Diabetes, inflammation, and the adiponectin paradox: Therapeutic targets in SARS-CoV-2

Gilbert Ho [a], Alysha Ali [a], Yoshiki Takamatsu [b], Ryoko Wada [b], Eliezer Masliah [c], Makoto Hashimoto [b],[*]

[a] PCND Neuroscience Research Institute, Poway, CA, USA
[b] Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, Japan
[c] Division of Neurosciences, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA

Aging and pre-existing conditions in older patients increase severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) severity and its complications, although the causes remain unclear. Apart from acute pulmonary syndrome, Coronavirus 2019 (COVID-19) can increasingly induce chronic conditions. Importantly, SARS-CoV-2 triggers *de novo* type 2 diabetes mellitus (T2DM) linked to age-associated cardiovascular disease (CVD), cancers, and neurodegeneration. Mechanistically, SARS-CoV-2 induces inflammation, possibly through damage-associated molecular pattern (DAMP) signaling and 'cytokine storm,' causing insulin resistance and the adiponectin (APN) paradox, a phenomenon linking metabolic dysfunction to chronic disease. Accordingly, preventing the APN paradox by suppressing APN-related inflammatory signaling might prove beneficial. A better understanding could uncover novel therapies for SARS-CoV-2 and its chronic disorders.

Introduction

Since the outbreak of the SARS-CoV-2/COVID-19 viral pandemic, confirmed disease cases with severe complications, and especially mortality rate, have shown a strong age dependency in most countries with adequate disease reporting, showing significantly fewer severe cases in younger compared with older individuals (Fig. 1a) [1,2]. Developing nations in Africa, despite reported earlier mortality, also match this pattern, such as in sub-Saharan Africa and South Africa [2,3]. Moreover, younger individuals appear less susceptible to infection or might lack symptoms, raising concern for epidemic asymptomatic viral spread. Notably, the SARS-CoV-2 infection not only triggers acute inflammatory pneumonia, but can also promote the emergence of numerous aging-associated chronic disorders, such as T2DM, cerebrovascular and chronic respiratory disease, hypertension, cancer, and even neurodegeneration (Fig. 1b) [4]. Interestingly, ApoE ε4/ε4, a well-known risk factor for late-onset Alzheimer's disease (AD) and CVD, might increase susceptibility and mortality from COVID-19 [5], suggesting that ApoE genotype variants have a mechanistic role in modulating the risk of aging-associated disorders, especially neurodegeneration, in COVID-19. Perhaps controversial, some evidence also suggests that normalized vitamin D and vitamin K reduce the severity of COVID-19 complications, perhaps also lowering the risk of aging-associated disease [6,7]. Similarly, deficiencies in both have been long associated with aging disorders, including cancers and neurodegeneration, and might also connect SARS-CoV-2 to such complications through anti-inflammatory properties and antithrombotic mechanisms [8,9]. Recently, a bidirectional relationship was established between SARS-CoV-2 and DM, such that DM increases severe complications from COVID-19, but also, and even more striking, COVID-19 leads to the *de novo*

∗ *Corresponding author.* Hashimoto, M. (hashimoto-mk@igakuken.or.jp)
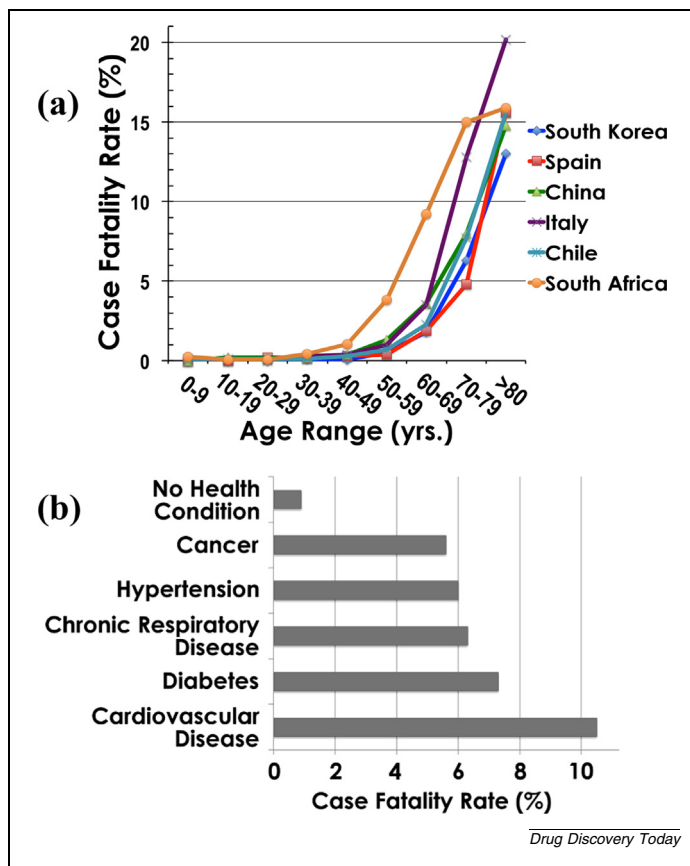
FIGURE 1

