife, 566/3 Soi Ramkhamhaeng 39 (Thepleela 1), Prachaouthit Rd., Wangthonglang, Bangkok 10310, Thailand

2   Occupational and Environmental Health Services, Feelgood Lund, Ideon Science Park, Scheelevägen 17, 223 63 Lund, Sweden

3   Department of Laboratory Medicine, Changi General Hospital, 2 Simei Street 3, Singapore 529889, Singapore

4   Department of Medicine, National University of Singapore, Singapore 119228, Singapore

lethality while various genetic determinants, environmental elements, geography, lifestyle behaviors, and early age, may engender SARS-CoV-2 protection [4, 5].

Upon host invasion, SARS-CoV-2 spike protein (S) interaction with angiotensin-converting enzyme (ACE)2 downregulates ACE2 expression in endothelial cells (EC) and impairs endothelial nitric oxide (NO) synthase (eNOS) activity and downstream NO bioavailability [6, 7]. ACE2 is an important peptide of the renin angiotensin aldosterone system (RAAS), with a crucial role in counterbalancing activation of ACE1 in the vascular endothelium of the lungs and kidneys by cleaving circulating proinflammatory Ang II to vaso-protective Ang 1–7 and promoting eNOS activation [8, 9]. Overwhelmingly generated via eNOS in ECs, NO production is fundamental in maintaining normal endothelial function and defense against insults, injuries, and inflammation [10, 11]. Bioavailable NO potently inhibits leukocyte adhesion and displays significant antithrombotic, antiproliferative, antioxidative, immunoregulatory and microbicidal properties [10, 11]. Thus, through the latent suppression of endothelial expression of ACE2 and eNOS/NO, SARS-CoV-2 renders ACE2's function in maintaining homeostatic endothelial biology void, and may promote a state of RAAS hyperactivity with elevated angiotensin (Ang II) and aldosterone (ALD) levels and impaired NO bioavailability, all in unison, contributing to the endotheliitis, vascular leakage, and resultant organ injuries observed in COVID-19 [6–9, 12–18]. In the young, however, despite the fact that this ACE1/ACE2 imbalance would be additionally potentiated by lower nasal ACE2 expression, and plausibly also by the serendipitous presence of certain RAAS activating single nucleotide polymorphisms (SNP), this enhanced RAAS overstimulation is apparently well tolerated and in addition renders SARS-CoV-2 infection mild or asymptomatic [17, 19–27].

How do we reconcile these observations? *First*, why, and how does this SARS-CoV-2-induced pro-inflammatory RAAS state in children and young adults become beneficial for the host? *Second*, how is the principal ACE1/Ang II/Ang II type 1 receptor (AT1R) axis, that mediates this RAAS hyperactivity, controlled and prevented from deluging into an uninhibited state of a cataclysmic inflammatory response, and progressing to a potentially lethal cytokine storm [8, 28, 29]? *Finally*, why is this faculty lost in the presence of old age and co-morbidities [3, 29]?

We have put forward an evolutionary congruent, mechanistic explanation accounting for the interaction between host and SARS-CoV-2, that involves an early age, erythropoietin (EPO)-dependent, protective evolutionary landscape [2, 4, 5, 30]. Such an ancestral, protective EPO evolutionary landscape provides the host with a fitness advantage, forming constraints against pathogen adaptation and invasion [31, 32]. The source of this highly significant, age-dependent,

anemia-independent EPO elevation observed during the first 13 years of life, highest in the youngest but declining during a child's development, is unknown. It could be, reasonably, attributed to the significantly higher, age- and genotype-related ACE1 activities in serum and lower nasal ACE2 expression, physiologically found in newborns, healthy children, and teenagers but not in adults [24–26, 33–37]. These early age, physiological states, in certain individuals also serendipitously enhanced by RAAS activating SNPs, elevate ACE1 and would appear to promote a tolerable RAAS hyperactivity, that through elevated Ang II and ALD, both known master regulators of EPO secretion, can plausibly account for the elevated EPO levels seen in the young [31–35]. All molecules in this early age protective evolutionary landscape, involving RAAS-EPO-eNOS interactions, are under significant genetic control aiming to support, augment, and extend EPO elevation and eNOS activity upon pathogen insult, as witnessed by the thalassemias, and protective RAAS and eNOS single nucleotide polymorphisms (SNPs) in malaria and Dengue virus (DENV) infection [27, 31, 32, 38–40]. The resulting elevated EPO levels and the consequently enhanced EPO-eNOS/NO pathway responsiveness, are associated with a better outcome in children with cerebral malaria and may reasonably also promote an early age protection against SARS-CoV-2; indeed, children below the age of 5, when EPO response is maximal, generally experience asymptomatic or mild SARS-CoV-2 infections [4, 30–32, 41–45]. EPO's non-erythropoietic, extensive tissue protective action is mediated through its immunological effects[30], and enhancement of eNOS/NO pathway activity and subsequently increased vaso-protective NO generation and bioavailability [46–49]. EPO and eNOS together are known to abrogate the NACHT, LRR, and PYD domains-containing protein (NLRP) 3 inflammasome, centrally involved in the development of SARS-CoV-2 endotheliitis, as well as effectively inhibit SARS-CoV-2 early replication and cell entry [16, 44, 47–52]. It is thus, evident, that the host intends, with this physiological, and genetically imprinted, RAAS hyperactivity, to ensure adequate EPO levels to support this EPO-mediated, age-dependent protective evolutionary landscape, plausibly explaining the *first* question regarding the uncomplicated and rare SARS-CoV-2 infections in the young [30]. While this physiological RAAS hyperactivity, enhanced by RAAS molecule SNPs, engenders beneficial evolutionary effects in the form of protection against malaria and SARS-CoV-2 at an early age, SNP effects can be pleiotropic, and may turn into a detrimental disadvantage in older individuals, as suggested by the malaria-hypertension hypothesis and their association with severe adult COVID-19 outcomes [28, 53–58]. This disadvantage presumably occurs through the loss of eNOS/NO protection and the unopposed action of Ang II via the AT1R, a central player in the RAAS that

