Alteration of Iron homeostatis in Ferroptosis biomarkers among COVID-19 patients: A Review Article

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Background

The first case of a patient infected by the SARS-CoV-2, causing viral pneumonia, which was presented in December 2019 in the city of Wuhan/ China (Guan et al., 2020). According to the World Health Organization, SARS-CoV-2 infection reached pandemic status on 20 January 2020 (Mahase, 2020). The disease caused by SARS-CoV-2 is named Coronavirus Diseases-2019 (COVID-19). Genome comparisons have shown that previous isolates, the SARS-related coronavirus (SARSr-CoV), including the SARS-CoV are closely related, yet different in disease manifestation (Low et al., 2021). Which is considered similar to SARS-CoV, invades human cells via the receptor angiotensin converting enzyme II (ACE2), lung cells that have ACE2 expression may be the main target cells during SARS-CoV-2 infection. Some patients also exhibit non-respiratory symptoms, such as kidney failure, implying that SARS-CoV-2 could also invade other organs(Zou et al., 2020), so, lung is not the only organ affected by SARS-CoV-2; the virus can affect various systems and result in multiple organ failure (Zaim et al., 2020). A recent reported case of SARS-CoV-2 myocarditis with cardiogenic shock showed a signature of myocardial and kidney ferroptosis, a novel, iron-dependent programmed cell death(Pasini et al., 2021). Ferroptosis is a relatively novel cell death type that was first termed by Dixon et al. in 2012, ferroptosis is an iron-dependent regulated cell death (RCD) characterized by iron overload and lipid peroxidation. The main morphological features of ferroptosis are mitochondrial shrinkage accompanied by increased mitochondrial membrane density and degenerated mitochondrial crista without changes in the nucleus(Dixon et al., 2012).

Cell death and Ferroptosis process

Cell death in multicellular organisms occurs in different mechanisms including apoptosis, autophagy, necrosis(Heim et al., 2002). The mode of cell death can be generally categorized based on its morphological characteristics, enzymological role and functional characteristics into different types(Galluzzi et al., 2018). The most common forms of Programmed cell death (PCD) are divided on the criteria as:

1. Apoptosis: is the process by which a cell ceases to grow and divide and instead enters a process that ultimately results in the controlled death of the cell without spillage of its contents into the surrounding environment. Apoptosis is also sometimes referred to as programmed cell death(Elmore, 2007). Apoptosis can be initiated by the cell itself when it detects damage via a number of intracellular sensors; a mechanism known as the intrinsic pathway. Alternatively, it can result from the interaction between a cell of the immune system and a damaged cell, which is known as the extrinsic pathway of apoptosis(Oppenheim et al., 2001). Classic apoptosis (both the intrinsic and extrinsic pathways) is characterized by the compartmentalization of intracellular components of the cell and removal of cellular debris without any collateral damage occurring to surrounding tissues(D'Arcy, 2019).
2. Necrosis: (Cell death with collateral damage), Unlike apoptosis, necrosis is an alternative uncontrolled form of cell death that is induced by external injury, such as hypoxia or inflammation. This process often involves upregulation of various pro-inflammatory proteins and compounds, resulting in the rupture of the cell membrane causing spillage of the cell contents into surrounding areas, resulting in a cascade of inflammation and tissue damage. In contrast to apoptosis, necrosis is an energy independent form of cell death, where the cell is damaged so severely by a sudden shock (heat, chemicals, hypoxia etc.) that it is unable to function(D'Arcy, 2019).
3. Autophagy: Autophagy is a process where cellular components such as macroproteins or even whole organelles are sequestered into lysosomes for degradation. The lysosomes are then able to digest these substrates, the components of which can either be recycled to create new cellular structures and/or organelles or alternatively can be further processed and used as a source of energy(Mizushima et al., 2008).
4. Ferroptosis: is an iron-dependent regulated necrosis characterized by the peroxidation damage of lipid molecular containing unsaturated fatty acid long chain on the cell membrane or organelle membrane(Ma et al., 2021), ferroptosis is a recently recognized form of RCD. It is characterized morphologically by the presence of smaller than

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normal mitochondria with condensed mitochondrial membrane densities, reduction or vanishing of mitochondria crista, and outer mitochondrial membrane rupture(Xie et al., 2016).

