Review

ER stress and autophagy induced by SARS-CoV-2: The targets for melatonin treatment

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ABSTRACT

Coronavirus disease 19 (COVID-19) is a viral disease caused by the new coronavirus SARS-CoV-2. Like other coronaviral infections, SARS-CoV-2 causes oxidative and ER stress triggering cellular response pathways, mainly PERK and IRE1 branches of the UPR. This excessive oxidative stress and the increasing of unfolded and misfolded proteins induce autophagy. Once this process is triggered, the blockage of the fusion of autophagosomes and lysosomes induced by virus leads to an incomplete autophagy. Double-membraned vesicles, which create a membranous support for viral RNA replication complexes, are formed. Melatonin is a pleiotropic molecule, which reduces oxidative and ER stress, regulates immune system, and modulates autophagy pathway. Thus, melatonin reinforces UPR and unlocks autophagy blockage, allowing autophagosomes to bind to lysosomes, completing the process of autophagy and decreasing viral replication capacity. Based on these activities of melatonin the recommendation of melatonin for patients with COVID-19 should be seriously considered, especially in elderlies and patients with different comorbidities, which are the highest risk population for serious cases.

Key words: Sars-CoV2, ER-stress, autophagy, melatonin, unfolded protein response (UPR), frailty, aging, viral infection.

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1. INTRODUCTION

A new member of the human coronavirus (HCoV), SARS-CoV-2, which causes coronavirus disease 19 (COVID-19), has become a threat to global health. So, it is most necessary ever that researchers contribute with their knowledge to develop a treatment to block or minimize the damages caused by the virus. This must lead them to be pragmatic and imaginative, without thereby moving away from scientific evidences.

In this sense, the methoxyindoleamine, melatonin (N-acetyl-5-methoxytryptamine), which is the hormone of the pineal gland of vertebrates and whose first described functions were as a

skin lightening agent in amphibians and as a regulator of circadian rhythms in mammals, has been also involved in antioxidant, antiexcitatory actions, vasomotor control, adrenal function, immunomodulation including antiinflammatory properties, and energy metabolism (1-3) Therefore, several clinical trials have shown that melatonin could be efficient in preventing cell damage in metabolic and neurodegenerative diseases, cancer, inflammation, and aging (4-7). These beneficial effects of melatonin can be explained by its properties as a potent antioxidant, a regulator of programmed cell death (PCD) mechanisms, such as apoptosis and autophagy, and a positive regulator of immune functions.

Viral infections, which usually come up with oxidative stress, inflammatory injury and triggering of PCD mechanisms, seems to be fully counteracted by the beneficial effects of melatonin. Nevertheless, there are a quite few of articles about the roles of this indolamine on animal viral diseases (8- 11). Surprisingly, a relatively large number of studies about melatonin on virus can also be found in plants (12-14).

The need to find an effective treatment for COVID-19 patients is urgent. Thus, the aim of this review is to explain the potential mechanisms of melatonin, which could justify its use as a treatment or adjuvant molecule for SARS-CoV-2 infection. Two approaches have been studied for melatonin's potential on COVID-19. Firstly, the role of melatonin as a regulator of immune system depends on the status of the host, especially frailty elderlies. Secondly, at the cellular level, melatonin modifies the endoplasmic reticulum (ER) stress and autophagy caused by the guest, the SARS-CoV-2.

2. THE HOST: IMPORTANCE OF THE RISK GROUPS

COVID-19 is an infectious disease caused by novel coronavirus SARS-CoV-2. it originated in the Wuhan, a city of China, in December 2019, then, the disease spread globally resulting in a pandemic, which has caused more than 3 million cases and more than 250 thousand deaths in almost all countries and territories of the world until now.

Most cases show mild symptoms, such as fever, cough, fatigue, breath shortness, and anosmia. Nevertheless, some cases progress to viral pneumonia, multiorgan failure, and eventually death (15).