Dependency of coronavirus 2019 (COVID-19) disease on age and pre-existing diseases. **(a)** Estimated case fatality rate (CFR) of COVID-19 by age. Historical data across multiple countries [South Korea (March 24, 2020), Spain (March 24, 2020), China (February 17, 2020), Italy (March 17, 2020), Chile (May 3[1], 2020), and South Africa (May 28, 2020)] suggest that globally, greater risk and mortality from the disease increases exponentially with age [1,2]. Consistently, from the May 28, 2020 data from South Africa, a developing nation, and more recently developed countries, such as Chile, CFR also appears to follow this trend, provided there is adequate reporting of COVID-19 data. Yet, interestingly, the CFR for South Africa, unlike other countries, appears to plateau at the oldest age group, which might be a function of population age distribution in that country. **(b)** CFR of COVID-19 by pre-existing health conditions. Current data from China suggests that COVID-19 risk and mortality is greatly increased in those with underlying health conditions including cardiovascular, diabetes, chronic respiratory disorders, hypertension and cancer, compared to those without. Of note, as shown in the top longest bar, 10.5% of persons with a cardiovascular disease who were diagnosed with COVID-19 were deceased. Data and graphs modified and adapted, with permission, from [1,2].

onset of T2DM along with worsening of existing DM and its complications [10].

Common during mid- to later life, T2DM promotes several aging-associated chronic conditions, including cardiovascular, renal, respiratory, and neurodegenerative disorders, such as AD and Parkinson's disease (PD) [11]. Since both advanced age and pre-existing aging-related chronic diseases are risk factors for more severe SARS-CoV-2, and given the bidirectional nature of the SARS-CoV-2 and T2DM relationship, T2DM might foster the development of chronic age-associated conditions related to SARS-CoV-2. Of relevance to T2DM, the importance of the APN paradox to insulin resistance and also to age-related conditions, including neurode-

generation, has been highlighted [12], suggesting that this paradox also has implications for COVID-19 infection and its chronic complications. Therefore, here we explore the mechanistic relationships connecting SARS-CoV-2 infection, T2DM, and chronic disease, through the perspective of the APN paradox. Moreover, we uncover the role of specialized inflammatory signaling that links SARS-CoV-2 infection to insulin resistance. Finally, as the role of the proinflammatory signalome in the development of the APN paradox is revealed, clues for novel therapeutic targets will emerge not only for COVID-19, but, perhaps more importantly, also for subsequent chronic disorders.

Links between SARS-CoV-2 infection and metabolic dysfunction

Indeed, the consistent bidirectional relationship of T2DM with SARS-CoV-2 remains central. In one direction, T2DM appears to increase risk for new coronavirus infection, and active T2DM acts as an independent predictor of mortality and morbidity in patients with SARS [13]. Alternatively, a recent report that SARS-CoV-2 induces *de novo* T2DM in previously nondiabetic patients is vital, emphasizing the hidden dangers of the infection [10]. Likely, pancreatic tissues, along with multiple other tissues affected by SARS-CoV-2, might be targeted because of expression of specific endogenous receptors for viral spike proteins essential for viral entry, such as angiotensin-converting enzyme 2 (ACE2), an enzymatic homolog of ACE.

A component of the renin-angiotensin system, ACE converts angiotensin I to proinflammatory angiotensin II (AII), whereas ACE2 further converts AII to angiotensin (1–7) counteracting inflammation (Fig. 2). Membrane-bound ACE2 acts as a cell membrane receptor for SARS family viruses, and, aided by trans-membrane serine protease 2 (TMPRSS2), facilitates SARS-CoV-2 cellular penetration by associating viral spike glycoprotein with human ACE2 [14]. Upon SARS-CoV-2 tissue entry, viral RNAs are released, triggering a 'cytokine storm' involving excessive release of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and other proinflammatory cytokines and chemokines, ultimately causing tissue inflammation and destruction [4]. Given that the virus concomitantly reduces functional circulating ACE2, a relative increase in AII with reduced angiotensin (1–7) compounds systemic inflammation (Fig. 2) [15]. Conceivably, because ACE2 is abundantly expressed in pancreatic β cells, SARS-CoV-2 might disturb normal pancreatic function, altering glucose metabolism and inducing T2DM. Yet, ACE2 is abundant in other key metabolic tissues, including adipose, small intestinal, and renal tissues, and interestingly, in the central nervous system, suggesting other viral targets [16]. Moreover, ACE2 over-expression improves insulin release in a diabetic mouse model [17], and also increases angiotensin (1–7) levels, further sensitizing the insulin receptor [18]. Interestingly, regarding chronic disease, ACE2 levels are significantly reduced in AD brain and inversely correlated with amyloid and tau pathology [19].