Free radical and reactive oxygen species

Reactive oxygen species (ROS) are partially reduced oxygen containing molecules. generally small, short lived, and highly reactive molecules that are formed by incomplete one-electron reduction of oxygen. ROS are free radicals and/or oxygen derivatives, including superoxide (O2.), hydroxyl (OH), alkoxyl (RO) and peroxyl (ROO), but also some non-radical compounds such as hydrogen peroxide (H2O2), the excited oxygen species singlet oxygen (1O2), ozone (O3), hypochlorous acid (HOCl), peroxynitrite (ONOO)(Halliwell & Gutteridge, 2015). Oxidative stress (OS) is defined as an imbalance between toxic ROS and antioxidants in favor of oxidants, leading to a disruption of redox signaling and/or irreversible oxidative damage to lipids, deoxyribonucleic acid (DNA) or proteins. Free radical production in the human organism is closely related to iron metabolism(Liebert & Jones, 2006).

Role of free-radical in COVID-19

Neutrophils are the first responders to invasion of pathogens and tissue damage mediating the killing of pathogens by oxidative burst and phagocytosis(Jenne et al., 2018). Neutrophil activation is an important clinical feature in COVID-19. Infiltrating neutrophils, is a hallmark of COVID-19, that release myeloperoxidase (MPO), which activate several pathways that lead to elevated cytokines and production of ROS(Tang et al., 2020). The link between neutrophil MPO activity generated during the "cytokine storm" provoked by COVID-19, ROS, that play role in nitric oxide (NO) consumption and heme destruction as well as subsequent iron release(Nguyen et al., 2017).

Neutrophils, eosinophils, monocytes, macrophages, mitochondrial damage, and NADPH oxidase are the major sources of generation of O2 •– at sites of inflammation(Robb et al., 2016). Another ROS generating enzyme is xanthine oxidoreductase (XOR), which metabolites hypoxanthine and xanthine to uric acid to instantaneously generate O2•–(Guérin et al., 2001).

In COVID-19, like other inflammatory diseases, a major damaging pathway mediated by overproduction of O2•- and subsequent oxidative stress is caspase-3 activation, which is closely associated apoptosis and therefore DNA fragmentation(Ivanova et al., 2016). However, O2•- is a short-lived molecule and is quickly consumed either through nonenzymatic pathways or a superoxide dismutase-catalyzed reaction to produce H2O2(Phaniendra et al., 2015), considerably more stable than O2•-, that diffuses freely through biological membranes, and is equally capable of inducing cytotoxicity when overproduced, as in COVID-19(Bartz & Piantadosi, 2010). In addition to its direct effects, H2O2 can react with O2•- or Fe2+, through the Fenton reaction, to generate the highly reactive and toxic hydroxyl radical, that can contribute to tissue damage, further worsening the condition in infected individuals(Winterbourn, 1995). Catalase, a key regulator of H2O2, scavenges H2O2 and catalyzes its decomposition, thereby protecting cells from H2O2 toxicity(Chelikani et al., 2004).

Lipid peroxidation in COVID-19

lipid molecule is oxidized upon lipid radical formation. The initiators of non-enzymatic lipid peroxidation are mainly hydroxyl and hydroperoxyl radicals that initiate oxidative chain reactions. The most sensitive molecules that undergo peroxidation are membrane phospholipids containing polyunsaturated fatty acids (PUFAs), including arachidonic, linoleic, linolenic, eicosatetraenoic, and docosahexaenoic acids. Enzymatic lipid peroxidation is primarily catalyzed by cyclooxygenases (COX)(B. Liu et al., 2015), lipoxygenases (LOX)(Murakami, 2015), and phospholipase A (PLA)(Adibhatla & Hatcher, 2006).

Lipid peroxidation involves three steps: initiation, propagation, and termination(Yin et al., 2011). The main primary products of lipid peroxidation are lipid hydroperoxides (LOOH). Among the many different aldehydes which can be formed as secondary products during lipid peroxidation, malondialdehyde (MDA), propanal, hexanal, and 4-hydroxynonenal (4-HNE). MDA appears to be the most mutagenic product of lipid peroxidation, whereas 4-HNE is the most toxic(Girotti, 1998). All these aldehydes have been found to play a role in the toxic effects of lipid peroxidation. Aldehyde toxicity is based on the alterations of several cell functions, which mostly depend on the formation of covalent adducts with cellular proteins(Grimsrud et al., 2008).