defines the biological efficacy of Ang II and mediates its vasoconstrictive and pro-inflammatory actions [8]. It is, consequently, imperative to answer the *second* and *third* questions, in order to understand how the host controls the resulting RAAS overactivity and diverts Ang II away from the AT1R, and why old age and co-morbidities impact on this ability.

The elusive regulator of the Ang II/AT1R axis within a RAAS hyperactive state

Receptor kinetic studies show that despite Ang II having similar affinities for both its receptors, AT2R stimulation will come into play only at unusually high circulating levels of Ang II, much higher than those needed for AT1R agonism [59]. Moreover, plasma Ang II rather than tissue Ang II is the agonist of AT2R, while the reverse applies to AT1R [59]. Consequently, since AT2R will only engage at high plasma Ang II concentrations and when most AT1R are occupied, the *second* question of how the Ang II/AT1R signaling is held under control, remains unanswered [59]. There is abundant information, expertly reviewed by Dhangadamajhi and Singh [28], that plasma Ang II in malaria, apart from being conducive to EPO secretion, also possesses immunomodulating properties and direct anti-plasmodial activity, able to inactivate up to 88% of plasmodial sporozoites [28, 60]. Ang II also seems to preserve blood–brain barrier (BBB) integrity, presumably by binding to AT2R [28]. Inhibition of Ang II/AT1R signaling, using pharmacological AT1R block (angiotensin receptor blockers (ARBs) or stimulation of Ang II/AT2R signaling, also appears to confer a survival benefit in an experimental model of CM [28]. Furthermore, studies on a human model of endogenous AT1R antagonism, in patients with Bartter's/Gitelman's syndrome (BS/GS), show that the elevated Ang II and ALD do not result in adverse cardiovascular phenotypes but instead, unopposed AT2R signaling may lie behind increased NO-bioavailability, increased NO-mediated vasodilation, normotension, elevated heme oxygenase 1 (HO-1) with increased plasma antioxidant power, along with elevated expression of EPO [33, 61]. This latter observation is of particularly interest considering that Ang II mediates its EPO secretion regulation through AT1R signaling [33–35, 62]! Evidently, Ang II–induced EPO production persists even when AT1R signaling is disrupted. Presumably, additional mechanisms preserving EPO formation come to play, such as hemodynamic effects and tissue oxygenation of EPO-producing cells, ALD via the mineralocorticoid receptor (MR), direct Ang II and ALD effects on hypoxia-inducible factor (HIF)-1α that induce EPO gene transcription, and compensatory Ang II activation of the AT2R [2, 33, 34, 61–64]. It is, thus, obvious that, RAAS regulation of EPO involves a summation of interconnecting mechanisms, and not exclusively Ang II/

AT1R signaling. Enthrallingly, in BS/GS individuals, the endogenous, overactive RAAS environment, elevated Ang II, and ALD, created through AT1R downstream signal disruption, with the simultaneous absence of hypertension and vascular remodeling, apparently also renders them resistant against SARS-CoV-2 infections/COVID-19 [4, 65].

Based on the above intriguing evidence, one must seek what mechanisms the host excogitates that confer endogenous regulation of the AT1R: is it through downregulation of receptor expression, blunting of Ang II/AT1R interaction, dampening of direct Ang II pro-inflammatory effects, or a combination of all of the above? Recently, non-coding RNAs (ncRNA) have been associated with host cell antiviral defense mechanisms, including coronaviruses [66]. One type of such ncRNAs are microRNAs (miRNA), small (18–25 nucleotide long), non-coding, one-stranded RNA molecules, that can target and silence around 60% of all human genes through translational repression [67]. MiRNAs bind to the 3′ untranslated region (3′UTR) of a specific target mRNA, enhancing messenger RNA (mRNA) degradation and inhibiting protein translation, thereby repressing (silencing) gene expression [68]. Viral infections may force the host to elicit hitherto unknown, but evolutionary predetermined, defense programs through miRNA-induced alterations of its immune response [69]. Since a particular miRNA may target one or many different mRNAs while one mRNA may bind many miRNAs, the host can at the same time control diverse aspects of antiviral systemic and immune responses, all in a concerted effort to modulate feedback and control inflammation [67–70]. Moreover, the role of certain miRNAs in the regulation of endothelial function with respect to the RAAS and NO bioavailability, as well as their influence on cytokine and interferon modulation, highlights their potential involvement in the pathogenesis of SARS-CoV-2 and COVID-19 [71, 72].