SARS-CoV-2 might promote the APN paradox of aging-associated disease

Among various DM-related biological responses, we highlight the 'APN paradox,' which has been proposed to be important
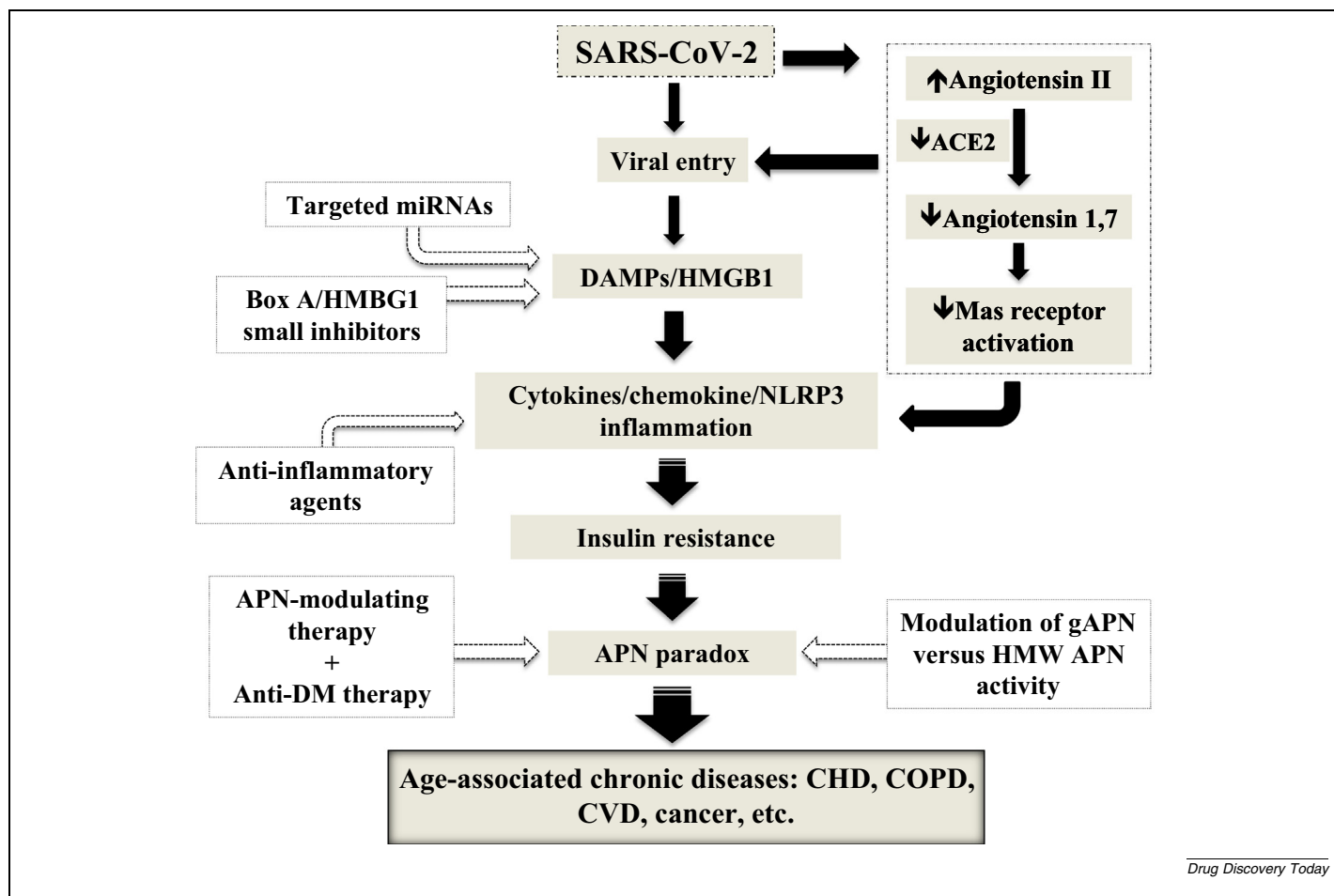
FIGURE 2

Schematic overview of proposed mechanisms and therapy targets in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the adiponectin (APN) paradox. In older patients, upon tissue entry via angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2, releases viral RNAs, which might trigger immunological responses. Under hyperinflammatory conditions, pneumonia and diabetes mellitus (DM) might be induced, associated with hyperadiponectinemia resulting from insulin and APN resistance, ultimately leading to the APN paradox. Subsequently, downstream aging-associated chronic diseases are triggered or exacerbated, including cardiovascular and pulmonary disease, cancer, and neurodegeneration. Specifically, inflammation is likely mediated by damage-associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1), activating signaling pathways involving toll-like receptors (TLRs), receptor for glycosylation end-products (RAGE), AMP kinase (AMPK), Forkhead box transcription factor (FOXO1), and ultimately nuclear factor (NF)-κB to induce cytokine and chemokine release. Pyroptotic tissue injury through induction of Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome might also be relevant. Accordingly, suppressing the APN paradox by various strategies (dotted boxes and dotted arrows), such as reducing APN signaling, mitigating inflammatory signaling components, combined with anti-diabetic treatments, might prove effective in treating SARS-CoV-2-induced age-related chronic conditions, such as chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic vascular disease (CVD). Abbreviations: gAPN, globular adiponectin; HMW, high molecular weight.

in the pathogenesis of AD and other age-associated conditions, and which might also hold relevance for age-dependent SARS-CoV-2 effects [12]. APN is an adipocytokine that sensitizes insulin receptor signaling, stimulates mitochondrial biogenesis, and suppresses inflammation [12]. The pleiotropic effects of APN on multiple tissues are mediated through the membrane-bound adiponectin receptors, AdipoR1 and AdipoR2, which both require the adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain, and leucine zipper motif [11]. AdipoR1 sensitizes the insulin receptor by inducing calcium influx to activate Ca^{2+}/calmodulin-dependent kinase, AMP kinase (AMPK), and also nuclear factor (NF)-κB with mixed effects on inflammation, depending on the circulating APN isoform. Meanwhile, AdipoR2 binding stimulates PPARα signaling

to influence fatty acid oxidation [20]. Both AdipoR1 and -R2 promote cellular growth by promoting Ras-Raf-ERK1/2 signaling [11].

