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Journal of Cellular Signaling Commentary

Ectodomain Shedding May Play a Pivotal Role in Disease Severity in COVID-19

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Ectodomain shedding mediated by a disintegrin and metalloprotease 10/17 (ADAM10/17) modulates the function of immune effector cells and may be involved in the novel coronavirus disease COVID-19. Toll-like receptor 7/8 (TLR7/8) recognizes single-strand RNA from viruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the virus that causes COVID-19) during the innate immune response [1], and TLR7/8 agonist activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to generate reactive oxygen species (ROS) [2]. ADAM10/7 was found to mediate ectodomain shedding to modulate immune responses [3] and to be activated by ROS [4]. These findings suggest that SARS-CoV-2 contributes to and induces ectodomain shedding, which may be associated with disease severity. In patients with COVID-19, studies found a higher blood concentration of the chemokine fractalkine [5]. Cell membrane-bound angiotensin-converting enzyme 2 (ACE2) has been identified as a binding site and entry receptor for the spike protein of SARS-CoV-2. After the

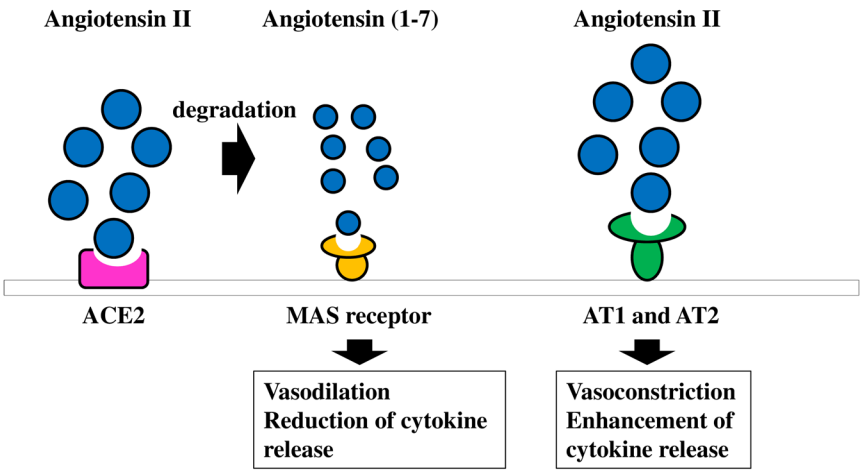

Figure 1: The role of Angiotensin-converting enzyme 2 (ACE2) degrades angiotensin II to angiotensin (1-7). Angiotensin II binds to angiotensin II type 1 and 2 receptors (AT1 and AT2), leading to vasoconstriction, but angiotensin (1-7) binds to the MAS receptor, leading to vasodilation. Furthermore, the angiotensin II/AT1/AT2 axis enhances cytokine production, whereas the angiotensin (1-7)/MAS receptor axis reduces cytokine secretion. The G-protein-coupled receptor MAS acts as an antagonist of AT1. Taken together, these mechanisms show how ACE2 regulates overproduction of cytokines (the so-called cytokine storm) through AT/angiotensin II pathway signaling.

Abbreviations: ACE: Angiotensin Converting Enzyme; AT1: Angiotensin II Type 1 receptor; AT2: Angiotensin II Type 2 receptor; COVID-19: Coronavirus Disease 2019; MAS receptor: MAS proto-oncogene -related G-protein-coupled receptor.

virus binds to ACE2, ACE2 is internalized; ACE2 shedding also is mediated and enhanced by ADAM10/17 [6,7]. ACE2 deficiency increases expression of fractalkine [5,8]. ACE2 catalyzes and degrades angiotensin II, leading to the production of angiotensin 1-7, which binds to the angiotensin 1-7 (MAS) receptor and acts as a vasodilator (Figure 1). Indeed, binding of SARS-CoV-2 to ACE2 leads to ACE2 deficiency, which potentiates angiotensin II activity. Excess angiotensin II then activates NF-κB through the angiotensin type 1 receptor (AT1) and type 2 receptor (AT2) signaling pathway to enhance cytokine production (Figure 2). This mechanism explains how COVID-19 induces a cytokine storm [9]. Most importantly, angiotensin II activates NADPH oxidase to generate ROS [10], ie, superoxide (O_2^-) and hydrogen peroxide (H_2O_2). In cells stimulated with interleukin-1β (IL-1β), the angiotensin II/AT1 and AT2 axis augments expression of inducible nitric oxide synthase (iNOS) to generate nitric oxide (NO) [11]; NO reacts with the peroxidase domain of the enzyme dual oxidase 2, which has both a peroxidase domain and an NADPH oxidase domain, to produce the strong biological oxidant agent peroxynitrite ($ONOO^-$). Both H_2O_2 and $ONOO^-$ contribute to enhanced activation of ectodomain shedding by ADAM10/17. The fractalkine receptor CX3CR1 is highly expressed by macrophages, and soluble fractalkine shed from cells because of cleavage by ADAM10/17 activates macrophages to cause a hyperinflammatory response. SARS-CoV-2 also induces cytotoxic $CD8^+$ T cells to produce perforin and granzyme B, which show aberrant hyperactivation and target cell killing [12]. CX3CR1 is expressed by these cytotoxic $CD8^+$ T cells, and fractalkine acts as a chemoattractant for them. Taken together, these findings indicate that ectodomain shedding may be closely associated with severity of COVID-19.

