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Intricate relationship between SARS-CoV-2–induced shedding and cytokine storm generation: A signaling inflammatory pathway augmenting COVID-19

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), through its ability to induce cytokine release syndrome, can set up a generalized inflammatory response together with activating multiple inflammatory pathways, which contributes to a dramatic increase in the number of mortalities and morbidities worldwide. Reportedly, the manipulative nature of coronavirus disease 2019 (COVID-19), which targets the immune system, often focuses on specific inflammation-related pathways, usually confined to interleukins and tumor necrosis factor-α (TNF-α), with a great emphasis on therapeutic approaches targeting the inhibition of these inflammatory mediators. The involvement of a disintegrin and metalloprotease 17 (ADAM-17) and matrix metalloproteinase-9 (MMP-9) in the pathogenesis of COVID-19, through their ability to potentiate the cytokine storm during an episode of SARS-CoV-2 infection, often goes unnoticed. In this review, the intricate relationship between ADAM-17 and MMP-9 together with angiotensin-converting enzyme 2 (ACE-2) as the main target for SARS-CoV-2 is highlighted in detail through a compilation of evidence-based literature; thus, we shed light on a proposed inflammatory pathway that COVID-19 may exploit to provoke an inflammatory response of a complex nature. Conclusively, our proposed mechanism acts as a means to developing a therapeutic approach aimed at modulating the intricate communication between ADAM-17 and MMP-9, where a great emphasis on the role of ACE-2 shedding and subsequent elevation in angiotensin II (Ang-II) levels is crucial to understanding the awry inflammatory response in patients with COVID-19. From this concept, designing a therapeutic strategy targeting multiple inflammatory mediators and enzymes simultaneously is another approach to unravel this global pandemic.

1. Introduction

SARS-CoV-2 is the seventh coronavirus to emerge as a causative agent of the unique upper respiratory tract infection in humans. SARS-CoV-2 together with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) can cause severe respiratory complications, whereas the other human coronaviruses, such as HKU1, NL63, OC43, and 229E, are associated with milder consequences [1]. COVID-19 pathogenesis brings forth fatal consequences globally with an increasing rate of mortalities across the globe [2]. Patients infected with SARS-CoV-2 show high infiltration of neutrophils and pro-inflammatory cytokines together with severe pneumonia and ground-glass opacities [3]. Interestingly, studies on COVID-19 often focus on inflammatory pathways, mediators, and therapeutic approaches targeting traditional instigators of inflammation [4]. The association of ADAM-17 with ACE-2 shedding and an elevated TNF-α level in patients with COVID-19 brings out the involvement of ADAM-17 in the pathogenesis of COVID-19 [5]. Together with cytokines, chemokines, and interleukins, matrix metalloproteinases (MMPs), especially MMP-9, contribute pivotally to cytokine storm by potentiating its destructive consequences [6,7]. Understanding the dynamics of cytokines is critical in comprehending the pathological basis of this syndrome [8]. An infamous consequence of cytokine storm is acute lung injury [9]. Acute lung injury is best translated into an acute respiratory distress syndrome (ARDS) characterized by exponentially elevated levels of TNF-α and its faithful companion IL-1, both of which are responsible for igniting the systemic response [10]. Of recognized significance is the ability of this inflammatory syndrome to generate generalized signs of hypotension, hypoperfusion, fever with increased heart rate, and altered mental status [11]. The cytokine storm characterizing COVID-19 is the main contributor to ARDS in patients infected with SARS-CoV-2 [12], where TNF-α expression, being highly elevated in ICU patients, plays a key role in predicting the acuity of the cytokine storm of COVID-19 [13]. Another prominent contributor to this storm in patients with COVID-19 is Ang-II, with its intrinsic ability to induce the enzymatic activity of ADAM-17, leading to an increase in TNF-α level, which together with shedding multiple other epidermal growth factors, results in increased NF-κB activity [14]. On the other side, MMP-9 had been as-

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signed as an early indicator of respiratory failure in COVID-19 patients [15], being highly expressed in COVID-19 with its ability to potentiate the inflammatory response [16]. Highlighting the intricate role of ADAM-17 and MMP-9 in the pathogenesis of the cytokine storm related to COVID-19 is pivotal to lessening the self-generated collateral damage during an incidence of SARS-CoV-2 infection and to understanding the signaling pathways that are implicated in the pathogenesis of COVID-19.