The beauty: MicroRNA-155 target gene repertoire

Minimally detected under normal physiological conditions and mainly expressed in the thymus and spleen, miR-155 is an ancient, evolutionarily well-conserved miRNA, with distinct expression profiles and multifunctionality [70, 73, 74]. MiR-155 targets over 140 genes involved in numerous physiological and pathological processes including hematopoietic lineage differentiation, immunity, inflammation, cancer, CVD, DM, and particularly viral infections [70, 73–77]. MiR-155, is a key modulator of both innate and adaptive immune responses, with critical roles in viral and parasitic infections mounting ancestral mammalian host defense mechanisms against pathogen challenge [70, 73, 74]. MiR-155's target genes that associate with host defense against malaria, dengue virus (DENV), influenza A, and SARS-CoV-2 infection with COVID-19 are, BTB

and CNC homology 1, basic leucine zipper transcription factor 1 (*BACH1*), suppressor of cytokine signaling 1 (*SOCS1*), HIF-1α, Arginase-2 (*ARG2*), E26 Transformation-specific Sequence 1 (*ETS-1*) factor, and *AGTR1* that encodes AT1R (Table 1) [73, 78–82].

Several studies have confirmed the prominent position of miR-155 in the regulation of inflammatory responses and RAAS/Ang II/AT1R effects in CVD [70, 82]. Most intriguingly, AT1R-mRNA is an authentic miR-155 target as are Arg2 and Ets-1 [70, 82]. As a repressor of *AGTR1*, *ARG2*, and *ETS-1* expression, miR-155 has the potential to answer the second question we posed earlier on how the host reconciles a pathogen-induced overtly hyperactive RAAS state with a protective CV phenotype in SARS-CoV-2. Furthermore, repression or modulation of additional gene targets in Table 1 will induce and/or potentiate EPO's favorable immunological, anti-inflammatory and cytoprotective evolutionary landscape (vide infra: hemoglobin E (HbE)/β-thalassemia) to fight off pathogen replication, imminent invasion, and lower the burden of infection.

The beast: the taming of SARS-CoV-2

In a young and/or previously healthy host, without evidence of comorbidities and/or pharmacological RAAS interventions, our proposed mechanistic pathway commences with the induction of miR-155 upon an impending pathogen invasion such as malaria, DENV, influenza A, or SARS-CoV-1/2. Elevated *in-vitro* and *in-vivo* miR-155 levels have been reported in all the above conditions [70, 73, 86–89]. Hadighi et al. found significantly elevated host miRNAs including miR-155 in patients infected with *P. vivax* [86]. SARS-CoV-1/2 reportedly induce a tenfold upregulation of the miR-155 host gene (*MIR155HG*) and trigger a 3–16-fold increase of miR-155 *in-vitro* [88]. SARS-CoV-2 appears to induce host innate immunity earlier and twice as effectively

as CoV-1, including miR-155 [88]. In clinical SARS-CoV-2 infection, upregulated miR-155 levels have been reported to date, in all but two studies (Table 2) [90–99]. Elevated miR-155 levels could differentiate between different degrees of COVID-19 severity [90–99]. The contradictory findings in the two studies could be due to differences in sampling timing and elevated BMI and advanced age, factors known to be associated with blunted miR-155 expression [98–101].

When SARS-CoV-2 binds to ACE2, its cognate receptor, the SARS-CoV-2 spike 1 protein (S)-ACE2 complex is internalized through AT1R-dependent endocytosis (Figs. 1, 2) and ACE2 is subsequently downregulated [102]. An immediate ACE1/ACE2 imbalance ensues, that strongly engages host humoral and tissue RAAS, leading to enhanced Ang II and ALD formation, while the protective arm of the RAAS is rendered void [2, 4]. As AT1R's level of expression, defines the biological efficacy of Ang II and thus the degree of RAAS hyperactivity, miR-155's robust *AGTR1*/AT1R-mRNA repression will reduce AT1R expression and membrane presence and blunt Ang II action through AT1R [70, 82, 103]. Persisting high plasmatic Ang II concentrations will now be diverted and increasingly engage the AT2R, increasing protective Ang II/AT2R signaling and eNOS/NO pathway activation [8]. AT2R and eNOS/NO are fundamentally involved in NLRP3 regulation, and robustly suppress NLRP3 activation and inflammatory cytokine release and pyroptosis, subsequently alleviating cardiopulmonary and cerebrovascular injury, cardiac remodeling, and inflammation (Fig. 2) [59, 73, 104–106]. In the absence of old age and comorbidities in SARS-CoV-2, miR-155's purposeful overexpression appears to induce a hyperactive, albeit protective RAAS state, very similar to the one seen with ARBs in CV disease and in BS/GS [2, 61, 73, 104]. Pharmacological RAAS inhibition (RAASi) effects in SARS-CoV-2 have been actively debated [107]. MiR-155 levels are reportedly decreased in coronary artery disease (CAD)

Table 1 Direct targets of microRNA-155 relevant to SARS-CoV-2

Gene symbol	Full gene name	Action	References
AGTR1	Angiotensin II type 1 receptor gene	Repressed expression mediates an endogenous AT1R antagonism	[70, 82]
ARG2	Arginase-2	Repression prevents L-arginine depletion, aids dendritic cell maturation, and averts lung pathologies	[78]
BACH1	BTB and CNC homology 1, basic leucine zipper transcription factor 1	Repressing BACH1 leads to anti-inflammatory, cytoprotective, antioxidant effects through HO-1, and to induction of antiviral interferon (IFN)	[73, 81]
ETS-1	E26 Transformation-specific Sequence-1	Repression negates some of Ang II effects involving gene regulation of inflammation, angiogenesis, and vascular remodeling	[70, 82, 83]
HIF-1a	Hypoxia-inducible factor 1α	Promotes HIF-1α recovery and induces EPO gene transcription	[64]
SOCS1	Suppressor of cytokine signaling 1	Repression of canonical negative regulation of type I IFN signaling leads to enhanced type I IFN-mediated antiviral response. Enhances JAK2/Y343/STAT5 axis: a crucial mediator of EPO-mediated protection against ischemic injury	[84, 85]

