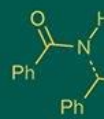


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COVID-19 and hyperinflammation: Could the methionine sulfoxide reductase enzymes play a role?

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Abstract

COVID-19 is a serious public health risk induced by novel SARS-like coronavirus, with currently almost 700 million infections and 5 million deaths. The disease can also exhibit serious illnesses, especially for patients with other chronic diseases such as cardiovascular diseases, diabetes, chronic respiratory disease, or cancer. A significant number of serious patients develops symptoms ranging from systemic shock to multi-organ failure, often with fatal outcome. The predominant cause of mortality is the impetuous inflammatory response mediated by a large amount of toxic reactive oxidative species released from phagocytic cells infiltrated into tissues. Methionine sulfoxide reductase (Msr) enzymes are physiologically involved in shielding against oxidative stress and thus malfunction or expression of these enzymes may result in a predisposition for the occurrence of inflammatory diseases. Accordingly, the role of this important Msr system in protecting against COVID-19 should be investigated.

Keywords: COVID-19, coronavirus, pandemic, COVID-19, inflammation, oxidative stress, oxygen therapy, methionine sulfoxide reductase, MsrA; MsrB

Introduction

Coronaviruses are a common family of several viruses; some of them infect humans and animals with different levels of severity, from common cold to severe pneumonia. Some of them are associated with respiratory syndromes that spread from person-to-person via close contact, resulting in high morbidity and, in some cases, mortality caused by the progression to acute respiratory distress syndrome. The new coronavirus called "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2), the recognized cause of the "Coronavirus Disease 2019" (COVID-19), has emerged in China in December 2019, probably originated in bats, and rapidly spread worldwide ^[1]. After the first hypothetical animal-to-human transmission, the contagion occurred exclusively human- to-human. The global population, perhaps also influenced by the famous 1947 romance by Albert Camus, *The Plague*, having found herself in front of a new and terrifying abstract item, was often carried to a collective psychosis; plus, we cannot forget the initiatives often lacking in objectivity supported by certain local or state administrations, undeniably dictated by lack of preparedness. This dramatic situation forcing the World Health Organization, on 11 March 2020, to officially declare it as a global pandemic, formally concluded on 5 May 2023. More than 700 million infections and 7 million deaths have been officially reported worldwide. The end of pandemic, characterized by several epidemic waves, has been certainly helped by the introduction of several specific vaccines, available from 2021. SARS-CoV-2 naturally undergoing to genetic mutations and new pathogenic variants will continue to emerge, therefore it is still circulating worldwide but with a lower impact on public health, associated with a significant reduction in lethality rate ^[2].

Spread very easily from person-to-person, also by touching contaminated objects, most frequently the infection by SARS-CoV-2 is not accompanied by evident symptoms or presents as a mild flu-like form of disease; however, in the first epidemic wave about 20% of the patients, especially among the elderly if already affected by other disabling diseases, develop a severe condition ^[3], which culminates in acute respiratory failure and often death ^[4]. SARS-CoV-2 binds the epithelial cells of the upper respiratory tract by attaching to a cellular receptor of acetylcholine 2 (ACE2).

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The respiratory component of disease, characterized by acute respiratory distress syndrome and respiratory failure, albeit perhaps the most critical and readily identifiable, appears to be not the only one of this complex disease. It is an “inflammatory storm” triggered by the virus and leads to a generalized inflammatory status with pro-thrombotic consequences that impact on the respiratory tract but also on the cardiovascular, renal and nervous systems [5]. The ongoing COVID-19 pandemic has taken dramatic toll especially on elder population already suffering from one or more disabling pathologies typical of the old age [6]. However, cases of relatively young and apparently healthy patients have been ascertained. The COVID-19 burden can be severe also in children but is far less frequent than in adults under the conditions described above [7]. Standard drug therapies are suitable only for mild and moderate forms of disease. In the severe forms, oxygen therapy (non-invasive nasal cannula application of bi-level or continuous positive airway pressure, or alternatively invasive mechanical ventilation) contributes to ameliorate dyspnea and disease progression in patients with acute respiratory diseases, with the possibility of complete recovery. Despite, approximately 40% of the patients treated by mechanical ventilation died anyway [8, 9]. The reason invoked for the poor prognosis to which these patients are intended, in addition to the direct action of COVID-19 disease, is the delay with which the mechanical ventilation was administered (being cannula application, not invasive but less functional for severe respiratory failure than mechanical ventilation, that is the therapy of choice). However, as a “friendly fire”, it is well known that oxidative stress mediated by reactive oxygen species (ROS) is a potential complication of hypoxia/reoxygenation (reperfusion injury), resulting in oxidative damage of proteinogenic amino acids, lipids, and nucleic/ribonucleic acids. Thus, in this case, oxidative stress induced by strong oxygen therapy specifically damages the lungs and other tissues of the respiratory system [10].