4-HNE directly contributes to many atherosclerosis-based cardiovascular diseases. 4-HNE is present in vascular smooth muscle cells of the atherosclerotic tissue, and its detection in both oxidized low-density lipoprotein (Ox-LDL) and fibrotic plaques in atherosclerotic patients has demonstrated its potential involvement in the pathogenesis of atherosclerosis(Leonarduzzi et al., 2005).

Atherosclerosis refers to the disease of arteries which commonly manifests as coronary heart disease leading to myocardial infarction and cerebrovascular disease leading to stroke and other complications. Atherosclerosis is a complex, progressive, inflammatory disease that mainly occurs in subendothelial space of medium to large sized arteries at regions of disturbed blood flow or bifurcates(Siasos et al., 2018). Experimental observations have explicitly pinpointed Ox-LDL, endothelium dysfunction, and oxidative stress as the most prominent risk factors in atherosclerosis(Winterbourn, 2008).

COVID-19 causes hyperactivation of the immune

system resulting in increased number of cytokines, and the occurrence of vascular inflammation contributing to the progression of atherosclerosis(Lin et al., 2020). SARS-CoV-.2 infection is a possible direct trigger of endothelial adverse effects. Endothelial dysfunction is an initial step in the development of atherosclerosis that precedes clinical symptoms and has prognostic value for future cardiovascular events(Sitia et al., 2010). Endothelial dysfunction emerges as one of the essential mechanisms corresponding to the enhanced atherosclerotic risk among HIV, HCV and other viral infected people(Anand et al., 2018). Therefore, endothelial dysfunction induced by SARS-CoV-2 infection indeed becomes a strong contributor to upcoming atherosclerosis in subjects who have recovered from COVID-19(Y. Liu & Zhang, 2021).

It is undoubtedly that the pre-existing cardiometabolic factors contribute to the severity of clinical manifestations of patients suffering from COVID-19. An intermediary condition is considered to be endothelial dysfunction(Zhu et al., 2018). Early stages of atherogenesis are characterized by endothelial damage, which is accompanied by the accumulation of multiple-modified low-density lipoprotein (LDL) and other lipoproteins. Epidemiological studies imply that elevated level of LDL is the chief contributor to atherosclerosis. This contributes to the inflammation of the arterial wall. Both the innate and adaptive immune systems play a crucial role in lesion formation and plaque characterization, supporting and contributing to the pro-atherogenic condition(Poznyak et al., 2021).

Mechanism of Ferroptosis

In physiological situations, duodenal cytochrome B, a small intestinal cell membrane reductase, reduces Fe3+ to Fe2+ and transports Fe2+ into intestinal epithelial cells through the divalent metal transporter (DMT1). Fe2+ in intestinal epithelial cells is transported to the blood through membrane iron transporters and is oxidized into Fe3+ by ferrous oxidase. In the blood circulation, Fe3+ binds to transferrin (TF) and undergoes various tissues and organs(Torti & Torti, 2013). The iron reductase six-transmembrane epithelial antigen of prostate 3 reduces Fe3+ to Fe2+ in the endosome. Fe2+ is transferred to the labile iron pool through DMT1, and excessive iron is transported to the bloodstream or stored in ferritin(Kuang & Wang, 2019). Under pathological conditions, excessive free Fe2+ will gather in the cytoplasm (iron overload), and Fe2+ produces vast amounts of hydroxyl radicals and ROS through the Fenton reaction, which destroys the cell membrane, DNA, and proteins in the cells and triggers ferroptosis(Conrad et al., 2018).

Iron homeostasis and ferroptosis

Iron is an essential trace element that plays a role in systemic oxygen transfer, and acts as an electron donor or acceptor in many biological functions. Ferritin is the primary site of iron storage in the cell mainly in its ferric state (Fe3+). Ferritin can carry up to 4500 iron molecules in its core(Kell & Pretorius, 2014). Generally, systemic inflammations are associated with increased serum ferritin levels. During a heightened inflammatory state, cytokines, particularly IL-6, stimulate ferritin and hepcidin synthesis(Daher et al., 2017).

There are two forms of iron in the cells: Fe (II) and Fe (III). On account of Fe (II)'s ability of transfer electrons and high solubility, Fe (II)-containing proteins always serve as cofactors and catalysts participating in various oxidation–reduction reactions, whereas iron is stored and transported in its stable Fe (III) form. However, the ease in electrons transfer also makes iron poisonous to cells for excess iron atoms can donate electrons to O2 and H2O2 to generate superoxide anion and the hydroxyl radical, both of which can damage cells by oxidizing proteins, lipids, and nucleic acids. Moreover, the mixture of Fe (II) and H2O2 can oxidize organics to generate ROS by the Fenton reaction(Pignatello et al., 2006).

