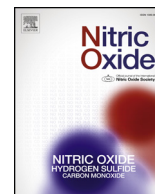




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Review

Tackle the free radicals damage in COVID-19

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ABSTRACT

COVID-19 is a severe pandemic which has caused a devastating amount of loss in lives around the world, and yet we still don't know how to appropriately treat this disease. We know very little about the pathogenesis of SARS-CoV-2, the virus which induces the COVID-19. However, COVID-19 does share many similar symptoms with SARS and influenza. Previous scientific discoveries learned from lab animal models and clinical practices shed light on possible pathogenic mechanisms in COVID-19. In the past decades, accumulated scientific findings confirmed the pathogenic role of free radicals damage in respiratory virus infection. Astonishingly very few medical professionals mention the crucial role of free radical damage in COVID-19. This hypothesis aims to summarize the crucial pathogenic role of free radical damage in respiratory virus induced pneumonia and suggest an antioxidative therapeutic strategy for COVID-19.

1. Text

Current therapeutic approaches to novel coronavirus SARS-CoV-2 induced severe acute respiratory syndrome (COVID-19) are in disarray. Doctors focus on the virus itself and try desperately to apply antiviral medicine such as remdesivir to COVID-19 patients. However, the benefits of antiviral drugs are not satisfactory, while severe drug-induced liver toxicities have been reported [1]. Due to the lack of specific treatment, patients have to rely on their own immune system to recover from the disease.

Free radicals such as superoxide, hydroxyl radicals, nitric oxide (NO) and peroxynitrite are highly active chemical substances that easily react with other molecules. They are exceptionally destructive, indiscriminately causing protein deterioration, cell membrane destruction, DNA damage, cell death, and organ failure. It is known that virus infection induces massive production of free radicals [2]. The pathogenic roles of free radicals in viral infection are profound, but overlooked. In all current official guidelines for COVID-19 treatment, there is no mention about the role of free radical damage in this disease.

2. The pivotal role of free radical damage in respiratory virus induced pneumonia

Dr. Takaaki Akaike and Dr. Hiroshi Maeda at the Department of Microbiology, Kumamoto University School of Medicine found that when laboratory mice were infected by the influenza virus, the replication of the virus increased rapidly and peaked on day 4, then dropped down to baseline on day 8. The lung consolidation scores (lung

damage index) raised from day 2 and peaked from day 8 to day 10. Mice began to die from day 8 to day 14 [3]. Reactive oxygen species (ROS) in the infected mice began generating from day 5 and peaked on day 8. In the meantime, another important free radical NO raised at the same time, peaked on day 8 [4]. From these results, it is evident that a free radical storm occurred in the influenza virus infection. By simply applying oxygen radical scavengers superoxide dismutase (SOD) [5] or NO synthase inhibitor L-NMMA [6], the infected mice were protected and recovered. Lab mice deficient in inducible NO synthase exhibited reduced morbidity and mortality when challenged with influenza virus [7]. These results explicitly tell us that the free radicals such as ROS and NO are the culprits in the virus induced pneumonia death.

3. The interplay of cytokine storm and free radical storm

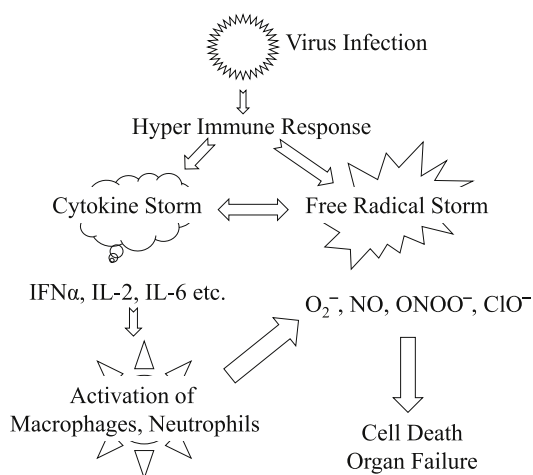
Inflammatory cytokine storm were reported in both COVID-19 [8–10] and SARS [11], and the cytokine storm is the most frequently mentioned pathological theory in COVID-19. These inflammatory cytokines are proteins that act as signaling molecules to recruit immune cells to the site of inflammation, induce vascular leakage and exudation, and stimulate the generation of free radicals and proteases. For example, IFN γ , IL-1 β , IL-6, TNF α can all stimulate the generation of NO [6,12]. IL-2 is highly up-regulated in COVID-19 patients [10], and IL-2 is known to significantly stimulate the generation of NO in patients [13], while NO is also the key mediator of IL-2 induced hypotension and vascular leak syndrome [14]. IL-6 is another major inflammatory cytokine up-regulated in COVID-19 patients [10]. IL-6 and TNF α can provoke the generation of superoxide in neutrophils [15,16], and