The APN paradox of chronic age-associated conditions indicates that, despite beneficial cardiometabolic APN effects in preclinical studies, paradoxically higher circulating APN concentrations have been associated with many chronic disorders and with higher mortality in patients with DM [21]. Beyond cardiovascular and metabolic involvement, the APN paradox might also have a critical role in the progression of other aging-related disease. For instance, a recent cohort study demonstrated that higher serum APN concentrations are associated with incident cancer and cancer-related deaths in T2DM, implying that the APN paradox contributes to cancer risk during aging

[22]. Notably, sporadic AD is linked to T2DM [12], and elevated serum APN concentrations in older women correlated with worse cognitive outcomes and increasing brain amyloid burden, as assessed by positron emission tomography [23], suggesting that the APN paradox is relevant to early-stage AD.

Consistent with beneficial APN activity, obesity is associated with hypoadiponectinemia related to APN gene variants and environmental factors, as observed in both insulin-resistant non-diabetic individuals [24] and various insulin-resistance animal models [25]. Conceivably, as insulin resistance progresses to chronic T2DM, APN resistance, and subsequent compensatory hyperadiponectinemia might emerge, which could involve dysfunctional AdipoR2 signaling, as shown in an insulin-resistant transgenic mouse model [26]. Also relevant to viral infection, elevated APN levels were found in aged lung tissue following influenza, not dissimilar to SARS-CoV-2 [27]. Accordingly, we propose that viral-induced pattern recognition triggers complex inflammatory signaling, transforming hypoadiponectinemia to pathological hyperadiponectinemia in the APN paradox (Fig. 2).

SARS-CoV-2 infection induces novel inflammatory patterns leading to the APN paradox

In response to SARS-CoV-2 infection, numerous cytokines and chemokines, including IL-1, IL-7, IL-10, granulocyte colony stimulating factor, monocyte chemoattractant protein-1, tumor necrosis factor (TNF)-α, among others, are released into the lungs and then systemically into plasma, generating a 'cytokine storm' [28]. With the aging-related compromise of T lymphocyte immunity, the bulk of the inflammatory response is coordinated through innate immunity [29]. Indeed, many viral infections, including coronaviruses, such as SARS-CoV-2, activate such innate immunity by triggering the release of DAMPs, which signal spontaneous unexpected cell death in the face of extreme environmental stress and overwhelming tissue damage via molecular pattern recognition receptors, such as toll-like receptors (TLR) (Fig. 2) [30]. Simultaneously, such patterns also trigger infiltrating neutrophils in multiple tissues to release 'neutrophil extracellular traps' (NETs) (Fig. 3), comprising decondensed chromatin and cytosolic protein networks, which limit viral spread [31]. Consistently, NETs are observed extensively throughout SARS-CoV-2 pulmonary and heart tissue (Fig. 3) and, despite neutrophil infiltration without expected NETs in liver and brain, NET formation might yet be delayed [32].

Prominent among DAMPs, the high mobility group box 1 (HMGB1), a highly conserved, 25-kDa nonhistone chromatin-binding protein, normally participating in gene regulation and chromatin repair, is instead released into the extracellular environment as an alarmin from dying or overly stressed cells in multiple tissues. DAMPs activate TLR2/4 and the receptor for glycosylation end-products (RAGE) on circulating neutrophils, which signal through NF-κB to promote inflammation [33]. When released extracellularly, HMGB1, through TLRs and RAGE, induces proinflammatory TNF-α, IL-1β, and IL-12, as well as CXC ligand 12 and CXC chemokine receptor type 4, a pattern mirroring the profile observed in patients with COVID-19 [28]. Moreover, many inflammatory disorders are associated with high levels of circulating HMGB1 [34] and, consistently, serum HMGB1 levels are elevated in SARS-CoV-2, correlating with worse disease outcome [35]. Of relevance, TLRs can activate NET formation, a reactive response triggered by HMGB1 in COVID-19 (Fig. 3) [36]. Ultimately, such DAMP-driven inflammation could promote both insulin and APN resistance, leading to the APN paradox. At present, APN levels have not been assessed in patients with COVID-19, but hyperadiponectinemia of the APN paradox is predicted to be operant.

Notably, ACE2 is sequestered during SARS-CoV-2 cell penetration, which simultaneously reduces available functional ACE2 activity. Therefore, because cardiac ACE2 is demonstrated to inhibit HMGB1, abnormally reduced circulating ACE2 levels under viral infection conditions might further stimulate HMGB1 activity, worsening the immune response and promoting T2DM [37]. Given that downstream HMGB1 signaling invokes two primary receptor pathways, namely TLR2/4-MyD88-IL-1 receptor-associated kinase (IRAK)-IκB kinase, and RAGE through both the CaMKK-β to AMPK and MAPK-Erk1/2 signaling branches, such activity might provide clues to the mechanistic nature of the APN paradox related to insulin resistance (Fig. 2). Ultimately, through pattern recognition activity in tissue damage, both pathways induce NF-κB nuclear translocation, the primary trigger of proinflammatory cytokine and chemokine release, leading to insulin resistance. Indeed, insulin resistance might be promoted by IκB kinase-induced NF-κB nuclear translocation and resultant proinflammatory cytokine production [38]. Moreover, NF-κB blockade in a high-fat diet mouse model was demonstrated to protect against insulin resistance [39]. Additionally, patients with newly diagnosed T2DM also demonstrated upregulation of TLR2, TLR4, MyD88, and NF-κB p65, with resultant elevated cytokine expression [40].

