COVID-19 Possibly Deteriorates the Conditions of Cancer Patients by Increasing Oxidative Stress

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SUMMARY

The extensive spread of COVID-19 all over the world has worried everyone. This pandemic caused by severe acute respiratory syndrome coronavirus 2, which has an envelope and is a positive-sense RNA. The virus causes mild-to-severe signs and symptoms in the patients. The aim of this study is to investigate the relationship between this virus and oxidative stress, which can worsen the conditions of cancer patients through some pivotal pathways. We utilize some international databases using keywords; COVID-19, neoplasm, and reactive oxygen species, and could attain interesting information about neoplasm, COVID-19, and oxidative stress. Based on the research, COVID-19 can induce some crucial routes, such as hypoxia-inducible factor-1α (HIF-1α) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways through overproduction of ROS. Although not proven, it is hypothesized that COVID-19 may enhance oxidative stress by inducing ROS-activated HIF-1α and NF-κB pathways in the cell, which subsequently can have a lot of disturbing effects on the body, and exacerbate the conditions of cancer patients. To conclude, understanding the precise molecular and cellular mechanisms of ROS-dependent HIF-1α and NF-κB pathways in the pathogenesis of COVID-19 can identify greater therapeutic and management strategies for COVID-19-infected cancer patients.

Keywords: COVID-19; neoplasm; reactive oxygen species.

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Introduction

It is universally accepted that after severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome, coronavirus disease-19 (COVID-19), also known as acute respiratory disease-2019 or nCoV acute respiratory disease-2019, is the third global pandemic to affect numerous countries all over the world. The pandemic is caused by the coronaviridae family and first was spread from Wuhan, China.

[1] Based on the findings of the studies, frequent symptoms are muscle pain, fever, dyspnea, chills, sore throat, cough, sputum production, shortness of breath, hypoxia, temporary loss of smell, odynophagia, and nausea. Besides, dangerous disorders, such as cardiomyopathy, disseminated intravascular coagulation, pulmonary embolism, arrhythmias, thromboembolism, hemorrhage, shock, sepsis, arterial clot formation, and multiorgan failure during the disease may threaten the patients. [1,2]
The risk of death during COVID-19 infection is being enhanced in people with some diseases, for instance, hepatic diseases, cancer, immune system disorders, diabetes, renal failure, respiratory dysfunction, cardiac disorders, or obesity. Although most patients who suffer from COVID-19, have mild symptoms, some cases progress to organ failure, especially lung and kidney dysfunction. Moreover, mortality caused by COVID-19 is calculated between 5% and 15%, nevertheless, this estimation relies on the health conditions of the patients.[2] Furthermore, COVID-19 is transmitted to healthy people by respiratory droplets when the patient coughs or sneezes. The ability of the transmission by this virus varies among strains that have been known so far. According to the studies that are being done on the latest strain (Omicron), it has been determined that Omicron has a strong ability to infect people, and may cause another outbreak in the world.[3,4] As seen by the studies and efforts of different scientific groups around the world, and the promising achievements attained so far, the possibility of having an effective drug and vaccine against all COVID-19 strains seems to be ambiguous yet.[5]

Recently, much research has been conducted on the mechanism of COVID-19 function in the body. One of the most important mechanisms in the pathogenesis of this virus is its association with oxidative stress. Some previous studies have shown that the virus can initiate or intensify oxidative stress in the cells through different cellular pathways.[6] The imbalance between antioxidants and oxidants, and the increased oxidative stress in the cells can cause the onset or exacerbation of some diseases, especially cancer.[6,7]

Therefore, the exact analysis of the cellular and molecular association between COVID-19 and oxidative stress with cancer is necessary. For this reason, in the following sections of this review article, we will discuss the relationship between COVID-19 and oxidative stress and their effects on the deterioration, and even death of cancer patients.

Materials and Methods

The bibliographic search was done on Web of Science, Google Scholar, PubMed, and Scopus databases. Search keywords including “COVID-19” OR “SARS-CoV-2” AND “Oxidative Stress” AND “Reactive Oxygen Species” OR “ROS” AND “Neoplasm” OR “Cancer” in all fields. Any language or date limitations were not applied. Defined articles and studies were screened by title, abstract, and full text. Then the articles from all the databases united and the studies and articles that were not relevant to our subject and inclusion index criteria excluded. Afterward, the available articles were carefully evaluated and the relevant articles were chosen.

