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MINI REVIEW ARTICLE

Role of melatonin in the treatment of COVID-19; as an adjuvant through cluster differentiation 147 (CD147)

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Abstract

COVID-19 caused by the SARS-CoV-2 outbreak quickly has turned into a pandemic. However, no specific antiviral agent is yet available. In this communication, we aimed to evaluate the significance of CD147 protein and the potential protective effect of melatonin that is mediated by this protein in COVID-19. CD147 is a glycoprotein that is responsible for the cytokine storm in the lungs through the mediation of viral invasion. Melatonin use previously was shown to reduce cardiac damage by blocking the CD147 activity. Hence, melatonin, a safe drug, may prevent severe symptoms, reduce symptom severity and the adverse effects of the other antiviral drugs in COVID-19 patients. In conclusion, the use of melatonin, which is reduced in the elderly and immune-compromised patients, should be considered as an adjuvant through its CD147 suppressor and immunomodulatory effect.

Keywords SARS-CoV-2 · COVID-19 · CD147 · Melatonin · Immunomodulator

Background

Coronaviruses (CoVs) are RNA viruses, which affect the respiratory, gastrointestinal and central nervous system, and may infect both humans and animals [1, 2]. In recent years, the coronavirus subtypes, SARS and MERS, through their contagiousness have led to the deaths of thousands of people. The current epidemic, namely, COVID-19 discovered in Wuhan, China, has become a global pandemic in a relatively short period. Despite the use of antiviral, anti-malarial, corticosteroid treatments and mechanical respiratory support, no specific treatment has been found for COVID-19, and mortality rates remain high, particularly in the elderly section of society [3].

CD147 and coronavirus

CoVs have been reported as non-segmented RNA viruses. CoVs leads to enzootic infections, particularly in birds and mammals, and are highly fatal in humans [4]. These viruses carry four known structural proteins; envelope (E), nucleocapsid (N), membrane (M) and spike (S) proteins. [5]. The S protein is the critical constituent during the cellular invasion of SARS-CoV-2 [6]. Angiotensin-converting enzyme 2 is the host cellular receptor (ACE2) for SARS-CoV-2 and expressed in different tissues [7–10]. The interaction of S protein and ACE2 contributes to SARS-CoV-2 invasion of host cells [11]. Direct interactions have been demonstrated between SARS-CoV-2 and CD147 [2, 12], which is a type I transmembrane protein from the immune-globulin superfamily that plays a role in tumour development, plasmodium invasion and viral infection [13]. In lung diseases, ACE2 and CD147 increase the vascular permeability and pulmonary edema, activate the

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renin-angiotensin-aldosterone system (RAAS) and contribute to the pathogenesis of severe lung damage [13]. Studies confirm that HEK293 expressing CD147 bind with high affinity to SARS-CoV-2, thus demonstrating the importance of CD147 in the host cells [14].

CD147 (Cluster of differentiation 147) is synthesized in various cell types and widely distributed to different tissues including lungs, brain, liver, spleen, intestines and the kidneys [15]. CD147 binds to certain receptors and ligands, including S100A9, mono-carboxylate carrier (MCT)-1 and MCT-4, CD98, CD44, CD43, glycoprotein VI (GPVI), E-selectin, apolipoprotein D (ApoD), CyP60, Annexin-2 and NOD2, Caveolin-1, syndecan-1 and also integrin α 3β1 and α 6β1 [16–19]. Targeting CD147 have been shown to reduce inflammation and severity of the disease by affecting these ligands in asthmatic pulmonary inflammation, multiple sclerosis and myocardial ischemia/reperfusion injury [20–22]. Previous studies have noted that the expression of CD147 increases matrix metalloproteinase (MMP) activity, which is induced by MAPKs-bound Angiotensin II [23–25]. Additionally, CD147 plays a role in inflammation that develops through pro-inflammatory cytokines, including interleukin-6 (IL-6), interferon-gamma (IFN-γ), tumor-necrosis factor-α (TNF-α), and monocyte chemo-attractant protein-1 (MCP-1) [26]. In most recent studies it has been suggested that SARS-CoV-2 infection stimulates the increased expression in these cytokines, which is referred to as a cytokine storm, and it is critical in disease progression [27, 28]. The cytokine storm, also referred to as hypercytokinemia, is an uncontrolled cytokine release that has been seen in some infectious and noninfectious diseases, prompting a hyper-inflammatory condition in the host [29].