Iron is both necessary to the body and potentially toxic. It is necessary for cellular respiration and oxygen transport and is potentially toxic for its ability to catalyze the conversion of hydrogen peroxide into free radicals. To prevent such damage, all life forms that use iron bind the iron atoms to proteins. Ferritin is the major intracellular iron storage protein in all organisms(Vlahakos et al., 2021). Several indicators were also proposed for the evaluation of iron status, including Hb, mean cell volume (MCV), mean cell hemoglobin (MCH), serum ferritin, transferrin saturation, and total iron-binding capacity (TIBC)(Northrop-Clewes, 2008).

Iron metabolism play an important role in multiple organ dysfunction syndrome in COVID-19. The innate immune response could restrict iron availability during infections to deprive the pathogen of it, a mechanism that would also lead to anemia(Weiss et al., 2019). Anemia, in turn, reduces oxygen delivery to the tissue and may thus play an important role in the development of multi-organ failure(Taneri et al., 2020).

Viruses and ferroptosis

According to a number of earlier investigations, all COVID-19 patients exhibited elevated serum ferritin levels, which is consistent with these data (Rayhaan et al., 2021). Viral activities such as viral gene expression, host-virus triggered signaling, virus-physiological stress, can destroy organelles of the host, the destruction of cellular organelles that abundant house iron-containing or iron-requiring proteins such as lysosome and mitochondria result in releasing the iron into the cytosol. The organelle contents are likely to participate in ferroptosis or infection progression(Wang et al., 2021).

Biomarkers of Ferroptosis

❖ HNE is α, β-unsaturated electrophilic compounds, the major type of 4-hydroxyalkenals end product, generated by decomposition of arachidonic acid and larger polyunsaturated fatty acids (PUFAs), through enzymatic or nonenzymatic processes(Esterbauer, 1996), besides being produced from the non-enzymatic peroxidation process, HNE could also be generated enzymatically by cyclooxygenase-2 and lipoxygenase. The most common source is the endogenous one, coming from the ROS produced by the mitochondrial electron transport chain, which triggers lipid oxidation(Duryee et al., 2004). So Shintoku et al., 2017 suggest that oxidative generation of 4-HNE from PUFA is associated with the execution of ferroptotic cell death.

❖ Lipid peroxides, increased levels of Prostaglandin-Endoperoxide Synthase 2 (PTGS2), and the decrease of nicotinamide adenine dinucleotide phosphate (NADPH) can be recognized as biomarkers of ferroptosis(Shimada et al., 2016; Yang et al., 2014).

❖ Ferroptosis is characterized by the accumulation of lipid peroxidation products that require abundant and accessible cellular iron(Xie et al., 2016), normal iron is essential for biological systems, but excessive iron can cause cell death by generation of ROS(Dixon & Stockwell, 2014). The iron-mediated ROS produced by Fenton reaction is important for inducing ferroptosis(Bystrom et al., 2014), so, ferroptosis is found closely related to intercellular iron concentration(Yang & Stockwell, 2016).

Knowledge gap

Many clinical and scientific studies on SARS-COV-2 have been published, but the conclusions on the prediction of illness severity in COVID-19 patients have not been completely finished. This work was conducted at the database that had been published in a number of reputable publications, and it focused on a wide range of biomarkers.

This review suggested the possibility of employing HNE level as a useful biomarker for predicting COVID-19 severity. Since in severe COVID-19 patients, the risk of HNE induction is relatively high, as a result, verifying this idea appears to be an essential undertaking, as discovery of the agents causing systemic problems through SARS-COV-2 infection could save many lives.

Conclusion

The cells' ferroptosis-sensibility is likely to vary depending on cell type, physiological conditions, and even individual lifestyle. Iron metabolism dysfunction has been widely documented in a large proportion of COVID-19 patients in response to SARS-CoV-2 infection, and this may cause iron accumulation and overload, triggering ferroptosis in cells of multiple organs. It was suspected that ferroptosis is a major cause of multiple organ involvement in COVID-19 and that it could be a new treatment target. Intracellular iron depletion or a new generation of ferroptosis inhibitors could be potential COVID-19 drug candidates.

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