Several studies have reported that the risk for severity and death rate from COVID-19 are higher in older age population. A recent study in the United States has shown that no ICU admissions or deaths were reported among persons aged ≤19 years, while 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of death associated with COVID-19 were among individuals aged ≥65 years and the highest percentage of severe outcomes was among persons aged ≥85 years (MMWR Morb Mortal Wkly Rep 2020). Another recent report has addressed the role of comorbidities in the outcome of infected patients. The results indicated that 94% of the patients had a chronic health problem, and 88 % of them had two or more health issues. The three most prevalent conditions were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%) (16).

Therefore, the elderlies, especially those with comorbidities, are the victims of highest risk for serious symptoms and death. Although elderly people are a very heterogeneous group including healthy individuals and those with age-associated pathologies, it is well known that even healthy elderlies show a clear differential response to conditions based on their frailty. The concept of frailty is defined as the condition that a person has a poor capacity to respond to stress. Based on this, a frail elderly has a higher predisposition to suffer both age-related disorders and non-age-dependent diseases (17). Among these latter, it has been reported that frailty is a powerful predictor of the vulnerability to HIV infection (18- 20) and the lack of an adequate response to retroviral therapy (21). Further studies are necessary to use the frailty as a predictor of the outcome of other viral diseases.

Studies carried out in our laboratory have showed a significant increase in Interleukin 6 (IL-6) levels in frail elderlies when they have faced an adverse event, which is not observed in non-fragile individuals (22-24). Thus, IL-6 increase has been served as a clear marker of dependency in the elderly. Other cohort studies have found that high levels of TNF-α are also markers of frailty (25).

The role of these proinflammatory cytokines in the serious cases of COVID-19 has been clearly established. In fact, an overproduction of early response proinflammatory cytokines (tumor necrosis factor (TNF), IL-6, and IL-1β, called as cytokine storm, causes an increased risk of vascular hyperpermeability, multiorgan failure, and eventually death (15). The need to find effective treatments for this SARS-CoV-2 infected frailty patients, especially those with comorbidities, is urgent. Since the reasons why this group of patients is particularly vulnerable are not clear, to consider all the possibilities is necessary. In this sense, it is worth to note the clearly established role of melatonin as regulator of immune system. Such role has been reported in several animal models where a treatment with this molecule helps to reduce age-associated functional deficits in many organs, including those of the immune system (26-28). Furthermore, several studies have reported that melatonin supplementation acts as anti-inflammatory factor attenuating the function of toll-like receptors (TLRs) and toll-like receptor-associated activator of interferon (TRIF) (29, 30), significantly decreased TNF-α, IL-6 and IL-1β levels in different proinflammatory disorders and diseases (31-34), the overexpressed cytokines in serious cases of COVID-19 (15). Furthermore, melatonin has been highly efficient in critically ill and especially vulnerable people (35, 36), such as is suggested by extensive bibliography about the beneficial effects of melatonin against multiple diseases (37, 38). All these facts support administration of melatonin in patients with COVID-19, specially in elderlies, whose endogenous production of melatonin is drastically reduced to practically zero levels from the age of 70 (28).

3. THE GUEST: THE NEED FOR REPLICATION

Based on sequence comparisons of entire viral genomes, the family *Coronaviridae* are a group of viruses infecting a wide variety of hosts including avian, swine and humans. They are categorized into four main genera, *Alpha-*, *Beta-*, *Gamma-* and *Deltacoronaviruses* (39). HCoVs are identified to be either in the *Alpha-* or *Alpha-Betacoronavirus* genera, including *Alphacoronaviruses* HCoV-229E and HCoV-NL63, and *Betacoronaviruses*, HCoV-HKU1 SARS-CoV, MERS-CoV and HCoV-OC43.

SARS-CoV-2, which is a new member of the genus *Betacoronavirus*, is an enveloped, spherical and about 120 nm in diameter virus. Its genome is a monopartite, linear ssRNA(+) of 27-32kb in size (the largest of all RNA virus genomes), which encodes for two ORFs (ORF1a and the longest ORF1ab containing ORF1a in its 5´ region). ORFs 2-10 encodes four structural and six auxiliary/accessory proteins, which are expressed as subgenomic RNAs. Structural proteins are spike (S), envelope (E) and membrane (M) proteins, which are involved in the formation of the coat, as well as the nucleocapsid (N) protein, which is involved in the packaging of the RNA. Other auxiliary/accessory proteins are responsible for several important functions in genome maintenance and virus replication (40).