Oxidative Stress

There is no doubt that oxidative stress is related to an imbalance between reactive oxygen species (ROS), such as $H_2O_2$ or $O_2^-$ and antioxidants, which are eliminated by the body using a variety of methods.[8] Furthermore, ROS is formed by different pathways, for instance, the electron transfer route in the mitochondria, in which Complexes I and III are involved.[8,9] Some of these molecules are produced by cellular aerobic metabolism in our body, moreover, environmental factors, such as chemicals and radiations, are involved in the production of ROS.[7] Eventually, the accumulation of ROS results in cell damage. However, when these molecules are at low or moderate amounts inside the cells, they can have beneficial effects on the body.[10] To illustrate, these molecules are made by the host defense immune system, specifically phagocytes, and are used to fight against many microorganisms. In addition, free radicals can be formed by non-phagocytic NADPH oxidase isoforms; which in case, they have a pivotal regulatory role in signaling pathways in some cell types, such as thyroid tissue, endothelial cells, cardiac myocytes, vascular smooth muscle cells, and fibroblasts.[10-12] To summarize, when free radicals be kept at low or moderate levels, have an important role in human health.[12]

Oxidative Stress and its Effects on the Human Body

Oxidative stress, due to its pivotal role in the cell and signaling pathways, can cause various diseases specifically, neoplasm, heart, blood, immune system, lung, kidney, and neurodegenerative diseases.[13,14] The reactive species inside the cell enhances oxidative stress, which can directly or indirectly lead to molecule damage, such as DNA and types of macromolecules. Eventually, this damage to different parts of the cells and tissues causes some diseases in different organs (Fig. 1).[15] Many intracellular reactions, in which oxygen molecules are involved, can produce ROS that ultimately may seriously damage to vital molecules. Interestingly, DNA damage eventually leads to the mutations; and if these mutations do not repair, they may result in cancer.[15]
Cellular Pathways of Oxidative Stress and Cancer

With regard to the studies, oxidative stress through various macromolecules damage can injury to the cells and tissues, which eventually leads to many diseases, especially neoplasm. Oxidative stress uses a variety of signaling pathways, although not all of these molecular pathways have been fully identified. Even more important, many different molecules and proteins have been identified that are involved in ROS metabolism and signaling pathways. Undoubtedly, two pivotal cellular pathways in which ROS is involved including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and hypoxia-inducible factor-1α (HIF-1α) routes, which play crucial key roles in oxidative stress and cancer.[16]

ROS-Dependent HIF-1α Pathways

HIF-1 and its signaling pathways play a significant task in metabolic adaptation and intracellular hypoxia conditions. HIF-1 is a specific transcription factor that is activated under hypoxic conditions. Furthermore, HIF-1 is involved in many particular physiological processes, such as the development of the cardiovascular system, cartilage growth, fetal nerve formation, as well as pathological processes, for example, tumor invasion and progression. Under oxidative stress conditions, ROS can stabilize and activate the HIF-1α route, which in case launches the cellular and molecular mechanisms, such as stabilizing metastasis, metabolic changes of cancer cells, growth, survival, and angiogenesis. Subsequently, ROS can directly or indirectly activate some genes in this pathway, which finally results in tumor invasion and progression (Fig. 2).[16]

ROS-Induced HIF-1α Contributes to Proliferation, Angiogenesis, Invasion, and Metastasis

Extensive studies on vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) have shown that HIF-1α can increment the expression of VEGF and VEGFR genes. It can be concluded that ROS-activated HIF-1α directly enhances VEGF and VEGFR, which finally results in angiogenesis.[17] In addition, another way that HIF-1α causes the proliferation of cancer cells is the activation of two typical pro-proliferative genes, c-Myc and cyclin D1. ROS may affect overexpressing of the two genes and end up proliferation.[18]

ROS in neoplastic cells causes the production of some proteases, such as matrix metalloproteinases (MMPs), especially MMP9. These enzymes contribute to the destruction of the basement membrane. Besides, ROS can cause the formation of invadopodia.[19,20] The expression of metastasis and invasion enzymes, to illustrate, MMPs are controlled by the HIF-1α route. Therefore, the invasion and metastatic potential of neoplastic cells can be enhanced following the overproduction of ROS-induced HIF-1α.[19,20] To sum up, the activation of HIF-1α by ROS directly or indirectly promotes proliferation, angiogenesis, invasion, and metastasis.[21]