Yet how these might be ultimately linked to APN overexpression in chronic disease is not yet fully understood, but the possible activation of Forkhead box transcription factor (FOXO1) might have an important role (Fig. 2). In response to inflammatory stimuli in cultured macrophages from insulin-resistant *db/db* mice, FOXO1 was found to activate IL-1β expression in concert with NF-κB [41]. FOXO1 was also shown to mediate resveratrol-induced APN expression, linking insulin resistance and inflammation to APN overexpression. Curiously, AMPK also mediates APN expression by resveratrol, which might be a reactive attempt to beneficially overcome excessive insulin resistance, but instead abnormally amplifies APN overexpression in the context of the APN paradox [42,43]. Furthermore, insulin reduces Adipo1/2 expression in a FOXO1-dependent fashion, where insulin and APN resistance might be interconnected through FOXO1 [44]. Lastly, TNFα was shown in cardiac failure skeletal muscle to reduce AdipoR1 mRNA and AMPK, resulting in chronic hyperadiponectinemia [45].

In addition, binding of SARS-CoV-2 spike protein to ACE2 was shown to activate the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome, a multimeric complex comprising NLRP3, the apoptosis-associated speck-like protein, and pro-caspase-1, which induces cell death by pyroptosis [46]. As demonstrated in activated microglia, HMGB1, induced by N4-acetylcytidine, stimulates the priming and activation of the NLRP3 inflammasome [47], also mediated by NF-κB [48]. Importantly, APN reduces NLRP3 inflammasome activation by signal-
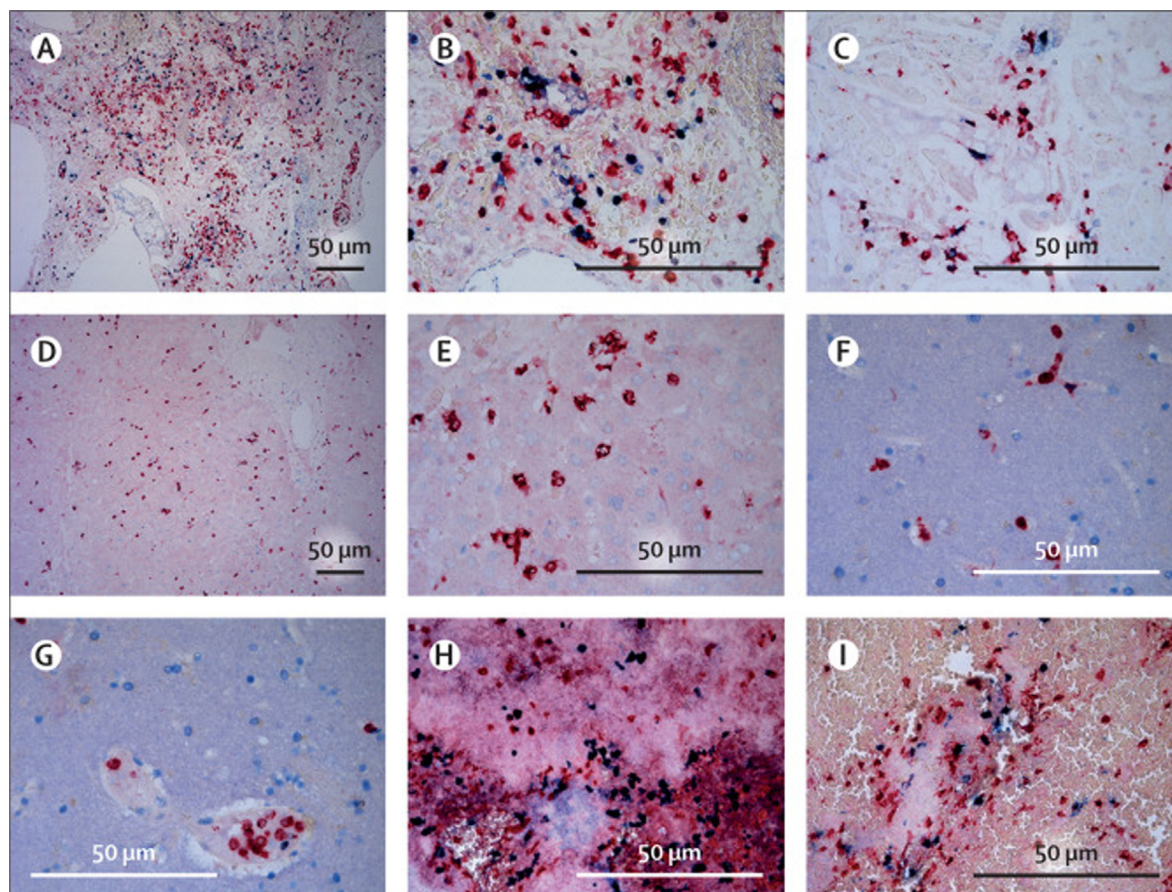
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FIGURE 3