Similar to other CoVs, the life cycle of SARS-CoV-2 begins with the binding of S protein to cellular receptor angiotensin-converting enzyme 2 (ACE2). Following entry into the host cell through an endosomal pathway, the viral RNA is unveiled in the cytoplasm. The translation of ORFs 1a and 1ab produce polypeptides pp1a and pp1ab, which are processed by two virally encoded proteases (3CLpro and PLpro) to yield 16 non-structural proteins that form the RNA replicase-transcriptase complex. This complex drives the production of full-length (−) RNA copies of the genome, which are used as templates for full-length (+) RNA genomes as well as

a subset of 10 sub-genomic (sg)RNAs through discontinuous transcription. These sgRNAs encodes both structural and accessory proteins. Viral nucleocapsids are assembled from genomic RNA and N protein in the cytoplasm. S, E and M proteins are translated by ribosomes that are bound to the endoplasmic reticulum (ER), presented on its surface and moved along the secretory pathway into the endoplasmic reticulum–Golgi intermediate compartment (ERGIC). There, viral genomes encapsidated by N protein bud into membranes of the ERGIC containing S, E and M structural proteins, forming mature virions. Virions are then released from the infected cell through exocytosis (41).

4. ROUGH ENDOPLASMIC RETICULUM: FACTORY OF VIRAL PROTEINS

Several stressors, such as aging (42, 43), frailty (24), chemotherapy (44), oxidative injury (45) and bacterial infections (46), can affect ER homeostasis and causes ER-stress. Among these agents, stand up viral infections, because viruses need ER machinery for producing their own proteins which overwhelms ER capacity (47). Such overload condition alters ER-associated proteostasis resulting the accumulated misfolded or unfolded proteins in the ER lumen and inducing a significant increase in oxidative stress (48). This ER-stress activates a signaling cascade, known as unfolded protein response (UPR) (47). This response is initiated by three ER transmembrane sensors, each of which triggers the activation of a different route to achieve a global action of cellular recovery. These sensors are pancreatic ER kinase (PKR)-like ER kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) (43). So, PERK starts a route that involves two main substrates: eIF2α and ATF4, which regulate antioxidant response and induces global arrest of protein synthesis among other functions (47). IRE-1 develops several functions as redox homeostasis, antioxidant response and facilitates degradation of unfolded and misfolded proteins by the proteasome via splicing of X-Box binding protein 1 (XBP1) mRNA (49). Finally, ATF6 branch is activated by cleavage of ATF6 obtaining a transcription factor implicated in expansion of the ER to better cope with the proteotoxic stress (50).

As mentioned above, translation of some SARS-CoV-2 proteins is necessarily via ER. The overload of this organelle causes oxidative and ER stress triggering UPR. This response can be considered common in viral infections and it is widely documented in several viral families (51-54). The subsequent viral induced UPR must be carefully interpreted , since the literature shows conflicting data depending on the virus, which could indicate that the virus may try to block or facilitate the response to ER stress (47, 55). For example, in Ebola infection, UPR seems to be considered as an antiviral mechanism (56) while in lytic infections, such as that caused by adenovirus, the triggering of UPR favors viral replication (57). Although no data about regulation of UPR by SARS-CoV-2 are available up to date, PKR and eIF2α phosphorylation was detected in SARS-CoV-infected cells. Nevertheless, PKR knockdown by using antisense peptide-conjugated phosphorodiamidate morpholino oligomers did not affect SARS-CoV protein replication and virus production. Therefore, a strategy to counteract against the antiviral effects of PKR enabling viral mRNA translation to proceed regardless of whether eIF2α phosphorylation is used. PERK was also found to be activated during SARS-CoV infection, possibly through its S and 3a proteins (58). The IRE-1 branch is also affected by SARS-CoV. Thus, a significant XBP1 splicing and higher rate of apoptosis was observed in infected cells by recombinant SARS-CoV containing deleted E protein (59). In the case of ATF6, no SARS-CoV induction of these branch has been reported.