The emergence and rapid spread of SARS-CoV-2 has highlighted the importance of reorganizing a global health system. Abnormal chest tomography findings are seen together with cough, fever and fatigue in COVID-19 patients [30]. Middle-aged and elderly patients who have concurrent illness have increased susceptibility to respiratory failure, with a poorer prognosis [31]. It has been stated that CD147 is involved in COVID-19 symptoms by being extremely expressed in tumor, inflammatory and infected cells [32, 33]. Thus, a drug that will target CD147 could prevent the virus from invading host cells. Hence, inhibiting the viral replication and limiting the overexpression is vitally important in COVID-19 treatment. In relation to this, CD147 antibody, Meplazumab, has been tried, and despite having achieved positive results, its administration via the parenteral route, non-availability in the market and having insufficient knowledge regarding its interaction with other antiviral drugs, have limited its widespread use [2].

The effect of melatonin on immune and antioxidant systems

The pineal gland is a neurochemical converter perceiving environmental information that can be integrated with the secretion of various biomolecules such as 5-methoxytryptophol, N-acetylserotonin, N-acetyltryptamine that work best with melatonin (N-acetyl-5-Methoxytryptamine). These secreted biomolecules have a function in the synchronization of the circadian and seasonal timing of various behavioural and physiological processes [34]. The melatonin rhythm is a powerful and vital message from suprachiasmatic nucleus signalling in order to maintain the circadian rhythm of the organism [35].

Melatonin is also a strong hydroxyl radical scavenger that protects cells from oxidative damage [36]. Besides, melatonin scavenges peroxyl radicals during lipid peroxidation [37, 38] and enhance the activity of antioxidant enzymes such as glutathione [39]. In light of the examples mentioned above, melatonin shows to be a crucial compound of the antioxidative system [40–42]. Indole initiates an increase in the immune response bound to T-helper cells [43]. Various immune functions, including the anti-tumorigenic defence and the cytotoxicity of natural killers, are seen to be modulated by melatonin [44]. Besides, exogenous melatonin administration has been shown to increase antibody production [45]. Thus, melatonin has immunomodulatory effects under physiological and pathophysiological conditions [46]. Notably, in cases where the immune system is suppressed, it shows an immunostimulant effect, and in cases of inflammation, it exhibits an immunosuppressive effect. It achieves its immunostimulant effect by increasing T cell activation, lymphocyte growth and humoral response. It shows its immunosuppressive effect by decreasing active iNOS and nNOS activities during inflammation, inhibiting COX-2, and preventing Toll-Like receptor-4 activation [47, 48]. In addition to its anti-inflammatory and pro-inflammatory effects, melatonin, unlike other modulators, has other very beneficial properties, such as antidepressant, anxiolytic, neuroprotective and antihypertensive effects [49].

The antiviral effect of melatonin through CD147

Viral infections are usually related to immunity-inflammatory damage, which includes a significantly increased oxidative stress level and adverse effects on multiple organs [50]. Melatonin does not have viricidal properties; however, it has indirect antiviral effects through