The apparent primary cause of severity and mortality observed in COVID-19 patients is the abnormal inflammatory response mediated by high levels of circulating pro-inflammatory cytokines, associated with infiltration in the lungs and in other organs (including heart and kidneys) of phagocytic cells such as neutrophils and monocytes/macrophages [11]. The tissue damaged resulting from inflammation is principally induced by a plethora of oxidative species, commonly released by activated phagocytes as potent bactericide substances to combat invading microorganisms. The production of these starts with the activation of the multi-enzymatic complex of NADPH-oxidase, followed by a well concerted pathway of enzymatic and non-enzymatic reactions (oxidative burst) [12]. ROS are critical in maintain an effective function of the innate immune systems, but their uncontrolled release contributes to the onset of many severe inflammatory diseases [13]. The oxidative damage targets many sensitive cellular components, including some proteinogenic amino acids. Particularly, the sulfur atom of L-methionine, free or inserted in proteins, can be easily oxidized to sulfoxide, often resulting in the loss of the functional properties of the protein affected. Being the sulfur atom in L-methionine a pro-stereogenic center, its oxidation to sulfoxide produces two stable diastereomers of L-methionine sulfoxide (conventionally labeled *S* or *R*). Reconversion of L-

methionine sulfoxide to L-methionine is physiologically promoted by methionine sulfoxide reductase (Msr) enzymes, which are classified based on their stereo selectivity: MsrA isoforms reduce the *S*-diastereomer, whereas MsrB isoforms reduce the *R*-diastereomer [14]. While the majority of Msrs use a cysteine in the active site to carry out their catalytic action, some employ a selenocysteine; this is the rare case of mammalian MsrB1. Among the plethora of enzymatic and non-enzymatic antioxidative systems, Msrs are ubiquitously distributed in prokaryotes and eukaryotes. In humans, both isoforms are abundantly expressed almost in every tissue, with different subcellular localization, highlighting the strategic role they play against oxidative stress. Conversely, the cyclic oxidation/reduction of specific methionine residues in certain proteins is involved in their biological activation and are involved in the modulation of signal transduction pathways [15]. Msrs also protect cellular components from hypoxia/reperfusion damage and increasing cell survival after ischemia or other deleterious events that produce oxygen deficiency [16].

The uncontrolled oxidation of proteins and their accumulation in cells, due to decreasing in levels of antioxidant systems and particularly the Msr enzymes, are probably implicated in the etiology and/or progression of a certain number of inflammatory and degenerative diseases, including Alzheimer's disease [17, 18]. It has been verified that levels of oxidatively damaged proteins in tissues of subjects affected by these diseases are significantly higher than those of normal subjects [19]. Genetic or non-genetic disorders could contribute to this condition, by affecting one of the numerous and still not completely understood key factors that contribute to the maintenance of the intracellular redox balance. This hypothesis includes a decrease in the expression or in the activity of Msr enzymes, which would compromise one of the main components of the “physiological ammunition” for contrasting oxidative stress. The factors that trigger a deleterious multi-organ hyperinflammation by COVID-19, and the so-called reperfusion injury by hypoxia/reoxygenations, are not well known; but do not seem to be due solely to the advanced age and the already precarious health conditions of the patients. These features can certainly predispose to negative effects of primary viral attack and the subsequent “cytokine storm”, although other triggering factors may be involved. Paradoxically among severe COVID-19 patients, there are young and apparently healthy subjects. Based on proofs collected through the pandemic years and the experimental observations reported in the literature, it seems that oxidative stress plays a major role as a mediator of severe COVID-19 disease [20]. Evidence for the involvement of protein oxidation with COVID-19 infections comes from recent published data on the elevation of irreversible total protein carbonylation and plasma protein deamidation in COVID-19 patients compared to healthy controls [21]. Additionally, severity of COVID-19 risk index was found to be associated with higher levels of advanced oxidation protein products and 8-hydroxy 2 deoxyguanosine [22]. Furthermore, selenium level in COVID-19 patients was lower than in healthy individuals and deficiency of this important antioxidant micronutrient was associated with severe disease progression [23].

Accordingly, we hypothesize that there is a possible correlation between a compromised function and expression

of the Msr system and the onset or severity COVID-19 related inflammation, resulting in the expression of clinical symptoms that are often treated with the most aggressive forms of oxygen therapy.

Even though the COVID-19 emergency seems to be over, understanding the dynamics of the SARS-CoV-2 is critical to prevent its circulating worldwide, while new strains have evolved. Indeed, in biomedical scientific literature of recent years the topic question is one: "Which Virus Will Cause the Next Pandemic?"^[24]. It is worth noting that more than 60% of the about 400 emerging viral infection diseases that have been identified since 1940 are of zoonotic origin, such as SARS-CoV-2. The most important causes that induce these novel pathogens to emerge are, beyond their rapid evolution and adaptation capacity, also the human increase in worldwide travel and the change in migratory habits of vector animal species due to climate change^[25]. A large extent of this emergence is still a "ticking time bomb" for humanity. From a probabilistic point of view, just as the pandemic by a coronavirus occurred in 2020, it cannot be excluded that others may occur in the coming years. Furthermore, lack of drugs capable of defeating coronavirus or other hypothetical novel viruses, increases the vulnerability of public health systems to a highly pathogenic pandemic, as reported just before the dramatic COVID-19 pandemic^[26].

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