2. Historical background of ADAM-17 and MMP-9

2.1. Structure, origin, and biological role of ADAM-17

ADAM-17 is a membrane-bound zinc endopeptidase, and its active site region is similar to that of the MMP family of enzymes. Black et al. (1997) were among the first researchers along with Moss et al. (1997) to report the novelty of ADAM-17 [17]. Before that, and specifically in 1994, a study postulated the presence of a particular endopeptidase that is responsible for the shedding of TNF-α. The endopeptidase's function, if inhibited, would pave the way to a new approach against inflammatory conditions with a revolutionary jump within the field of therapeutics [18]. Shedding of trans-membrane or membrane-bound proteins is the main function of ADAM-17. According to this biological role, ADAM-17 is related to a family of enzymes known as sheddases. Sheddases, also called secretases, are a group of enzymes with a common functional role, which is the cleavage of cell membrane proteins–either receptors or functional proteins–to liberate a soluble free ectodomain with intrinsic activity [17]. A diverse list of molecules can undergo shedding, and one of the most important substrates to the shedding process is ACE-2, a target of the novel SARS-CoV-2 [19].

2.2. Structure, origin, and biological role of MMP-9

Early studies reported the generation and secretion of a gelatinase, or a metalloproteinase, by inflammatory cells, including neutrophils and macrophages, which potentiate the destruction of the extracellular matrix during an inflammatory episode [20]. In 1989, MMP-9, which is also known as the 92 kDa gelatinase/collagenase, or gelatinase B, was first characterized. The complete structure of this protease was introduced and demonstrated to be synthesized as a preproenzyme with a 78,426 molecular mass containing a 19-amino-acid-long signal peptide and secreted as a 92,000 glycosylated proenzyme, which in turn undergoes cleavage of 73 amino acids from its NH_2 terminus region, releasing an active form of MMP-9 capable of digesting type IV and type V collagens [21]. MMP-9 is secreted from a vast number of cells, including monocytes, activated macrophages, early trimester trophoblasts, fibroblasts, and mammary epithelial cells together with tumor cell lines. In addition, epidermal growth factor, interleukin-1β, and TNF-α can induce the production of this collagenase [22]. MMP-9 is a matrix metalloproteinase and is considered the largest and the most complex member of the zinc-dependent, extracellularly acting endopeptidases [23].