Several reports have shown the role of melatonin in ER protection by reduction of both oxidative and ER stress produced by several medical conditions including obesity, cardiopathy or Alzheimer (60- 63), and the consequent reduction of UPR (64, 65). Furthermore, melatonin has also been implicated in activation of UPR and favoring cellular survival (66), suggesting

that melatonin could have a beneficial role in regulation of the UPR, which is triggered by viral induced ER stress. The fact that melatonin reduced both oxidative and ER stress produced in cardiomyocytes of coxsackie virus B3-infected mice (67), as well as activated UPR in hepatocytes of rabbits infected by rabbit hemorrhagic disease virus (68), support the use of melatonin in viral infections such as those caused by SARS-CoV-2.

It is worth to note that UPR is effective only in conditions of low-to medium ER stress. An excessive high stress overtakes UPR capacity and, then, the survival mechanisms, such as autophagy, has to be triggered. This is the last step before the activation of pro-death signaling (47, 69) and induction of apoptosis.

5. ENDOPLASMIC RETICULUM STRESS AND LUNG

The lungs deserve special attention due to the essential role that they play in the fight against SARS-CoV 2 since they become one of the targets for virus attacking and the hosting organs of this virus during infection. In lungs. Type II alveolar cells, whose transformation into Type I or Type II pneumocytes depends on organ requirements, are essential part of local immune system and they are also a common destination for viral invasion (70, 71). They face a highly increase in oxidative stress after infection and this favors the development of lung fibrosis and a significant reduction of pulmonary capacity (72-75). The pathway from oxidative stress to UPR by increased ER stress has been extensively discussed above and this process has also been addressed in the lungs (76). ER stress is favored not only by such oxidative stress but also by viral infection, which, in turn, increases oxidative stress developing a vicious circle hardly to avoid (77). The reduction of oxidative and ER stress by treatment with antioxidants is a successful therapy for lung damage (78, 79) and viral infections (80). Among these antioxidants, the role of melatonin on pulmonary ER has been well documented (81, 82).

Angiotensin-converting enzyme 2 (ACE2), which is the main receptor for several human coronaviruses including NL63, SARS-CoV and SARS-CoV2, is expressed in Type II alveolar cells. Thus, these pneumocytes become the target for SARS-CoV-2 infection (83, 84). After pneumocytes have been invaded, virus spread at the pulmonary level followed by those previously mentioned steps as a pattern of viral invasion: oxidative stress (85), ER stress and UPR (77). Therefore, treatment with several antioxidants, including melatonin, to reduce these events on the lungs have been repeatedly proposed (86-88).

6. AUTOPHAGY: DUAL ROLE IN VIRAL INFECTIONS

Unfolded and misfolded proteins from ER are usually degraded by ubiquitin-proteasome system (89, 90). When ER stress is triggered, cytosolic proteasomes are overwhelmed, and proteins are accumulated. The protein aggregates must be degraded via macroautophagy, which is the only survival mechanism that the cell can activate before triggering apoptosis (47, 91).

Macroautophagy (hereafter referred to as autophagy) is an evolutionarily conserved lysosomal degradation pathway in all eukaryotic cells, which is critical for maintaining cell homeostasis. Autophagy is upregulated in response to extra- or intracellular stress and signals, being present in several physiological and pathological situations from cell development (92) to cancer (93) and pathogen infection (94). An altered autophagy is observed during aging (95), being an impairment hallmark of frailty (24).

ER stress and autophagy tightly interplay each other usually via UPR system (96), the PERK and IRE1 branches are the main autophagy signaling pathways (97, 98). Furthermore, ER-stress triggers autophagy by downregulation of mammalian target of rapamicine (mTOR), one of main regulators of mammalian metabolism (99).