Neutrophils and neutrophil extracellular trap (NET) formation suggest damage-associated molecular pattern (DAMP) and toll-like receptor (TLR) activation in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) tissues. The presence of activated pattern recognition signaling, such as DAMP-induced stimulation of TLR and receptor for glycosylation end-products (RAGE), in SARS-CoV-2-infected tissues is supported by neutrophilic infiltration and the emergence of NETs. For instance, tissue sections from patients deceased from SARS-CoV-2-related severe acute respiratory syndrome were stained for myeloperoxidase (red), as a neutrophilic granulocyte marker, and citrullinated histone 3 (blue), as an extracellular DNA trap marker, where extracellular colocalization suggests trap formation by neutrophils. **(a,b)** Lung tissue showed abundant neutrophils in lung vasculature and lung parenchyma with neutrophil extracellular traps following 8-day disease course. **(c)** Heart tissue showing neutrophils and NETs in and surrounding cardiac vessels and in the cardiac parenchyma with 17-day disease course. **(d,e)** Liver tissue showing neutrophils, but no NETs after a 27-day course. **(f,g)** Brain tissue showed neutrophils within the cerebral vasculature but no NETs after 8-day disease course. **(h,i)** Main bronchus thrombus showing abundant neutrophils and NETs after 8-day disease course. Reprinted, with permission, from [32].

ing through AMPK, which, in response, might paradoxically augment APN expression to cope with systemic pyroptotic cell damage, further contributing to the APN paradox in chronic disease [49]. Collectively, these mechanisms plausibly connect specialized inflammatory stimuli and processes to metabolic insulin resistance and the APN paradox in the context of SARS-CoV-2 and aging-related chronic disease.

SARS-CoV-2 inflammation and the APN paradox as a form of antagonistic pleiotropy

Similar to amyloidogenic proteins in chronic disease, inflammation during aging can be considered an antagonistic pleiotropy derived from the beneficial effects of inflammation during reproductive stages in early to mid-life, with detrimental chronic disease emerging during aging (Fig. 4) [50]. As such, dysregulated

neuroinflammation caused by APs generates increased proinflammatory and cytotoxic mediators, contributing to neurodegenerative diseases, such as AD and PD, in aging. By contrast, neuroinflammation might also be beneficial to clear debris from protein aggregates during earlier life. Similarly, the APN paradox in aging could be regarded as an antagonistic pleiotropic phenomenon derived from the beneficial effects of APN during earlier stages of life, including cellular protection and perhaps increased amyloidogenic evolvability [12].

Similarly, given that SARS-CoV-2 can increase both chronic inflammation and APN, we suggest that SARS-CoV-2 disease, in a sense, represents a form of antagonistic pleiotropy, in that immune response and increased APN are beneficial during younger ages to combat acute infection, whereas chronic disease might subsequently result during aging (Fig. 4). In this regard, in response to SARS-CoV-2 infection, the activation of DAMP path-
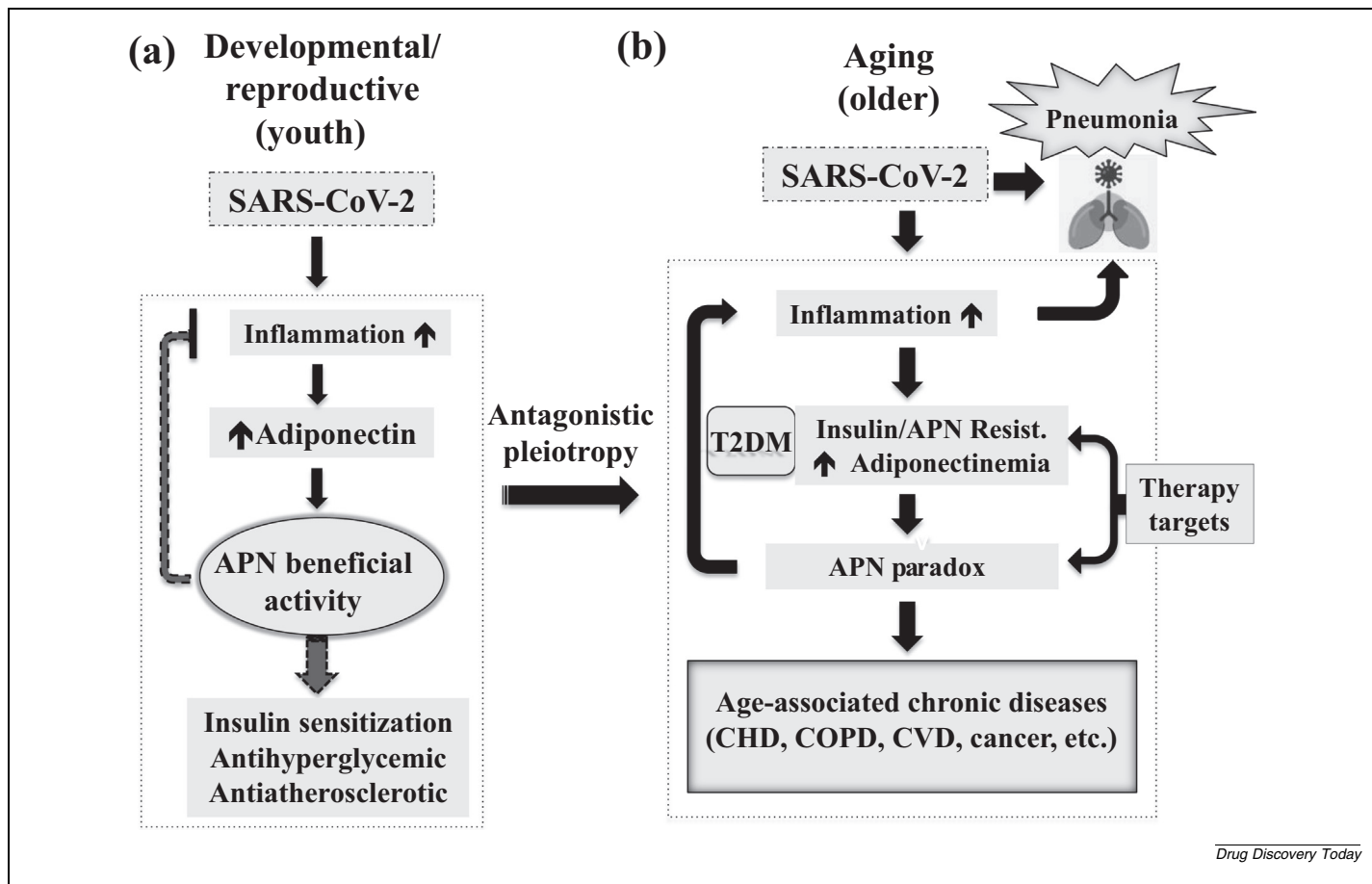
FIGURE 4