3. General role of ADAM-17 and MMP-9 in inflammatory responses and cytokine storm generation

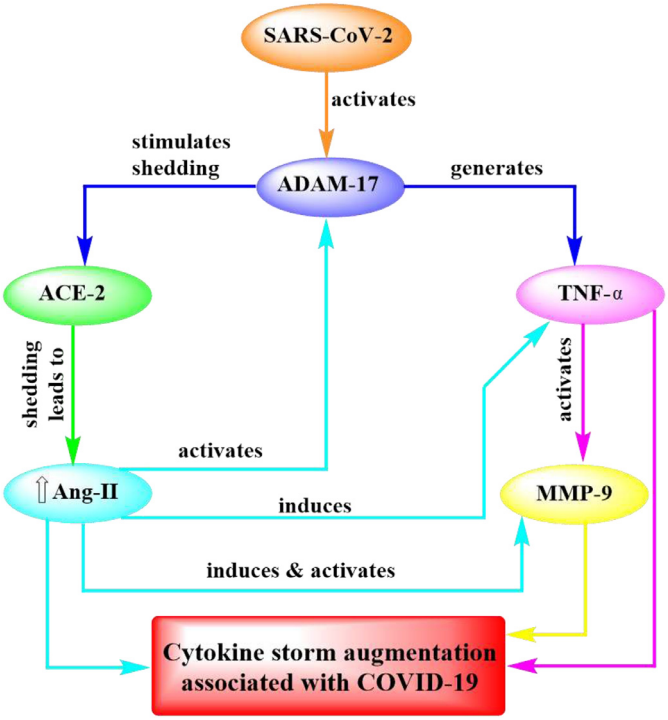
The functional release of TNF-α is a fundamental role of ADAM-17 to date, making it a potential therapeutic target [18]. TNF-α is a pleiotropic inflammatory mediator produced by several cells of the immune system to regulate a wide variety of immune responses. Two related entities of this cytokine have been reported to play distinct roles: a soluble form, known as sTNF-α, and a membrane-bound form, known as mTNF-α [24]. TNF-α is made of 157 nonglycosylated amino acids following proteolytic cleavage of the membrane-bound form, which is made of 233 amino acids [25]. There are two type I membrane receptors with which TNF-α interacts to generate its biological and pathological responses; these cell surface receptors are identified as TNFR-1 (p55/p60) and TNFR-2 (p75/ p80) [24]. It was clearly evident that the level of the endogenously produced TNF-α is a detrimental factor in its benefit to risk resonance. Numerous trivial signs and symptoms of inflammatory conditions that were once thought to be physiologically normal were found to be induced by TNF-α release; now, it is clearly established that this pivotal cytokine is the mediator behind what is known as a systemic inflammatory response syndrome [26]. It is the field of inflammatory conditions and immunity within which TNF-α shines the most with its ability to manage a wide array of cytokines and inflammatory mediators involved in an inflammatory event [27]. Of significant importance is the relation between TNF-α and the current COVID-19 situation [28]. TNF-α plays a central role in mediating the cytokine response required to initiate and potentiate the inflammatory response in the lungs [26], which leads to increased accumulation of pulmonary inflammatory fluid and vascular permeability [29], together with its malevolent ability to induce a generalized systemic inflammatory response by leaving the primary site of infection acting as a messenger to inflammation through the blood [30]. Also, it has been found that TNF-α solely can induce an inflammatory pattern characteristic of several diseases of the lungs and hence can be expected to be the principal instigating cytokine of lung injury in multiple histopathological examinations of different airway diseases [31]. The expression of TNF-α has been found to be increased during lung injury, where it provokes a variety of biological responses to modulate the anomaly by inducing the expression of numerous other inflammatory mediators, which is a key step consisting of stimulating multiple genes involved in protective processes [32]. It was noticed that patients with COVID-19 demonstrated significantly elevated levels of TNF-α upon admission to hospitals [33]. Such an alarming conclusion prompted the medical field to investigate the ability of antitumor necrosis factor therapies to control the awry immune response triggered by SARS-CoV-2 [34]. With the ability of SARS-CoV-2 to induce the shedding of ACE-2 through the activation of ADAM-17, increased generation of TNF-α is expected; treatments targeting the antagonism of this cytokine seem to be lacking the required attention [5], although the immunosuppressant adalimumab seems to be the first medication to be trialed against this cytokine [35].

In another context, neutrophils are considered a key source in synthesizing MMP-9 to be deployed during an event of inflammatory reaction following storage in specific intracellular granules [36]. Surprisingly, reactive oxygen species (ROS), which are released during a pathological process, can increase the collagenolytic activity of MMP-9, and hence an episode of oxidative stress driven principally by H_2O_2 can potentiate extracellular matrix degradation [37]. Furthermore, inflammatory mediators and cytokines produced and activated during an episode of inflammation, such as IL-1 and TNF-α, constitute a principal pathway to MMP-9 expression and activation together with a remarkably concomitant increase in gelatin degradation as shown by gel-zymography [38]. The pivotal role of this enzyme within the immune system is often unclear; thus, it was proven to have a key role in cytokine regulation and recruitment together with being critically involved in potentiating the inflammatory response upon induction in the lungs [39]. The capability of MMP-9 to degrade the extracellular matrix, releasing multiple components such as alarmins, including heparin and fibronectin, which are considered chemotactic and immune-activating proteins, contributes significantly to the undesirable effects of the cytokine storm [40]. It was found that neutrophils, upon stimulation by TNF-α, rapidly release MMP-9 by degranulation into the surrounding media, magnifying the inflammatory actions of the cytokine storm [6]. TNF-α and MMP-9 are interrelated, and it seems that both of these stimulate the release of the other during an immune response [41]. The MMP-9–dependent cytokine storm, which is induced by the production of plasmin and the generation of TNF-α during an acute episode of graft versus host disease, demonstrates conclusive evidence of how critical these mediators are in navigating the storm [42]. The involvement of MMP-9 in the medical condition of multi-organ dysfunction syndrome generates further interest in the role of MMP-9 regarding fueling excessive inflammatory responses [43]. It seems that MMP-9's contribution to inflammatory reactions and

responses is behind the pathological outcomes of many diseases, making it a vital therapeutic target [44].