ROS-Induced HIF-1α and Telomerase

As seen by some studies, one way that cancer cells escape from apoptosis is the activation of telomerase.[22] One research on hepatocellular carcinoma has been shown that ROS plays a certain role in telomerase activation. Furthermore, it has been proved that ROS can activate HIF-1α pathways to stabilize telomerase in cancer cells, which eventually causes to promote proliferative potential and regulates mitochondrial function, signaling pathways, and survival of neoplastic cells.[22,23]
ROS-induced HIF-1α and drug resistance

In neoplastic cells, especially cancer stem cells, drug and chemotherapy resistance have been observed. This resistance is due to the increased expression of ATP-binding cassette (ABC) transporters by the HIF-1α transcription factor. As mentioned before, ROS can trigger HIF-1α pathways, and the overactivation of the HIF-1α route causes the production of ABC transporters, like multidrug resistance mutation 1, and ultimately results in drug and chemotherapy resistance.[24,25]

ROS-Induced HIF-1α and Tumor Metabolism

Many intracellular molecules and proteins, such as ROS and HIF-1α, are involved in metabolic programming in normal and neoplastic cells. These factors are required to increase the expression of proteins, such as glutaminase for glutamine consumption, carbonic anhydrase IX for control of pH, hexokinase II for glycolysis pathway, and glucose transporter 1 for glucose expenditure. Eventually, all of these metabolic changes within the cancer cells will cause tumor perdurable and progression.[26]

ROS-Dependent NF-κB Pathways

The NF-κB modulates many signaling pathways within the cell. This transcription factor regulates inflammatory responses, and innate and adaptive immune functions. In addition, this factor is activated by some cellular agents, such as ROS, and some external factors, for example, bacteria, viruses, and other parasites. Eventually, NF-κB causes the production and development of some molecules and enzymes that are involved in the overproduction of oxidative stress (Fig. 3).[16]

ROS-Induced NF-κB Contributes to Proliferation, Angiogenesis, Invasion, and Metastasis

ROS-induced NF-κB activates several inducible enzymes and considers the example of iNOS, 5-LOX, COX2, and NOX, which participate in some metabolic pathways for the production of mediators, such as nitride oxide, prostaglandins, leukotrienes, and plasmalogens, which will eventually cause the activation of the inflammatory-reparative response (IRR). [27,28] It has been shown that the expression of these enzymes in cancer cells leads to the production of some mediators, which will subsequently result in tumor migration and progression, and vasodilatation through changes for epithelial-mesenchymal transition, and neoangiogenesis.[29]

On the other hand, in activated leukocytes, some pathways cause the generation of MMPs and tissue inhibitor of MMPs by ROS-dependent NF-κB and HIF-1α.[30] Furthermore, ROS can directly stimulate MMP generation. As mentioned before, by activating these enzymes, especially in cancer cells, the extracellular matrix (ECM) is broken down, eventually leading to metastasis and cancer progression.[16,30] As stated above, ROS-induced NF-κB, similar to HIF-1α, causes the induction of some important pathways in activated leukocytes and mesenchymal cells within the cancer cells, which these activated cells (leukocytes and mesenchymal) ultimately lead to the production of VEGFs and VEGFRs. As a result, VEGFs and VEGFRs can contribute to the induction of angiogenesis.[16,31]

In addition, tumor cells can produce chemokines and their receptors depending on the degree of malignancy. The production of chemokines by malignant cells causes the absorption of leukocytes into advanced tumor sites. Besides, the production of chemokine receptors will cause the metastasis of neoplastic cells. C-X-C chemokine receptor type 4, as an important receptor for stromal cell-derived factor 1α, has been identified as a receptor in the neoplastic cells, which is associated with the progression and metastasis of malignant cells in many human cancers. A study on prostate cancer has proven that ROS-induced NF-κB reinforce the function of this receptor in the neoplastic cells.[32,33]

ROS-Induced NF-κB Contributes to Detachment and Homing

One of the most important cells involved in inflammatory responses is the leukocyte. NF-κB can activate some signaling pathways in these cells. Moreover, by launching these cellular pathways, NF-κB leads to the expression of several adhesive molecules that play critical roles in migration and homing. ROS-dependent NF-κB-induced
expression of adhesive molecules occurs in malignant cells, which causes some changes, such as the activation of ECM molecules for migration, the ability to connect to a new location after metastasis, and eventually the identification of the detachment and homing sites.[16,34]

