The growth factor/ cytokine midkine may participate to cytokine storm and contribute to the pathogenesis of SARS-CoV-2 infected patients

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Abstract

The current coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged in Wuhan, China and has rapidly become global challenges, creating major challenges to health systems in almost every country in the world it has turned into a pandemic. COVID-19 poses a risky clinical situation that can range from mild illness to severe respiratory failure requiring admission to intensive care. It is known to cause cytokine storm in some critically ill patients. However, more and more evidence showed that there is a dramatic increase in cytokine levels in patients diagnosed with COVID-19. Midkine (MK) is involved in various physiological and pathological processes, which some of them are desired and beneficial such as controlling tissue repair and antimicrobial effects, but some others are harmful such as promoting inflammation, carcinogenesis and chemo-resistance. Also, MK is expressed in inflammatory cells and released by endothelial cells under hypoxic conditions. Considering all this information, there are strong data that MK, an important cytokine known to increase in inflammatory diseases, may overexpressed in patients who are positive for COVID-19. The overexpression of MK reveals a picture leading to fibrosis in the lung damage. Therefore, questions arise about how the concentration of MK changes in CoVID-19 patients and can we use it as an inflammation biomarker or in the treatment protocol in the future.

1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (COVID-19), created an extremely important worldwide problem not only in health management, but also generate disturbances in societies economy, social and cultural structure (Zhu et al.,2020). Although, the majority of COVID-19 infected patients are asymptomatic or have "mild" symptoms, such as fever, fatigue and dry cough, some patients can progress to severe disease manifestations, including pneumonia, pulmonary edema, vascular hyper-permeability and acute respiratory distress syndrome (ARDS) (Huang et al.,2020). In addition, very seriously conditions such as respiratory failure, septic shock, multiple organ failure and even death occur in approximately 5% of patients (Williamson et al.,2020). In such seriously ill COVID-19 patients, the production of pro-inflammatory mediators and cytokines, including tumor necrosis factor alpha (TNF-α), interleukin (IL) 1 beta (IL-1β), IL-6, IL-18 and interferon gamma (IFN), are abnormally increased that result in a "cytokine storm", causing a diffuse alveolar damage (Gao et al., 2020; Ye, Wang & Mao 2020). Some symptoms attributed to these cytokines are fever, chills, headaches, dizziness and fatigue caused cytokines can contribute to severe pathologies such as cardiomyopathy, lung injury and septic shock.

Midkine (MK), a low molecular-weight growth factor (a heparin-binding cytokine), is strongly expressed during embryogenesis, whereas it is downregulated to relatively low levels in healthy adults (Kadomatsu, Tomomura & Muramatsu 1998). However, MK is overexpressed back in various pathologies, including inflammatory diseases and many malignancies (Weckbach, Preissner, & Deindl 2018; Filippou, Karagiannis,

& Constantinidou 2020). It is involved in several physiological and/or pathological cell functions, including survival, reproduction, repair and growth and has chemotactic activity as well as pro-inflammatory actions [Muramatsu 2014; Muramatsu 2010). Since the overproduction of pro-inflammatory mediators and cytokines play important role in the pathogenesis of COVID-19, we propose that besides other cytokines, MK may be also overexpressed in SARS-CoV-2 infection and participate to or modulate the course of COVID-19. MK has chemotactic actions, resulting in accumulation of inflammatory cells, such as macrophages and neutrophils, which in turn aggravate the inflammatory response (Takada et al., 1997). Additionally, in the context of COVID-19, that uses angiotensin-converting enzyme 2 (ACE-2) receptor for its clinical manifestations, MK activates angiotensin converting enzyme (ACE), leading to higher concentrations of Ang II, leading to impaired functions of the alveoli (Hobo et al., 2009). These and other pathophysiological functions of MK and the possible relationship to SARS-CoV-2 infection is discussed in this review.

2 | MAIN PATHOPHYSIOLOGICAL MECHANISMS INVOLVED IN COVID-19

2.1. | Inflammation and cytokine storm inSARS-CoV-2 infected patients

Actually, cytokines attend to normal immune response to infectious agents in healthy individuals. However, several pathogenic infections, including SARS-CoV-2, are often associated with an excessive cytokine release called as "cytokine storm", which result in tissue damage (Channappanavar & Perlman 2017). At the time by the binding of SARS-Cov-2 to ACE-2, that serves as a functional receptor for SARS-Cov-2, the immune system of patients become activated (Li et al., 2003; Matthay et al., 2019). This in turn, induce the accumulation of inflammatory cells with subsequent production of pro-inflammatory cytokines and chemokines at the infection area, which can also spread to many extra-pulmonary organs (Huang et al.,2020).