Table 2 *In-vitro* and clinical studies investigating miR-155 levels in COVID-19

| Authors	Type of study	Result
Wyler et al. [88]	*In-vitro*: SARS-CoV-2- infected Calu-3 cells	Ten-fold upregulation of the miR-155 host gene (MIR155HG) and a 3–16-fold increase of miR-155
Haroun et al. [90]	Clinical study	Increased miR-155 expression level in COVID-19 patients vs. controls, in severe vs. moderate COVID-19 patients, and in non-survival vs. survival COVID-19 patients
Abbasi-Kolli et al. [91]	Clinical study	Significantly increased miR-155-5p levels in the acute phase of COVID-19 vs. a healthy control group
Garg et al. [92]	Clinical study	Significantly increased miR-155 levels in COVID-19 patients vs. healthy controls. MiR-155 levels could distinguish between COVID-19 and Influenza-acute respiratory distress syndrome (ARDS) groups
Donyavi et al. [93]	Clinical study	Significantly upregulated miR-155-5p expression level in the COVID-19 group vs. controls. Significant inverse correlation between miR-155-5p and SARS-CoV-2 N-gene and RdRp-gene
Gedikbasi et al. [94]	Clinical study	Significantly upregulated miR-155-5p levels in COVID-19 patients and associated with disease severity *SOCS1* expression robustly and negatively correlated with miR-155
Eyileten et al. [95]	Clinical study	MiR-155-5p expression levels differed between healthy individuals and COVID-19 patients and showed increasing trend at day-7 and day-21 after admission
Li et al. [96]	Clinical study	Markedly elevated miR-155 in mild/moderate COVID-19 disease vs. severe/critical disease and negative controls
Gaytán-Pacheco et al. [97]	Clinical study	Significant upregulation of miR-155 in severe COVID-19 patients versus negative controls
Giannella et al. [98]	Clinical study	Significantly downregulated miR-155 levels in severe vs. mild COVID-19, in ICU vs. non-ICU. Predicted increased risk of COVID-19-related sequelae and/or death
Kassif-Lerner et al. [99]	Clinical study	2.5-fold and fivefold less circulating miR-155 in mild and severe COVID-19 disease, respectively, vs. healthy people

COVID-19 coronavirus disease 2019, *ICU* intensive care unit, *miR-155*, MicroRNA-155, *SARS-CoV-2* severe acute respiratory coronavirus 2

compared to healthy subjects and concurrent ARB or ACE inhibitor (ACEi) treatment induced further reduction in miR-155 levels versus no ARB/ACEi [108, 109]. It is thus plausible that, despite a valuable AT1R blockade, the observed miR-155 reduction by ARB/ACEi deprives the host of other miR-155-induced beneficial, antiviral, immunological and cytoprotective effects, or that RAASi is not as potent or efficient as miR-155-induced AT1R downregulation, to promote cardioprotection during COVID-19 (Table 1) [70]. Furthermore, ACEi treatment, known to inhibit EPO secretion through Ang II reduction, may negate EPO's protective effects [34, 110, 111]. Moreover, while miR-155 levels in BG/GS patients have not been reported, it is worthwhile noting that miR-155 functions as a negative regulator of Ras homolog gene family, member A (RhoA) signaling, reportedly downregulated in BG/GS [112, 113].

Given the AT1R-mediated signaling in EPO-producing renal cells one would expect that EPO should be reduced when miR-155 is elevated [33–35, 62]. However, Ang II stimulation of HIF-1α expression via AT2R-mediated posttranscriptional mechanism and miR-155's actions on HIF-1α degradation can induce EPO formation and bypass the hurdle of AT1R repression (Table 1) [61, 64, 114]. The elevated EPO will be available to exert its tissue protective, antiapoptotic, anti-oxidative, and NLRP3 inflammasome abrogating, anti-inflammatory effects via the tissue protective receptor (TPR) that engages eNOS and increases NO bioavailability (Fig. 2) [4, 16, 50, 115, 116]. Interestingly, miR-155 also controls the Janus Kinase (JAK)2/Y343/STAT5 signaling axis required for EPO-mediated protection against renal ischemic injury (Table 1) [85]. Furthermore, increased eNOS activity promoted via unopposed AT2R signaling when AT1R is downregulated (similarly to an ARB block), and through eNOS-AT1R dissociation due to reduced AT1R membrane availability, will ultimately, further increase NO-bioavailability (Fig. 2) [73, 117, 118]. Increased NO bioavailability may halt SARS-CoV-2 infection at an early stage by inhibiting i) palmitoylation and fusion of the SARS-CoV-1/2 spike (S) protein to ACE2, and ii) early production of viral RNA, processes critical in controlling membrane fusion and virion infectivity (Fig. 2) [44]. As SARS-CoV-2-S-ACE2 complex is internalized through an AT1R-dependent endocytosis, reduced AT1R membrane presence through miR-155-induced AT1R repression could theoretically directly inhibit SARS-CoV-2 cell entry (Fig. 2) [102].