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as a form of antagonistic pleiotropy. In older patients **(b)**, SARS-CoV-2 cellular penetration causes the release of viral RNAs, which triggers robust immunological responses. Under conditions of upregulated inflammation, pneumonia and type 2 diabetes mellitus (T2DM) might be induced, associated with hyperadiponectinemia resulting from insulin and adiponectin (APN) resistance, leading to the APN paradox. As a result, aging-associated chronic diseases, such as coronary heart disease (CHD), chronic vascular disease (CVD), chronic respiratory disease (CRD), cancer, and Alzheimer's disease (AD), are triggered or exacerbated. Of importance, both inflammation and the APN paradox in aging might be regarded as an antagonistic pleiotropic phenomenon derived from the beneficial effects of these phenomena during younger developmental/reproductive stages of life **(a)**. Thus, given that the SARS-CoV-2 positively regulates both inflammation and APN activity, its effects might be beneficial in earlier developmental/reproductive life, becoming detrimental during aging.

ways, such as the HMGB1/DAMP-TLR-RAGE signaling axis, as well as the NLRP3 inflammasome, are beneficially protective against acute pulmonary and other tissue damage. Furthermore, this might represent hormesis because of the development of some immunity against future infection. Subsequently, however, a longer-term inflammatory state might cause insulin resistance and a compensatory APN paradox, eventually leading to the development of T2DM and chronic, age-associated conditions, such as cardiac disorders, neurodegenerative diseases, and cancers (Fig. 4). Interestingly, HMGB1, in terms of inflammation as an antagonistic pleiotropy, might have a role in the pathogenesis of multiple aging-associated conditions where inflammation is a key component. More specifically, aged rats showed elevated hippocampal HMGB1 levels in brain and cerebrospinal fluid associated with 'inflammatory priming' leading to hippocampal degeneration, which might hold significance not only for neurodegenerative conditions such as AD and PD, but also that potentially induced by COVID-19 [51]. Also, with relevance to aging, p53 in cultured senescent human and mouse cells and

in vivo was observed to redistribute acetylated HMGB1 to the extracellular space, activating downstream cytokine release through TLR-4 with senescence-related cellular growth arrest [52]. By contrast, consistent with antagonistic pleiotropy, HMGB1 is also implicated in the genesis of multiple cancers and in metastasis, but the exact mechanisms involved remain incompletely understood [53]. In this regard, consistent with the APN paradox, in patients with T2DM and insulin resistance, hyperadiponectinemia increases the risk of several cancers, which might also be predicted following SARS-CoV-2 infection [22].

Adiponectin and related molecules as novel therapeutic targets in SARS-CoV-2 disease

Given the COVID-19 pandemic, there has been a major concerted effort to develop vaccinations and treatments against SARS-CoV-2. Although the methodological basis of vaccination is well established, development remains challenging, and vaccination could harbor deleterious adverse effects and inevitably

lose efficacy following viral protein mutation altering viral antigenicity [54]. Also, various antiviral compounds are being extensively investigated in parallel [55], but their efficacy has yet to be established. Beyond such agents, novel strategies must be developed to address disease exacerbation and downstream chronic complications. Given the pathogenic importance of inflammatory signaling in SARS-CoV-2 and chronic disease, such as T2DM, an anti-inflammatory approach emerges as one obvious strategy (Fig. 2).

Provided that the APN paradox promotes T2DM and chronic disease in SARS-CoV-2, involving a complex interplay among reduced functional ACE2, innate DAMP-triggered inflammatory signaling, NLRP3 inflammasome activation, and others, these targets might be therapeutically important. For instance, suppressing APN using antisense oligonucleotides (ASO) targeting APN mRNA might be effective to downregulate APN expression (Fig. 2).

Yet, the pleiotropic actions of APN are not only complex, but also diverse, and several relevant factors should be considered. First, despite abnormally elevated APN levels associated with chronic aging disorders, evidence strongly indicates that APN has a normally beneficial role, improving insulin resistance and also reducing inflammation [56]. Naturally, APN exists in multiple forms, including the multimeric high-molecular-weight (HMW), medium-weight, low-molecular-weight trimeric, and proteolytically generated globular forms, which might all have different functional activities, with the HMW variant generally considered the predominant metabolically active beneficial form [57]. Although their precise action remains unclear, one study identified that, in endothelial cells, HMW APN more rapidly inhibited TNFα-induced NF-κB activation, whereas globular APN (gAPN) potently activated NF-κB and proinflammatory and cell adhesion genes [58]. This suggests that a differential strategy of boosting HMW APN activity, while blocking gAPN would be effective in blocking the inflammatory response in SARS-CoV-2 (Fig. 2).