The autophagy in viral infection plays dual roles (100). On the one hand, autophagy can reduce virus induced ER stress and thus achieve cell survival by cleaning damaged ER and viruses in autolysosomes, a process called virophagy (101). Example of this mechanism is the autophagic degradation of Sindbis virus by selective degradation of the viral capsid (102). On the other hand, the virus can hijack the process of autophagy and use it to accelerate different stages of the viral life cycle (103-106). Thus, induction of autophagy via UPR by expression of the replicase protein NS4A of flaviviruses, such as dengue virus and Modoc virus, protects cells against death and enhances virus replication (107). Some viruses can increase their replication capacity by inhibition of the fusion of the autophagosome to the lysosome. This leads to an incomplete autophagy creating double-membraned vesicles (DMV), which provide membranous supports for viral RNA replication complexes (108). A similar mechanism has been described for several coronaviruses. Thus, an incomplete autophagy has been induced in HEK293T cells transfected with the membrane-associated papain-like protease PLP2 (PLP2-TM) of MERS-CoV and SARS-CoV. Furthermore, PLP2-TM interacts with the key autophagy regulators, LC3 and Beclin1, and promotes Beclin1 interaction with STING, the key regulator for antiviral IFN signaling (109). A recent study has reported that ubiquitination of BECN1 by S-phase kinase-associated protein 2 (SKP2) resulted in reduction of BECN1 levels and blocks the fusion of autophagosomes and lysosomes in MERS-CoV infected VeroB4 cells (110). The co-localization of viral proteins and LC3, a protein marker for autophagic vacuoles, at DMVs has been reported in SARS-CoV infected Vero cells (111). Nevertheless, replication of a coronavirus, mouse hepatitis virus (MHV), was impaired in autophagy knockout, APG5-/-, embryonic stem cell lines, suggesting that autophagy is required for formation of double membrane-bound MHV replication complexes (112). Although some authors consider that induction of autophagy and following blockage are contradictory (113), others suggest that this can be a strategy of certain viruses (11, 111, 112).

Autophagy has also been involved in regulation of innate and adaptive immunity systems. Thus, secretion of inflammatory mediators, such as type I interferon (IFN) and cytokines, such as IL-1β and IL-18 to fight microbial infection is promoted by innate immune system, which is stimulated by pattern recognition receptors (PRRs) (114). An aberrant activation can cause excessive inflammation and provoke a severe tissue damage (115). The regulation of the secretion of inflammatory cytokines by autophagy is essential for the correct functioning of the innate immune system (114, 116). On the other hand, processed peptides from pathogen proteins are presented on major histocompatibility complex (MHC) class I and II molecules and recognized by adaptive immune system CD8+ and CD4+ T cells, respectively. The crucial role of autophagy in the presentation of MHC class I and II molecules has been widely reported (116).

Several studies have reported that melatonin can induce or inhibit autophagy in different biological processes (11). Regarding to viral infections, it has been described that rabbit hemorrhagic disease virus (RHDV) induce autophagy in rabbit hepatocytes, which is inhibited by melatonin administration (117). The dual role of melatonin as autophagy inductor or inhibitor is based on its antioxidant activity. Thus, an incomplete autophagy produces an accumulation of autophagosomes increasing the oxidative stress, whose reduction by melatonin action leads to complete autophagy (118). Thus, the melatonin can be classified as an autophagy regulator.

Several treatments for COVID-19 are being developed, including those based on the blockage of autophagy flux directly by using rapamycin or mTOR activators (119) or indirectly by using chlorpromazine, which produces an incomplete autophagy and inhibition of clathrin-mediated endocytosis (113). The inhibition of SKP2 protein has also been considered as a target to inhibit viral replication, such as has been suggested by Gassen and coworkers (110). Given that the mechanism of melatonin is the oxidative stress reduction, the use of this molecule to

increase the antioxidant capacity as coadjutant to antiviral treatments has ben also suggested (77, 120-122) alone or combined with vitamin D since both share many control and modulation mechanisms on immune system (123) or with other potential drug combinations (124). Melatonin can also act against COVID 19 as mitochondrial metabolic modulator in immune cells (125, 126). Further studies are necessary to find a useful treatment to fight against SARS-CoV-2.