Furthermore, another direct target for miR-155, *ARG2*, constitutively expressed and also inducible in endothelial and kidney cells, is a critical regulator of L-arginine
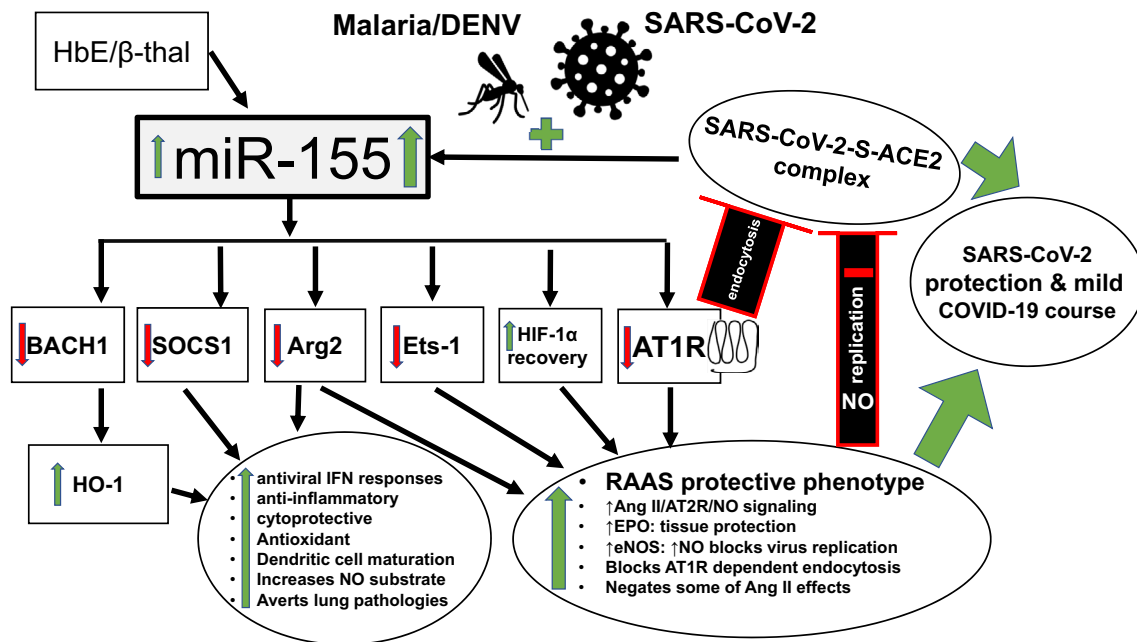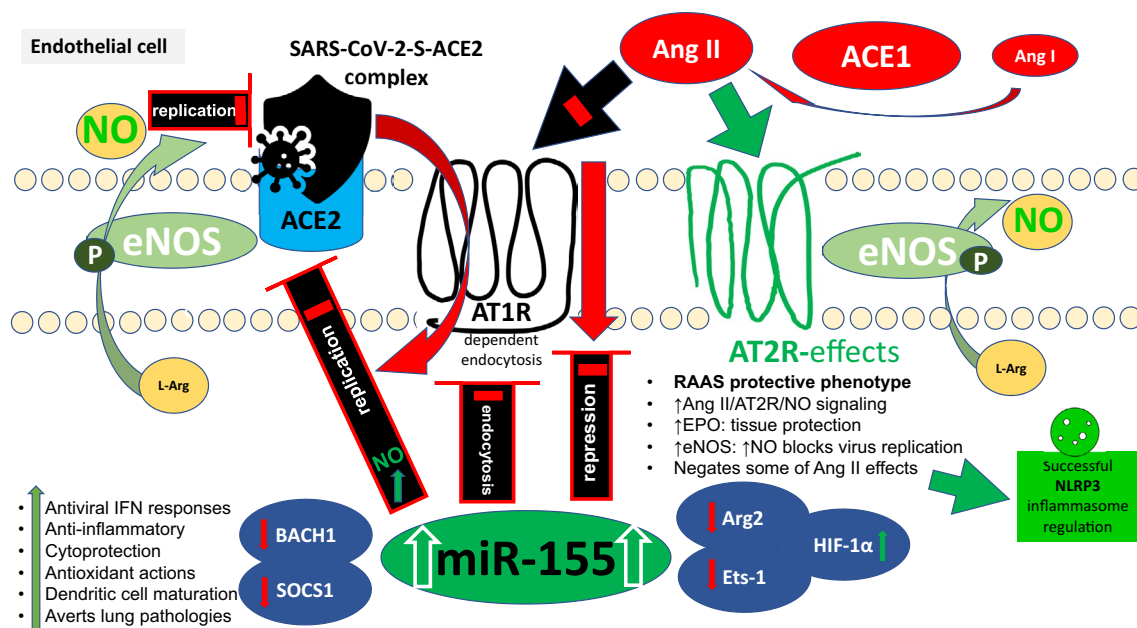
Fig. 1 Severe acute respiratory coronavirus 2 (SARS-CoV-2) but also hemoglobin E (HbE)/β-thalassemia (β-thal), malaria and dengue virus (DENV) robustly increase miRNA-155 (miR-155) levels that, through translational repression of target genes, will lead to SARS-CoV-2 protection and/or asymptomatic or mild coronavirus disease 2019 (COVID-19) course. Repression of angiotensin II type 1 receptor (AT1R), arginase 2 (Arg2) and E26 Transformation-specific Sequence-1 (Ets-1) leads to a protective renin-angiotensin aldosterone system (RAAS) phenotype with erythropoietin (EPO) and endothelial nitric oxide (NO) synthase (eNOS) increase. Repression of BTB and CNC homology 1, basic leucine zipper transcription factor 1 (BACH1), suppressor of cytokine signaling 1 (SOCS1), and promotion of hypoxia-inducible factor 1α (HIF1α) recovery will enhance heme oxygenase (HO)-1 levels and induce anti-inflammatory and cytoprotective programs along with antiviral interferon (IFN) responses. Red colors and signs decrease or inhibit. Green colors and signs increase or stimulate/promote