Also attractive as a novel target in SARS-CoV-2, recent attention has been paid to the HMGB1 inhibitor, Box A, a functional domain of HMGB1 that competitively antagonizes receptor binding, and can effectively downregulate TLR and NF-κB signaling, possibly ameliorating the APN paradox and chronic disease development (Fig. 2) [59]. Box A was shown to specifically block inflammation [60] and protect against sepsis-related organ injury [61]. Although limited information exists on Box A and HMGB1 small-molecule inhibitor effects on T2DM and APN, this is a promising area of investigation, especially in the context of SARS-CoV-2 and chronic disease.

Alternatively, miRNAs, short noncoding RNAs that post-translationally regulate various proteins by RNAi, might also be of particular therapeutic value in SARS-CoV-2 and chronic disease (Fig. 2). Interestingly, miR-146b-5p in monocytes from obese individuals can modulate gAPN action by negatively regulating TLR signaling, specifically at the level of IRAK, upstream of NF-κB [62]. Of importance, miR-146b-5p appears to reduce inflammatory TNFα production, while enhancing APN-mediated insulin sensitization. Conversely, in the brain, miR-146a is abnormally upregulated by proinflammatory NF-κB through activation of the TLR/MyD88/IRAK-1/IRAK-2 pathway.

Dysregulation of this pathway by miR-146a might contribute to driving neuroinflammation and the underlying pathology in AD brain. In the case of SARS-CoV-2, antisense against miR-146a could be efficacious in decoupling COVID-19-associated inflammation from subsequent neurodegenerative conditions, such as AD and PD [63]. This strategy of specifically targeting various miRNAs regulating DAMP-triggered inflammation might also benefit insulin resistance in T2DM and correct possible APN resistance in the APN paradox.

Another possible therapeutic approach might be to improve APN signaling at the level of the APN receptor to potentially relieve APN resistance related to viral infection. As such, the polyphenol compound, resveratrol, has attracted attention as an anti-inflammatory agent for many chronic conditions and, with regard to diabetic complications in this context, might be beneficial. For instance, resveratrol was demonstrated to upregulate renal AdipoR1 and -R2 expression in diabetic *db/db* mice, improving complications, such as diabetic nephropathy [64]. Yet, resveratrol exacerbates hyperadiponectinemia [42], which raises an interesting novel possibility in which its therapeutic benefit might also be dependent on antagonistic pleiotropy. In other words, agents such as resveratrol might only be beneficial during early stages for disease prevention, but antagonistically exacerbate the APN paradox in later stages, having the opposite effect in exacerbating chronic disease. Thus, the actual benefit of resveratrol might be only as an early preventative therapy, in this case to maintain insulin sensitivity and limit the onset of the APN paradox in SARS-CoV-2 in younger individuals.

Finally, because T2DM is a central player in this scenario, combining anti-inflammatory and APN-modulating therapy with anti-DM therapy [e.g., metformin and dipeptidyl peptidase-4 (DPP-4) inhibitors] might synergistically enhance the therapeutic effect against this devastating syndrome (Fig. 2). The future significance of combined therapy strategy in the treatment of AD and neurodegeneration has been highlighted previously [65]. Interestingly, regarding the antidiabetic action of metformin, it was recently shown to also bind to, and inhibit, the proinflammatory activity of HMGB1 [66]. Furthermore, because inflammation and the APN paradox might also be involved in SARS-CoV-2-associated long-term chronic diseases during aging, the same therapeutic strategy could be applied and might prove an effective and promising approach for treating this complex infectious disorder.

Concluding remarks

The occurrence of COVID-19 unexpectedly provides unique insights into the pathogenesis of T2DM and other age-associated conditions. Collectively, we propose that the differential effects of SARS-CoV-2 related to aging are attributed to an antagonistic pleiotropy related to SARS-CoV-2-induced HMGB1 proinflammatory signalome, leading to T2DM and the APN paradox, which is beneficial at younger ages, but detrimental during aging (Fig. 4). SARS-CoV-2 might induce DAMPs to activate TLR and RAGE, leading to chronic inflammatory state, insulin and APN resistance, and finally multiple chronic conditions. As discussed, novel therapeutic targets emerging from these APN paradox-related inflammatory mechanisms could be combined

into 'treatment cocktails' to prevent complications from SARS-CoV-2. The current SARS-CoV-2 infection is highly pathogenic and life threatening, and the differential effects and lethality of the virus across the age spectrum are striking. Possibly, early in evolution, such viruses were more benign, conferring immunity to populations. Progressively, however, with extended human longevity, antagonistic pleiotropy has allowed more virulent pandemics to emerge through evolution. Despite the pathophysiological importance of the APN paradox in chronic conditions, reports describing APN alterations or its role in SARS-CoV-2 pathogenesis are lacking. Further studies are clearly warranted to explore these important mechanisms and their long-term impacts during aging, especially with regard to therapeutic implications.

Declaration of interests

The first author, Dr. Gilbert Ho, has previously served on an Advisory Board for Biogen, Inc. The remaining authors declare no known competing financial interests that might influence this paper.

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