2.2. | Association and interaction between RAS and COVID-19

In physiological conditions, after the biotransformation of angiotensinogen to angiotensin I (Ang I) by renin, the ACE converts Ang I to angiotensin II (Ang II), which may contribute to inflammation, fibrosis, tissue damage and edema in the lungs. On the other hand, Ang II is converted by ACE-2 to angiotensin (1–7), which has anti-inflammatory and vasodilatory properties that balanced the effects of Ang II. However, in COVID-19, the SARS-CoV-2 interact with the RAS through ACE-2, that is necessary for the entry of the virus into pneumocytes as well as its replication (Li et al., 2003). Consequently, the expression of ACE-2 is downregulated by SARS-CoV-2, causing overactivation of renin-angiotensin-system (RAS) that result in increased pulmonary vasoconstriction, edema, hypoxia and lung damage in COVID-19 patients (Wan et al., 2020; Hoffmann et al., 2020).

2.3. | Τηε εφφεςτ οφ ηψποξια ανδ αςτιατιον οφ ηψποξια-ινδυςιβλε φαςτορ 1α (HIΦ-1α) ιν "Ο"ΙΔ-19

The lung, an organ exposed to high amount of oxygen is subject to various infections, including SARS-CoV-2. Due to fluid accumulation in the alveoli, as a result of SARS-CoV-2 invasion, the effectiveness of air exchange decreases dramatically, which then results in hypoxemia and subsequently ARDS (Lee 2017; Sarkar, Niranjan & Banyal 2017). This hypoxic effect of viral occupation contributes to several pathophysiological changes in the lung and is also involved in all stages of COVID-19. Hypoxia, a powerful inflammatory stimulant, is also induced in inflammatory conditions (Gonzalez & Wood 2010; Eltzschig & Carmeliet 2011; Fröhlich, Boylan & McLoughlin 2013; Minamino et al., 2001; Watts & Walmsley 2019). Besides leading to high amount of pro-inflammatory cytokines and creation of cytokine storm on the infection region, hypoxia triggered simultaneously several pathophysiological processes, including induction of hypoxia inducible factor-1α (HIF-1α). HIF-1α is expressed in certain cell types, including immune cells, and regulates cell metabolism and inflammation (Cramer 2003; Walmsley 2005). Under normal pressure of oxygen in blood stream, the expression of HIF-1α caused by phagocytic cells, such as neutrophils and macrophages, is low. However, in infection sites they increase HIF-1α expression, which in turn stimulates the expression of several pro-inflammatory cytokines (Nizet & Johnson 2009; Jahani, Dokaneheifard & Mansouri 2020). Owing to its pro-inflammatory properties, it has been suggested that inhibition of HIF-1α activity can reduce the SARS-CoV-2 related inflammation and relieves the severity of COVID-19 (Serebrovska, Chong, Serebrovska, Tumanovska & Xi).

2.4. | NETosis, oxidative stress, ROS and COVID-19

Several pathophysiological mechanisms occur simultaneously when SARS-CoV-2 binds to ACE-2 in lung. Primarily, monocytes recruited into the alveolar space secretes pro-inflammatory cytokines which is responsible for cytokine storm. Additionally, recruited macrophages releases also cytokines and chemokines, that augmented capillary permeability, pulmonary edema and followed by neutrophil recruitment. Increased neutrophil invasion leads to the release of neutrophil extracellular traps (NETs) that are intracellular contents such as DNA, histons and proteins. Several studies showed that this process, called NETosis, is associated closely with COVID-19 (Veras et al., 2020; Arcanjo et al.,2020). The excessive neutrophil degranulation precipitate lung injury and damage the alveolar-capillary barrier. In addition, NETosis is associated with increased levels of intracellular reactive oxygen species (ROS) of neutrophils (Reshi, Su & Hong 2014). ROS can destroy pathogens directly by causing oxidative damage as well as indirectly, by inducing pathogen elimination via NET formation in neutrophils (Nguyen, Green, & Mecsas 2017).

3 | POSSIBLE RELATIONSHIP BETWEEN COVID-19 PATHOGENESIS AND MK

MK is involved in various physiological and pathological processes, which some of them are desired and beneficial such as controlling tissue repair and antimicrobial effects, but some others are harmful such as promoting inflammation, carcinogenesis and chemo-resistance (Ikutomo, Sakakima, Matsuda & Yoshida 2014; Svensson et al., 2010; Kang et al., 2007). Although, animal models of myocardial infarction have shown a protective role of MK for the injured cardiac tissue by its anti-apoptotic effect and its role in angiogenesis (Takenaka et al., 2009; Sumida et al., 2010), most studies showed that MK is harmful under chronic inflammatory conditions (Maruyama et al., 2004).