4. Relationship between ADAM-17, MMP-9, and ACE-2 as a proposed mechanism augmenting the cytokine storm of COVID-19

ACE-2 is a zinc metalloprotease and a strict carboxypeptidase, which differs from its first homologue, angiotensin-converting enzyme (ACE), by its ability to cleave a C-terminal single amino acid [45]. ACE-2 plays a critical role in regulating numerous physiological events, including those of the cardiovascular system, the immune system, and the respiratory system [46]. The role of ACE-2 in the renin-angiotensin system (RAS) is of prodigious significance [45]. ACE-2 catalyzes the formation of highly critical vasodilator peptides, including angiotensin 1–7 (Ang 1–7), thus, counterbalancing the potent vasoconstrictor effects of Ang-II. Also, the balance between ACE and ACE-2 is essential for the proper functioning of the RAS [46] because a downregulation or loss of ACE-2 expression is directly related to significantly elevated Ang-II levels [47]. Ang-II has a major vasoconstrictive hypertrophic role in the pathogenesis of vascular remodeling and hypertension; it is responsible for increasing blood pressure and inducing vascular endothelial injury through its ability to generate ROS, leading to vascular inflammation. Ang-II is strongly associated with inflammation and macrophage-induced oxidative stress [48]. The actions of Ang-II are mediated by two receptors of opposite activities upon stimulation, which are Ang-II receptor type 1 (AT1) and Ang-II receptor type 2 (AT2). AT1 receptors are responsible for the hostile actions of Ang-II, representing inflammation and vasoconstriction with hypertensive reaction, whereas AT2 counterpart receptors compensate for those actions mediated by AT1 activation through nitric oxide (NO) release and reduction of platelet aggregation [49]. The magnitude through which this mediator contributes to inflammation can extend into a deeper level of inflammatory interaction through AT1 receptor binding, leading to transcriptional factors production followed by a release of chemokines and adhesion molecules together with the large participation of ROS [48]. It seems that this mitogen initiates a burst of inflammatory mediators characterized by cytokine and chemokine production combined with the ability of Ang-II to induce a leukocyte-mediated pro-inflammatory effect. The production of ROS seems to lessen NO bioavailability with subsequent endothelial damage. Moreover, Ang-II interrupts insulin signal transduction, hindering the anti-inflammatory actions of insulin [49]. Moreover, the effect of Ang-II on the transcription level of NF-ϰB showed that levels of this inflammatory inducer are highly increased upon stimulation of both effecter receptors, AT1 and AT2—more specifically AT1 [48].. The ability of Ang-II to stimulate the production of pro-inflammatory cytokines, such as TNF-α, seems to be in great alliance with MMP-9 induction and activation [49]. In addition, the capacity of Ang-II to activate MMP-9 in a direct fashion constitutes a synergistic pathway to that of Ang-II–mediated TNF-α induction [50]. It was noticed that patients with COVID-19 exhibit significantly elevated levels of Ang-II [51], which were found to be linear with viral load and lung injury [52], together with its intrinsic ability to exaggerate the inflammatory profile that is characteristic of COVID-19 [53]. Ang-II plays an important role during an event of acute lung injury. Following an acute episode of an injurious pulmonary situation, this mediator arises to initiate pro-collagen production with a fibrotic response via the release of transforming growth factor-β (TGF-β) [54]. In addition, an interesting study revealed that Ang-II induces the expression of hypoxia-inducible factor (HIF-1), which is expressed normally during an episode of hypoxia, together with generating a hypertrophic pulmonary arterial smooth muscle response [55]. The functions of ACE-2 within the respiratory system are of great importance, and the imbalance that results from impaired ACE-2 can lead to fatal complications [56]. ACE-2 can undergo ectodomain shedding as a function of extracellular substrate interactions, including a viral binding to the ectodomain region of the receptor that initiates an intracellular signaling reaction to modulate gene expression and regulate the number



Scheme 1. ADAM-17–induced shedding of ACE-2 together with the anticipated elevated levels of TNF-α as a result of SARS-CoV-2–induced activation of ADAM-17 will substantially increase the levels of Ang-II. The synergistic increase in the levels of Ang-II and TNF-α will induce the expression and activity of MMP-9 in addition to the intrinsic ability of Ang-II to induce the activation of ADAM-17. The intricate relationship between ADAM-17, MMP-9, and ACE-2 will be detrimental to the magnitude of the cytokine storm in COVID-19.