ROS-Induced NF-κB and Growth and Survival Factors

Some studies have proven that HIF-1α and NF-κB control many survival and growth factors, as well as their receptors. This control occurs in activated leukocytes during tissue repairing, as well as in cancer cells under hypoxic conditions. Survival and growth factors are provided by tumor cells and activated leukocytes, which lead to the expression of transforming oncogenes, which in state, the activation of tumor cells and leukocytes is accomplished by ROS-induced NF-κB route.[35]

5-2-4. ROS-Induced NF-κB and Cytokines

Based on the findings of studies, ROS can play a pivotal role in inducing cytokine synthesis in different pathways by activation of NF-κB. Cytokines can have an important effect on IRR through activating T helper 1 or 2, targeting leukocytes, and the activation of multiplication of crucial cells, such as CD45+ to sustain the IRR.[36] On the other hand, cytokines have also been produced by neoplastic cells in several human cancers. It has also been shown in various malignancies that tumor cells express receptors for cytokines. Thus, ROS-dependent NF-κB-induced production of cytokine and their receptors can have a significant effect on the detachment, homing, and metastasis of cancer cells.[36]

COVID-19-Infected Cancer Patients and Oxidative Stress

There is no denying that vascular regulation is necessary for the health and survival of humans. In the human body, the cardiovascular system regulation is controlled by the function of vascular endothelial cells. Endothelial cells lead to launching the constriction and dilation of blood vessels and match vascular concentrations of many chemicals in response to numerous external and internal stimuli.[37]

One of the most important ways of this regulation is the renin-angiotensin-aldosterone system (RAAS), which engages some critical enzymes, including angiotensin-converting enzyme (ACE) 1 and 2. Moreover, the ACE2 receptor plays a significant task in reducing oxidative stress, which in case has a key role in regulating the binding of proteins involved in SARS-CoV-2 infection, such as ACE2 and S protein (one of the most pivotal antigens on the surface of the coronavirus).[38,39] RAAS pathway begins with the production of angiotensinogen from the liver into the bloodstream, which interacts with renin that is produced in the kidney. After the secretion into the bloodstream, renin interacts with angiotensinogen, which converts the angiotensinogen into angiotensin I (Ang 1), then Ang 1 becomes angiotensin II (Ang II) by ACE 1.[39] Ang II has some critical functions, which one of them is a certain role in the pathophysiological effects of the RAAS system. In addition, Ang II generates ROS through actuating NADPH oxidase, which triggers the production of superoxide species and ultimately leads to the overproduction of oxidative stress. Degrading Ang II into angiotensin 1–7 (Ang 1–7) is done by ACE2, in which Ang 1–7 is a vasodilator factor.[38,39] Converting Ang II into Ang 1–7 through ACE2 reduces oxidative stress by inhibiting NADPH oxidase and Ang II-dependent ROS production. Several studies have shown that if ACE2 connects to the S protein, the amounts of Ang II will enhance, resulting in overproduction of superoxide species, then ending up cell damage, increasing oxidative stress, and eventually promoting the risk of severity of malady that originates from COVID-19 (Fig. 4).[38-40]

Oxidative stress is produced through the high amounts of Ang II and low values of Ang 1–7. Furthermore, ROS oxidizes the cysteine residues on the domain of ACE2 receptors and receptor-binding domain (which is a pivotal domain of S protein for binding SARS-CoV to a host receptor) of SARS-CoV and SARS-CoV-2 S proteins, which keep them in oxidized (disulfide) state, as opposed to decreased (thiol) state.[39,40] It is possible that oxidation of thiol groups to disulfides, under
oxidative stress conditions, would enhance the affinity of S proteins of SARS-CoV-2 for the ACE2 receptor, and hence, augment the severity of COVID-19 infection in numerous diseases, especially cancer.\[39,40\]

As explained before, NADPH oxidase can be activated by COVID-19 and participated in reducing O\(_2\) to superoxide and is first found in cardiac myocytes, endothelial cells, vascular smooth muscle cells, and phagocytic cells.\[40\] Just as important, connecting the viral S protein to ACE2 enhances the amount of Ang II, then ACE2 cannot transform Ang II to Ang 1–7. In this state, Ang II connects to the angiotensin type 1 receptor, which launches NADPH oxidase activity. This phenomenon leads to the overproduction of ROS in the cell. Eventually, since the binding of SARS-CoV-2 to the ACE2 receptor causes to inactivate the enzyme, Ang 1–7 will not be produced from Ang II.\[40\] In conclusion, COVID-19-induced NADPH oxidase-activated ROS can also enhance oxidative stress in SARS-CoV-2 patients and finally deteriorate the conditions of the patients, and even increase the risk of death.\[40\]