metabolism and NO synthesis, implicated in the development of endothelial dysfunction, CV disease, and diabetic nephropathy [78, 119, 120]. When repressed, Arg2 prevents the depletion of L-arginine, the obligate substrate of eNOS, leading to improved substrate availability and additional increases in NO-production and NO-bioavailability, further aiding the above-mentioned cardio- and renoprotective and antiviral actions (Table 1, Figs. 1, 2) [78, 119]. L-arginine is crucial in promoting dendritic cell maturation and their ability to drive T cell proliferation further improving antiviral responses [78, 79]. Low L-arginine levels impair T cell proliferation and IFN-γ production through reduced expression of the CD3ζ chain, a crucial part of the T-cell antigen receptor complex [121]. Moreover, Arg2 is essential for interleukin (IL)-10/miR-155 axis-induced metabolic reprogramming of inflammatory macrophages, including IL-1β secretion, deciding the fate of a cell's inflammatory status [80]. Finally, deranged control of Arg2 repression by miR-155 is a potential parameter contributing to the pathogenesis of lung diseases, an observation pertinent to COVID-19 lung pathology[78].

Evincing miR-155's decisive role in RAAS modulation

The link between miR-155 and its repression of the AT1R is particularly enthralling. The AT1R 1166A/C is a mirSNP (SNP disrupting microRNA targets) as it occurs in the AT1R 3′-UTR [70]. MiR-155 binding is, thus, disrupted in the +1166C-allele harboring the SNP, as the target for its seed sequence binding to it is absent, rendering the *AGTR1* gene with the +1166C-allele unresponsive, and consequently only the +1166A-allele expression can be downregulated [70, 103]. This observation biochemically accounts for the increased frequency of hypertension, CV, and metabolic disease associated with the +1166C polymorphism, due to increased AT1R expression, additionally worsened by Ang II/AT1R downregulation of eNOS phosphorylation and potentially unfavorable eNOS polymorphisms [73, 122, 123]. Captivatingly, and maybe not unexpectedly, in carriers of AT1R +1166C-allele, the severity of COVID-19 and oxygen dependency was higher compared to the A allele carriers[53]. This observation provides remarkable *in-vivo* evidence evincing that the impact of miR-155 on RAAS significantly influences COVID-19 course. In addition, reduced

Fig. 2 MiRNA-155 (miR-155)-induced angiotensin (Ang) II type 1 receptor (AT1R) downregulation and reduced membrane expression will inhibit Ang II pro-inflammatory and vasoconstrictive effects, impede severe acute respiratory coronavirus 2 (SARS-CoV-2) AT1R-dependent endocytosis, dissociate endothelial nitric oxide (NO) synthase (eNOS) from AT1R, and enhance its activity and NO bio-availability, consequently blocking virus replication, and cell entry. Moreover, elevated plasmatic Ang II will increasingly engage the AT2R and induce eNOS/NO-mediated vasculoprotective cellular pathways, resulting in successful regulation of NACHT, LRR, and PYD domains-containing protein (NLRP) 3 inflammasome. Repression of arginase 2 (Arg2) and E26 Transformation-specific Sequence-1 (Ets-1) will improve eNOS substrate availability and negate Ang II-induced endothelial and vascular inflammation, respectively, while hypoxia-inducible factor 1α (HIF1α) recovery will further enhance Ang II-mediated erythropoietin (EPO) secretion. BTB and CNC homology 1, basic leucine zipper transcription factor 1 (BACH1) and suppressor of cytokine signaling 1 (SOCS1) repression will induce robust anti-inflammatory, antioxidant, cytoprotective and interferon (IFN)-mediated antiviral programs

membrane expression of AT1R may aid in dampening persistent pro-inflammatory Ang II effects mediated through functional AT1R-autoantibodies (AT1-AA), that may arise through uncontrolled NLRP3-mediated pyroptosis [12, 124–126]. AT1-AAs significantly correlate with IL-6 levels and are implicated in the pathogenesis of systolic blood pressure, pre-eclampsia, and COVID-19 [127, 128].

Finally, Ets-1, acts as a transcriptional mediator of Ang II-induced endothelial and vascular inflammation, angiogenesis, and remodeling[83]. Ets-1 downstream targets include cyclin-dependent kinase inhibitor p21^{CIP} (promoting hypertrophy in vascular smooth muscle cells and dysfunction and cell death in endothelial cells), plasminogen activator inhibitor–1 (PAI-1: critical determinant of the fibrinolytic system and contributing to the development of perivascular fibrosis), vascular cell adhesion molecule 1 (VCAM-1: cell adhesion molecule induced in inflammation), Fms Related Receptor Tyrosine Kinase 1 (FLT-1: a receptor for vascular endothelial growth factor involved in angio- and vasculogenesis), and monocyte chemoattractant protein–1 (MCP-1: mediates inflammatory response in hypertensive vascular disease)[83]. MiR-155 with two target sites in the 3'-UTR of *ETS-1*, robustly represses it, and its markedly

upregulated downstream effectors, thus potently dampening Ang II's direct pro-inflammatory cardiovascular effects (Table 1, Fig. 1) [82].