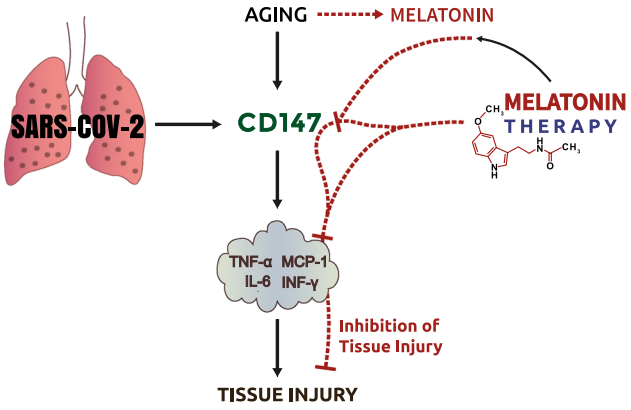

Fig. 1 SARS-CoV-2 causes tissue damage by increasing TNF-α, MCP-1, Il-6 and INF-γ levels through CD147. Due to both the excess of CD147 levels and the decrease in melatonin levels in elder people, tissue damage is more severe with cytokine storm. Melatonin therapy may have the ability to inhibit tissue damage by causing a decrease in CD 147 levels and thus cytokine levels

anti-inflammatory, antioxidant and immunity-enhancing effects [51]. Previously, melatonin was been shown to suppress the features of viral infections [50, 52]. Melatonin use was seen to reduce virus-mediated stroke and death, and the potency of the virus by modulating the IL-2 and IFN-γ concentrations during Venezuela equine encephalomyelitis (VEE) virus infection in mice [53]. Melatonin has also been reported to reduce acute lung damage in respiratory syncytial virus models, through the inhibition of oxidative damage and pro-inflammatory cytokine release. Current studies have reported that SARS-CoV-2 invades the host cells through a CD147 S protein [2]. To date, no studies have reported the influence of melatonin on CD147 S protein in COVID-19 patients. However, melatonin was demonstrated to possess a protective effect through the inhibition of CD147 signalling pathway via its antioxidant effects in AngII-induced cardiac hypertrophy models [54] (Fig. 1).

The processes that prevent the free radical formation as a result of exposure to stress, viral infections or toxic agents lead to a decrease the melatonin levels in older age and under suppressed immune system conditions [36, 55]. This could be part of the explanation for the poor prognosis and respiratory system failure seen in many middle-aged and elderly patients. Despite the absence of studies investigating melatonin use in COVID-19 patients, melatonin administration has yielded promising outcomes through suppressing the circulating cytokine levels in other diseases and in cases with elevated inflammation levels [51, 56, 57]. Melatonin was shown to stimulate a significant decline in serum MMP, TNF-α, IFN-γ, IL-6, MCP-1 and C-reactive protein (CRP) levels in experimental and clinical studies [58, 59]. These mediators are known to have a critical role in CD147-mediated inflammation pathway. Melatonin has also been reported to have an anti-diabetic effect. Evidence from experimental studies show that melatonin induces insulin growth factor synthesis and promotes insulin receptor tyrosine phosphorylation. Disruption of the internal circadian system causes glucose intolerance and insulin resistance, and this can be restored with melatonin administration [60–62]. Further, melatonin administration has been proven to reduced cellular apoptosis and promote antioxidants in diabetes [63]. Thus, it is suggested that CD147 may play a role in the emergence of these effects of melatonin in diabetic patients with COVID-19.

The safety of melatonin administration is of vital importance when its use is suggested for treating COVID-19. Previously, short-term administration of melatonin has shown to be secure even when used at relatively high doses [64, 65]. Additionally, the use of melatonin, together with other drugs in COVID-19 treatment, was shown to increase their potency and reduce their side effect potential [66].

Conclusion

One could speculate that melatonin may be a candidate drug to provide relief from the clinical symptoms of COVID-19 even though its antioxidant effect cannot eliminate or stop the viral replication or transcription. Together with ACE2, CD147 has a vital role in the activation pathway of COVID-19. It could be suggested that the possible reason for the greater impact of COVID-19 on the elderly part of populations is both related to reduced melatonin levels and increased CD147 levels. Thus, in light of current literature and the above discussion, we suggest that the use of melatonin in combination with antiviral agents could yield more effective outcomes through its CD147 suppressor effect, immune-modulatory effect and reducing the potential negative side effects of antiviral agents.

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