of expressed ACE-2 receptors on the cell surface. This results in the release of two soluble forms of equivalent enzymatic activity known as the large soluble form and the small soluble form [57]. Considering the striking similarity between SARS-CoV and SARS-CoV-2 when it comes to spike protein sequence and target binding affinity [58], it is highly likely that the novel strain's binding to ACE-2 will result in downregulation of its expression and cell-surface translocation as an outcome of its internalization following cell-surface interaction [59]. It was found that shedding and downregulation of ACE-2 following viral interaction with the receptor is actually due to ADAM-17, which is induced to initiate the release of a soluble form of ACE-2 detectable in plasma and hence, enhancing its clearance from the cell surface [60]. In contrast to ACE, ACE-2 is considered a substrate for the sheddase ADAM-17 [57]. Numerous studies have demonstrated the relationship between ACE-2 shedding and ADAM-17 as a principal enzyme of this physiological phenomenon, which if imbalanced, can result in pathological outcomes. Overshedding and downregulation of ACE-2 are reportedly linked to lung injury and respiratory pathological conditions [61]. The relation between MMP-9 and the vasoconstrictive peptide Ang-II, which is known to have a potential role in gene expression, was established following the conclusive evidence that NF-ϰB activation in response to the interaction between Ang-II and its receptor AT1 results in the activation of multi-intracellular pathways with subsequent upregulation of MMP-9 at the transcriptional level [62]. An important role was assigned to TNF-α when it comes to modulation of MMP expression. It was reported that this cytokine, in a dose and time-dependent manner, can increase the expression of MMP-9 [63]. In an optimum respiratory condition, the expression of MMP-9 is tightly restricted and thus, presents itself in very low numbers. Such restricted presentation is highly altered in the event of respiratory inflammation, where numerous cells confined to the respiratory space contribute to MMP-9 secretion and expression and

hence, tissue injury [64]. MMP-9, which is the major proteinase responsible for airway tissue remodeling, acts principally by potentiating the migration of eosinophils and neutrophils across basement membranes; infiltrating ovalbumin, which contributes to airway inflammation; and inducing airway hyperresponsiveness [65]. Furthermore, it was demonstrated that MMP-9 is the predominant MMP presenting during an event of an asthmatic episode, with its expression being highly enhanced during an acute inflammatory response [66]. Acute lung injury and ARDS are of high importance among the wide spectrum of respiratory conditions, and MMPs are indispensable in their generation and progression by contributing to alveolar cell injury and basement membrane degradation [67]. A biomarker of pulmonary inflammation, known as neutrophil elastase (NE), had been linked to MMP-9. It is a potent inflammatory protease that is highly involved in the process of respiratory tissue remodeling and degradation through activating MMP-9 as a main inflammatory mediator contributing to pathological findings [68]. Cytokines and chemokines interact intensely with MMP-9, where it cleaves IL-8 into a 10-fold more potent derivative and participates in the generation process of TNF-α and TGF-β active forms in addition to its ability to release IL-1β from its inactive proform. It seems evident that neutrophils, with their ability to secrete their internally stored MMP-9, are a major causative factor for tissue destruction taking place during an episode of infectious disease or respiratory distress syndrome [69]. Also, it seems that a decrease in ACE-2 expression is strongly related to an increase in MMP-9 activity [47]. The intricate relationship of ADAM-17, MMP-9, and ACE-2, along with the contribution of TNF-α and Ang-II to their activation and expression and hence, augmentation of the cytokine storm generated during COVID-19, is detailed in scheme 1.

5. Conclusion

As a biological target, ACE-2 naturally undergoes shedding by ADAM-17, but such shedding as a regulatory process seems to be exploited by the novel SARS-CoV-2. It was established that during a SARS-CoV-2 infection cycle, the virus interacts with ACE-2 as a target receptor to cell entry. Such interaction leads to internalization of the target receptor together with an additional overlooked mechanism, which is the activation of ADAM-17. This leads to multiple consequences, with the shedding of ACE-2 and mTNF-α being a prominent outcome. Thus, a rise in the level of the inflammatory metabolite of ACE-2, which is Ang-II, with sTNF-α being generated simultaneously will activate MMP-9, leading to further destructive inflammatory outcomes. Hence, a cytokine storm of hazardous magnitude is set to occur with greater overall collateral damage. Further studies focusing on the activation of ADAM-17 and MMP-9 by SARS-CoV-2 together with the introduction of selective inhibitors of these two target enzymes as a therapeutic strategy should be foregrounded. Thus, the shedding process of ACE-2 and mTNF-α would be relatively suppressed and better control of the serum levels of Ang-II and sTNF-α consequently achieved. Expectedly, the controlled rise in the level of these inflammatory mediators will have a positive therapeutic effect, with the main target being the cytokine storm of COVID-19.

Declaration of Competing Interest

The authors declared no conflicts of interest. No funding was received for this study.

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