Too much of a good thing: excessive miR-155 levels

A vasoplegic state resembling profound RAAS inhibition (even in the absence of ACEi/ARBs), has been reported by certain research groups in sepsis and COVID-19 [129, 130]. MiR-155 elevation is part of an early-stage human septicemic response, peaking at 12 h and decreasing at 48 h, kinetics similar to its induction in SARS-CoV-2 infected human cell lines [74, 88]. However, contradictory miR-155 levels in sepsis underline the need of understanding how miR-155 is implicated in uncontrolled septic inflammatory responses. Elevated levels have been associated with severe condition, poor prognosis, and non-survival, while low levels are implicated in reduced survival in young (< 65 years) critically ill patients [74, 131]. Moreover, persistent miR-155 elevation could lead to decreased AT1R expression with excessive AT1R signaling impairment, contributing to sepsis-induced acute kidney injury [129]. Furthermore, protractedly elevated miR-155 levels may lead to impaired

Ang II vascular reactivity due to synergism between AT1R downregulation and Ets-1 repression and could account for COVID-19-induced vasodilatory shock that may improve with Ang II infusion [132–134]. Low miR-155 levels on the other hand, as in the old and/or in comorbidities, could explain a RAAS hyperactive state with cytokine storm [76, 100, 101, 135]. It is to date unclear how miR-155 finetunes this delicate balance in sepsis, but age and comorbidities appear of paramount importance [74, 131]. Clearly more studies are needed to understand its molecular underpinnings in order to reduce excessive inflammation and alleviate tissue and organ damage through tissue and/or systemic miR-155-modulating pharmacological interventions.

MiR-155 engenders SARS-CoV-2 protection in hemoglobin E (HbE)/β-thalassemia carrier state

In our initial review on the HbE/β-thalassemia trait conferring resistance against SARS-CoV-2 infection, subsequently supported in independent reports, we proposed miR-155 as the mediator for this protection [5, 136–138]. Supporting an antiviral effect for the HbE/β-thalassemia trait, akin to its anti-malarial effect, red blood cell precursors in Thai carriers of HbE/β-thalassemia trait were significantly less susceptible to DENV infection[5, 139]. MiR-155 is elevated in HbE/β-thalassemia, enhancing monocyte erythrophagocytic activity, while its exogenous overexpression appears to limit DENV replication *in-vitro* [81, 140–142]. MiR-155 targets and downregulates *BACH1*, a sensor of heme levels and a strong repressor of the anti-inflammatory, cytoprotective, and antioxidant protein HO-1, ultimately leading to erythrophagocytosis and induction of antiviral interferon (IFN) responses (Table 1, Fig. 1) [70, 73, 81, 141, 143]. HO-1 is known to exhibit antiviral activity against human immunodeficiency and hepatitis B, C viruses[143]. The anti-DENV effects of HO-1 are exerted through its enzymatic product, biliverdin, an inhibitor of DENV proteases (NS2B/NS3), and DENV protease-suppressed antiviral IFN response is thereby rescued [70, 81, 143]. In experimental models of severe malaria and DENV, HO-1 was shown to control resistance and susceptibility to cerebral malaria and malaria-associated acute lung injury while its pharmacological induction with cobalt protoporphyrin (CoPPIX) reduced experimental cerebral malaria incidence, and demonstrated significant delay in DENV disease onset and mortality, along with lower cerebral DENV load [143, 144]. HO-1's cytoprotective, anti-inflammatory, and antiviral properties may aid in SARS-CoV-2 protection as its upregulation by the SARS-CoV-2 S protein has been documented *in-vitro* and some repurposed drugs reportedly protective against COVID-19, increase HO-1 [143, 145, 146].

Furthermore, SOCS1, a canonical negative regulator of type I IFN signaling, is targeted by miR-155 in macrophages,

and *SOCS1* knockdown mediates the enhancing effect of miR-155 on type I IFN-mediated antiviral response (Table 1, Fig. 1) [84]. MiR-155's central role in host defense in a model of coronavirus-induced neurological disease underscores its importance in enhancing antiviral T cell responses including IFN-γ secretion, cytolytic activity, and homing to the central nervous system (CNS) in response to viral infection [147]. Aggravated disease course, increased morbidity/mortality, and an inability to control viral replication within the CNS was reported in miR-155-knockout (KO) mice[147]. Induction of ectopic upregulation of miR-155 in the liver of mice using hepatotropic adeno-associated virus 8 (AAV8) vectors achieved complete protection against infectious parasite challenge through direct suppression of SOCS1 [148]. MiR-155 mediated downregulation of AT1R (vide supra) in antigen-specific CD8 + T cells could affect a variety of downstream functions ushering the host towards a malaria protective phenotype, highlighting miR-155's fundamental role in Plasmodium liver infection *in-vivo* [148–150]. As previously mentioned, Hadighi et al. found significantly elevated host miRNAs, including miR-155, in patients infected with *P. vivax* [86].

Elevated miR-155 levels with repression of relevant target genes could convincingly account for the favorable inflammatory profile (Ets-1 repression with lower PAI-1 levels), better lipidemic and metabolic profile (SOCS1), better ambulatory blood pressure control (lower AT1R expression), and EPO-mediated renoprotection against ischemic injury through the SOCS1/JAK2/Y343/STAT5 axis, altogether leading to overall better CV health, repeatedly reported in HbE/β-thalassemia carrier state [151–153]. An advantageous basal health condition in thalassemia carriers at the time of the initiation of SARS-CoV-2 infection, may potentially lead to a more favorable COVID-19 outcome [138]. MiR-155 can thus eloquently engender HbE/β-thalassemia's protective effects in malaria, DENV, and SARS-CoV-2 (Fig. 1) [4, 5, 81, 85, 86, 89, 139, 141, 142, 148–150, 154].