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Scheme 1. The interplay of cytokine storm and free radical storm in virus infection induced overactive immune response.

hydrogen peroxide can stimulate the generation of IL-6 [17]. Inhibition of NO synthesis can decrease the production of IL-6 for more than 50% [18]. The cytotoxicity effect of inflammatory cytokines can be blocked by lipid peroxidation inhibitor [19]. In summary, when discussing the cytokine storm in COVID-19, it is critical to understand that free radicals, the downstream product of cytokine storm, are the executive factors for direct damage to cells and multiple organs (See Scheme 1).

4. Suppressing free radical damage as the essential strategy for COVID-19 therapy

SOD is an enzyme that can eliminate superoxide and has been shown to rescue virus infected lab animals [5,20]. Since there is no SOD available for clinical use at this time, SOD mimic compounds [21] should be considered for COVID-19 patients.

Vitamin C and vitamin E are well known as strong antioxidants and free radical scavengers. It was reported that vitamin C given orally between 3000 and 8000 mg helped reduce the duration and relieve symptoms of the common cold [22]. The common cold is largely different from SARS and COVID-19 in the severity, urgency, and the scale of free radical production. Due to the short half-life of vitamin C in plasma, large dose and continuous intravenous infusion of vitamin C should be considered. Currently, there are several on-going clinical trials of intravenous Vitamin C infusion therapy for COVID-19 patients.

Nrf2 is a transcription factor for up-regulating the expressions of many anti-oxidative factors such as SOD and catalase, therefore plays a crucial role in maintaining cellular redox homeostasis [23]. However the level and activity of Nrf2 decreases with age [24], which gives a possible explanation why elder people are particularly vulnerable to the SARS-CoV-2 infection. Therefore, Nrf2 activators might be considered for elder people suffered COVID-19.

Combination of hydroxychloroquine, azithromycin and Zinc exhibits certain therapeutic benefits on COVID-19 patients. Regardless the cardiac toxicities, hydroxychloroquine and azithromycin can suppress NO and superoxide generation [25–27]. Zinc is crucial antioxidant known to be cofactor of SOD [28]. Thus this combination could simply be an antioxidant combination for decreasing host oxidative stress rather than suppressing virus replication. Similarly, erythromycin may be effective for COVID-19 as it can also suppress the generation of NO and superoxide [29]. Other less toxic antioxidant medicines such as glutathione [30] and N-acetylcysteine [31] should also be considered for COVID-19 treatment.

5. Conclusions

The Koch's postulates are the dogma of infectious disease, hence people focus on targeting SARS-CoV-2 in COVID-19. However it could be a problematic strategy. The amount of SARS-Cov-2 virus is high in the first week then decreases sharply in the second week [32], just like the observation in lab animals [3]. Therefore, antiviral therapy should commence at the early stage of infection. When COVID-19 patients seek medical help and hospitalization, the disease has most likely already developed into the second or third stage, with respiratory difficulties and multiple organ failures. Thus from the second stage on, we should look beyond the virus, focusing on the cytokine storm and free radical storm as the actual pathogens. “Because pathological consequences of microbial infections are determined by the interaction of the host and the pathogen, a central theme in modern microbiology is overall understanding of the mechanism of host–pathogen interaction rather than gaining insight about a particular microbe” [33].

Declaration of competing interest

None.

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