Tremendous studies have proven that COVID-19-infected cancer patients have a high fatality rate. In addition, it is more difficult to identify proper medical care for COVID-19-infected cancer patients. Furthermore, this problem increases confusion and anxiety among patients with cancer to deal with COVID-19 and cancer, together.\[41\] In addition to the patients, oncologists are also counteracting many challenges, because no one has observed and experienced the novel COVID-19, and there are also enormous unanswered questions to consider the proper management of COVID-19-infected cancer patients.\[41\]

Recently, numerous studies have been performed on cancer patients, and it has been shown that cancer patients who suffer from another disease, such as infectious diseases, are at a higher risk of mortality. In 2021, Zhang et al.\[42\] conducted a systematic review and meta-analysis study on COVID-19-infected cancer patients. The results of this extensive study showed that the patients have a higher mortality risk than COVID-19 patients without cancer. In the same way, in 2020, Patt et al.\[43\] carried out a huge study, in the USA, on COVID-19-infected cancer patients, and stated that patients with different cancers could not be diagnosed in time, and also their treatment would face serious problems, as well as cause to increase mortality risk in these patients. Similarly, in 2020, Liang et al.\[44\] conducted a study on patients with cancer and COVID-19 disease. Their results showed that cancer patients are at greater risk than those without cancer to catch severe form of COVID-19 infection, and their treatments, such as chemotherapy and using immunosuppressive drugs, would face serious problems. In addition, in 2020, Zhang et al.\[45\] carried out a retrospective cohort study on 28 cancer patients with COVID-19 in Wuhan, China, to assess mortality risk factors associated with mechanical ventilation and ICU admission. The results of this study showed that patients with COVID-19-infected cancer patients are at high risk for weak clinical results, and even mortality.

Despite the extensive research that has been conducted on COVID-19-infected cancer patients in recent years, the exact cellular and molecular mechanisms which COVID-19 causes to deteriorate the conditions of these patients are still unknown.\[46\] Even more important, based on the findings of a lot of studies that have been done on COVID-19 and ROS, COVID-19 can increase oxidative stress in the infected cells by the cellular and molecular pathway, which is associated with the RAAS system.\[38,46\] Furthermore, the different research on ROS, which has been performed in various diseases, especially cancer, has shown that ROS can cause cell and tissue damage, and eventually harm the organs through different cellular pathways.\[9,47\] One of the most important cellular pathways that cause cell damage is the HIF-1\(_\alpha\) route. As mentioned before, the ROS-dependent HIF-1\(_\alpha\) pathway causes to deteriorate COVID-19-infected cancer patients by the activation of different mechanisms, specifically angiogenesis, proliferation, invasion, migration, and glycolysis in tumor cells, and even their treatment may be more difficult through drug and chemotherapy resistance.\[16\] In addition to the ROS-dependent HIF-1\(_\alpha\) route, the NF-\(\kappa\)B pathway is another critical mechanism that is associated with ROS. ROS through launching NF-\(\kappa\)B route, leads to trigger pathways, such as IIR, migration, invasion, proliferation, angiogenesis, and vasodilation, and also detachment and homing by adhesive molecules, which eventually will increase the morality in COVID-19-infected cancer patients.\[16\]

To sum up, it seems that COVID-19 might have a direct or indirect effect on the inducing ROS-activated-HIF-1\(_\alpha\) and NF-\(\kappa\)B pathway in the cells, which may exacerbate the conditions of COVID-19-infected cancer patients, and eventually result in the death of these patients.\[16\] In a word, revealing the role of ROS-induced HIF-1\(_\alpha\) and NF-\(\kappa\)B pathways in the pathogenesis of COVID-19-infected cancer patients will pave the way to identify cellular and molecular mechanisms for effective potential therapeutics and medical cares, nevertheless, extensive molecular studies are required to prove this hypothesis (Fig. 5).
Conclusion

Putting it all together, ROS-induced HIF-1α and NF-κB pathways are playing a pivotal role in promoting oxidative stress in the cell, even more important, are associated with COVID-19 infection. Consequently, it is hypothesized that COVID-19 might enhance oxidative stress by activating HIF-1α and NF-κB pathways through overproduction of ROS. For this reason, identifying the precise mechanisms of ROS-activated HIF-1α and NF-κB routes, in the pathogenesis of COVID-19, can pave the way to find better therapeutic and management strategies for COVID-19-infected cancer patients.

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