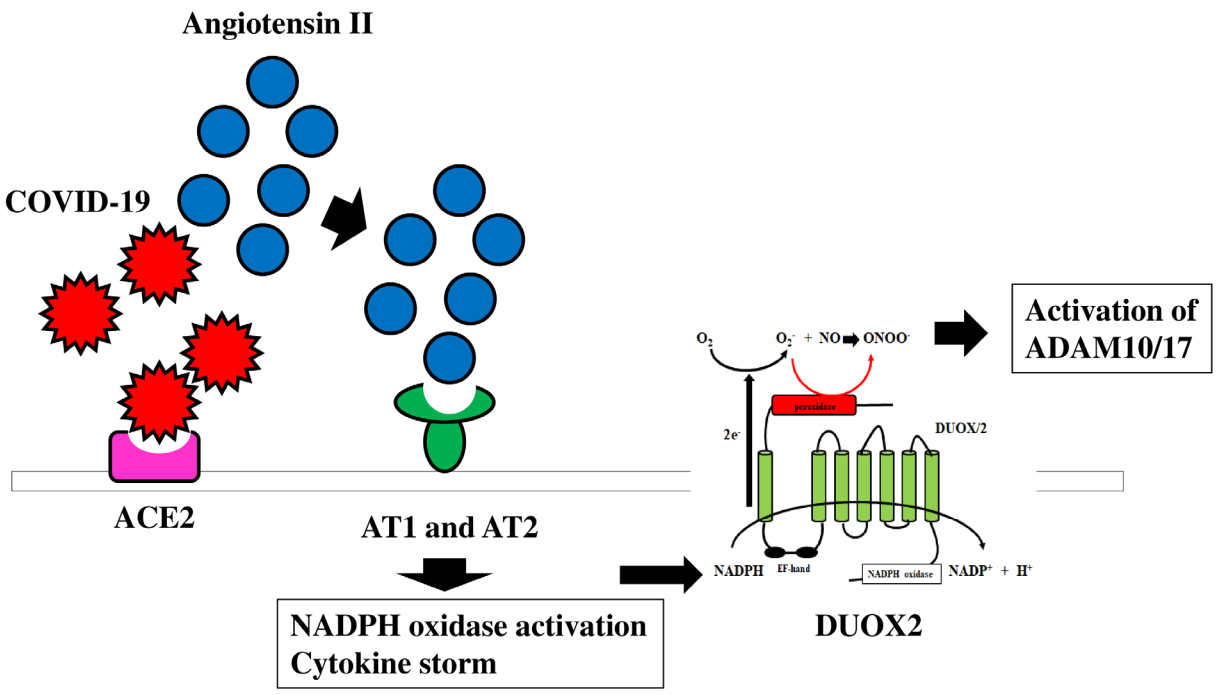

Figure 2: Possible mechanism by which severe acute respiratory syndrome coronavirus 2 causes cytokine storm through binding to angiotensin-converting enzyme 2. Severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease 2019, binds to angiotensin-converting enzyme 2. As a result, most angiotensin II is not degraded; the excess angiotensin II stimulates angiotensin type 1 and 2 receptors (AT1 and AT2, respectively), leading to a cytokine storm. The angiotensin II/AT1/AT2 axis reacts with dual oxidase 2 to activate nicotinamide adenine dinucleotide phosphate oxidase to induce superoxide (O_2^-) and generate hydrogen peroxide (H_2O_2). Most importantly, angiotensin II activates nitric oxide synthase and induces nitric oxide production. Peroxidase reacts with NO to generate peroxynitrite ($ONOO^-$). Together, H_2O_2 and $ONOO^-$ induce activation of a disintegrin and metalloprotease 10/17 (ADAM10/17) for ectodomain shedding.

Abbreviations: ACE: Angiotensin Converting Enzyme; ADAM: A Disintegrin and Metalloproteinase domain-containing protein; COVID-19: Coronavirus Disease 2019; AT1: Angiotensin II Type 1 receptor; DUOX: Dual Oxidase; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; NOS: Nitric Oxide Synthase; NO: Nitric Oxide

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