Conclusions and future perspectives

As a multifunctional miRNA, miR-155 critically modulates innate, humoral, and cellular immune responses during viral infections [155]. In the current review, we propose that the elevated miR-155 levels in SARS-CoV-2 infection appear, anticipatorily and purposefully, to prepare the host for a SARS-CoV-2-S-ACE2-induced RAAS hyperactivity [88, 90–99]. At a young age, and in the absence of comorbidities or pharmacological interventions, a judiciously initiated and choreographed miR-155 circuitry is expected to promote immediate, early, and late protection against SARS-CoV-2 and its complications[2, 4, 70, 73, 85, 156]. MiR-155-mediated translational repression of *AGTR1*, *ARG2* and *ETS-1*

(Table 1), purposefully tames this SARS-CoV-2-induced RAAS hyperactivity into a balanced, tolerable, and defensive RAAS state, that through AT2R, promotes a protective EPO evolutionary landscape and NLRP3 inflammasome regulation (Fig. 1, 2) [30, 106]. MiR-155 engendered AT1R downregulation and reduced membrane availability coaxes a RAAS cardioprotective state [73], avails increased eNOS/NO pathway activation [47, 157], the latter further potentiated by Arg2 repression [80, 119, 158], leading to increased NO-bioavailability and impaired AT1R-mediated endocytosis, SARS-CoV-2 replication, and cell entry (Fig. 2) [44, 102]. Furthermore, Ets-1 repression negates proinflammatory Ang II effects [83]. Disrupted miR-155 repression of the AT1R + 1166C-allele, associated with adverse CV and COVID-19 outcomes, biochemically manifests this miR's decisive role in RAAS modulation [53, 122, 123]. Finally, *BACH1* and *SOCS1* repression enhances host antiviral responses to fight off pathogen invasion, simultaneously creating an anti-inflammatory, cytoprotective, antioxidant milieu, through HO-1 increase, that robustly lowers inflammatory burden (Fig. 1) [73, 81, 84, 85]. In situations when miR-155 homeostasis is compromised (T2DM, sarcopenia, obesity, smoking, aging, male gender, CVD and renal disease, or pharmacological interventions), unimpeded RAAS stimulation and inappropriately low EPO levels, with subsequent EPO/eNOS-NO protection override, may allow NLRP3 dysregulation, and progress towards a particularly aggressive COVID-19 course with aberrant immune response and immunopathological consequences [2, 4, 63, 76, 77, 100, 101, 109, 135, 159, 160]. Genetic variants of the molecules in the RAAS and of eNOS may additionally and differentially impact on SARS-CoV-2 protection [30].

MiR-155 convincingly integrates disparate evidence in SARS-CoV-2 infection and COVID-19 course and appears as a valuable diagnostic marker and prognostic tool [90–93]. Further studies on miR-155, and other miRNAs and their genetic polymorphisms, will clarify discrepancies in their differentially expressed miRNA profiles and improve our understanding of their pathophysiology. Tissue specific studies and characterization of miR-155 temporal expression trajectory, are particularly important. MiR-155 modulation approaches could offer innovative prevention and treatment strategies, but specific and directed tissue, rather than global modulation, might offer superior therapeutic advantages [87, 135]. ARDS in influenza A responded better with lung alveolar type II cell miR-155 inhibition rather than global inhibition that also involved miR-155 from inflammatory leukocytes that invaded the lung at a later stage [87]. In the present clinical management of COVID-19, careful combination of MR-antagonists (aldactone, eplerenone, finerenone) to avoid hyperkalemia, with a calcium channel blocker may prove effective in the elderly [135, 161]. MR inhibition will rescue and restore the profoundly low basal serum miR-155 levels in the aging vasculature and block two sequential steps involving miR-155 targets, Cav1.2 (L-type calcium channel (LTCC) subunit) and AT1R that contribute to hypertension [135]. On the other hand, ARB or ACEi treatment further reduces miR-155 levels versus no ARB/ACEi [108]. Moreover, adding metformin in selected patient groups (obesity and T2DM) might confer additional benefits since metformin therapy prior to admission in patients with COVID-19 and pre-existing T2DM is associated with a significant reduction of in-hospital mortality [162]. Metformin has also been reported to improve high fat-induced inflammation in vascular endothelium through increased expression of miR-155 levels [163].

In the coevolutionary virus-host arms race, viral miR-NAs have possibly evolved to exploit pre-existing host gene regulatory pathways, in yet unknown ways, to provide a viral replicative advantage [164]. Kaposi's-sarcoma-associated herpes virus, Marek's disease virus, and Ebola virus, all encode miR-155 analogs, while Epstein Barr virus can even induce host miR-155 [73, 88]. It is thus, conceivable, that viral miR-155 induction is an invasive viral strategy in SARS-CoV-2 infection [73, 88]. Numerous miRNAs are part of the vast and intricately coordinated processes, interactively affecting multiple regulatory pathways [68]. We undoubtedly acknowledge that additional miRNAs are involved in the etiopathology of SARS-CoV-2. However, our translational approach on miR-155 offers an understanding of this multifunctional miRNA's permeative effects in health and disease and highlights the need for circulating miRNA profiling to identify clusters and signatures, that will aid in patient stratification and treatment.

Declarations

Informed consent Not applicable.

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