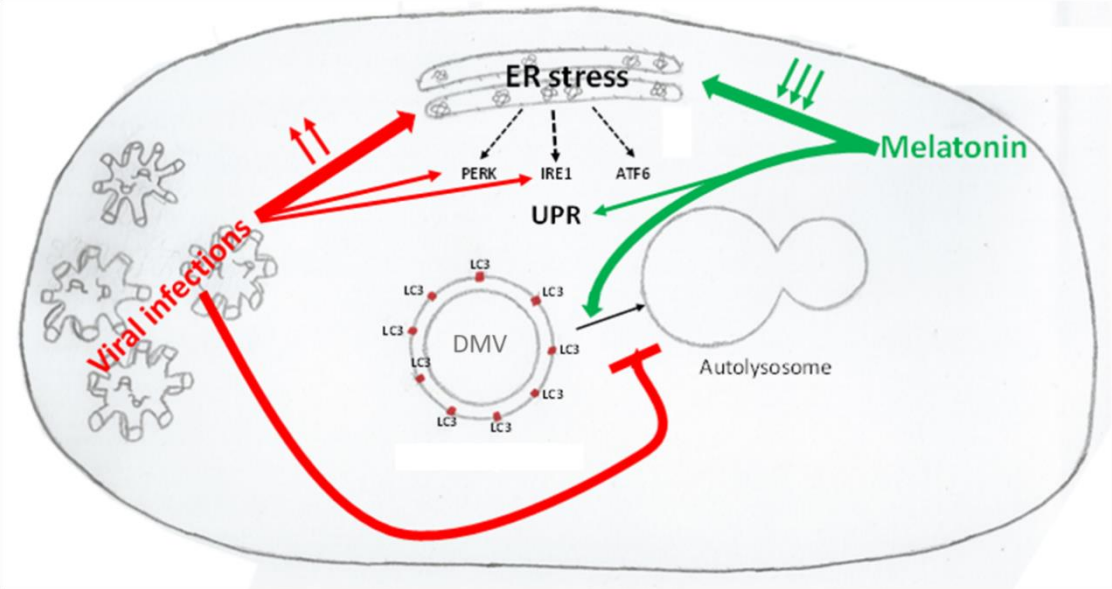

Fig. 1. Effects of viral infection and melatonin on the process of autophagy.

SARS-CoV-2 infection causes ER stress that increases oxidative stress and triggers cellular response pathways, such as PERK and IRE1 branches of the UPR. An excessive oxidative stress and unfolded and misfolded proteins also induce autophagy. An incomplete autophagy by blocking the fusion of autophagosomes and lysosomes is also induced by virus. The incomplete autophagy generates d ouble-membraned vesicles (DMVs) where viral proteins and LC3 are co-localized, are a membranous support for viral RNA replication complexes. Melatonin reduces oxidative stress, reinforces UPR and unlocks the blockage of autophagy caused by virus, allowing autophagosomes to bind to lysosomes and decreases the DMV formation and viral replication capacity.

7. CONCLUSIONS

SARS-CoV-2 infection causes ER stress that increases oxidative stress and triggers cellular response pathways, such as PERK and IRE1 branches of the UPR. An excessive oxidative stress and unfolded and misfolded proteins induce autophagy. The fusion of autophagosomes and lysosomes is blocked by some virus infections leading an incomplete autophagy and forming double-membraned vesicles, which create a membranous support for viral RNA replication complexes. Such as has been discussed in this review, these processes triggered by SARS-CoV-2 may be counteracted by the beneficial effects of melatonin. This indolamine reduces oxidative stress, reinforces UPR and unlocks autophagy blockage induced by virus, allowing autophagosomes to bind to lysosomes and decreasing viral replication capacity (Figure 1). So, the administration of this indolamine should be seriously considered in patients with COVID-19, specially in elderlies and patients with different comorbidities, which are the population with the highest risk for serious symptoms and death.

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AUTHORSHIP

Both authors have equally contributed to develop of the article.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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