MK is a cytokine with strong pro-inflammatory characteristics, causing macrophage and neutrophil recruitment to the inflamed region and interact with other growth factors and cytokines, particularly TNFα. Furthermore, MK mediates and exhibits enhancement of fibrinolytic activity, which are important processes in the initial stage of inflammatory responses of various pathologies. (Wang et al., 2008; Takada et al., 1997; Sato et al., 2001). The expression of MK is induced by TNFα, an important component of cytokine storm in COVID-19, and vice versa (Shindo et al., 2017). Therefore, it is highly possible that MK is contributed to the cytokine invasion and interact with other cytokines and chemokines in SARS-CoV-2 infections. This pro-inflammatory effect and subsequently occurring several pathophysiological processes, in that MK is involved, could be detrimental rather than protective.

In an animal study, it has been found that the expression of MK was induced in the lung endothelium of micro-vessels and alveolar-capillary endothelial cells by oxidative stress and upregulated by ACE, which hydrolyses Ang I to form Ang II. Ang II induced NADPH oxidase (Nox) expression, and the expression of Nox significantly increased, which initiated ROS production, induced further oxidative stress and subsequently accelerated MK and ACE generation (You et al., 2008). Hypoxia, resulting from cytokine storm, inflammation and other molecular mechanisms, including induction of hypoxia-inducible factor 1-α (HIF1-α), is an important component of SARS-CoV-2 infection (Taniguchi-Ponciano et al., 2021; Jahani, Dokaneheifard & Mansouri 2020). It has been shown that MK expression increased during hypoxia by the binding of HIF1-α to hypoxia-responsive elements located in the MK promoter (Reynolds et al., 2004). MK expression is also significantly increased in response to HIF-1α in nonsmall-cell lung carcinoma cells, which is important in the progression and metastasis of these cells (Hobo et al., 2009). These findings suggest that a close relationship exist between MK, hypoxia and HIF1-α, by enhancing each other's pathophysiological effects.

An important issue of COVID-19 is the development of ARDS, a result that may cause severe pulmonary injury and even death. Several studies demonstrated that MK is closely involved in the pathogenesis of ARDS. To clarify the possible role of MK signaling pathway in ARDS, Zhang et al., showed that exposure to mechanical stretch of lung epithelial cells led to an epithelial–mesenchymal transition profile associated with increased expression of ACE which was attenuated by silencing MK. Furthermore, they found out that the plasma levels of MK were higher in patients with ARDS than healthy subjects (Zhang et al., 2015). Similarly, in idiopathic pulmonary fibrosis patients, the serum MK level was also higher compared to healthy subjects,

supporting the role of MK in the development of ARDS (Misa et al., 2017). Moreover, in midkine-deficient mice, low expression of collagen and α-smooth muscle actin, as well as a low value for the pathological lung fibrosis score was detected. Thus, MK participate to the progression of pulmonary fibrosis, mainly by regulating inflammatory cell migration into the lung and augmenting TNF-α and tumor growth factor β (TGF- β) expression.

4 | CONCLUSION REMARKS

Current clinical observations indicate that SARS-CoV-2 infection can range from an unapparent non-symptomatic infection, to severe pulmonary damage and multi-organ failure. The excessive secretion of several cytokines is closely related to the development of clinical symptoms in COVID-19 patients. This abnormal and uncontrolled production of cytokines has been observed in most of the patients with SARS-CoV-2 related pneumonia, increasing the progression of COVID-19 and mortality. Furthermore, overproduction of inflammatory cytokines contributes to acute lung injury and ARDS. Therefore, to improve the outcome and reduce mortality of SARS-CoV-2, cytokine monitoring is recommended for the diagnosis and treatment of COVID-19.

MK, which is a cytokine and growth factor and is significantly upregulated upon exposure to various harmful stimuli, including inflammation, is likely to accompany the cytokine attack that occurs in SARS-CoV-2 infections. Thus, among the many alternative treatment strategies targeting cytokines (e.g. inhibition of TNFα or IL-6), drugs that suppress the generation and / or action of MK or, better still, prevent the effects of a broad spectrum of "harmful" cytokines may be a useful part of therapeutic modalities applied in the management of COVID-19.

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