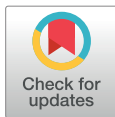Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

LETTER TO THE EDITOR

Response to: Bioactive Lipids and Coronavirus (COVID-19)-further Discussion

To the editor,

I appreciate the interest shown by Sora Yasri, and Viroj Wiwanitkit on my proposal that bioactive lipids can inactivate Coronavirus (COVID-19) and thus, may be of significant clinical benefit (1). The following are the likely actions of bioactive lipids with specific reference to Coronavirus (COVID-19).

COVID-19 and ACE2

COVID-19 uses angiotensin-converting enzyme 2 (ACE2) and the cellular protease transmembrane protease serine 2 (TMPRSS2) to enter the target cells. The spike glycoprotein (S protein) of COVID-19 is needed to mediate receptor recognition and facilitate membrane fusion. The S protein is cleaved during the COVID-19 infection into S1 and S2 subunits. S1 contains the receptor binding domain (RBD) that binds to the peptidase domain (PD) of ACE2, whereas S2 is needed for membrane fusion. The ectodomain of the SARS-CoV-2 S protein binds to the PD of ACE2 (2). ACE2 is a type 1 integral membrane glycoprotein that is expressed and active in most tissues and its highest expression is observed in the kidney, the endothelium, the lungs, and in the heart.

The renin-angiotensin system (RAS) is a modulator of vascular function and is needed for regulation of blood pressure, natriuresis, and blood volume control. RAS is needed for regulating regional renal blood flow. The RAS has a number of different regulatory components and effector peptides to facilitate the dynamic control of vascular function (Figure 1). Angiotensin I (Ang I) is metabolized by angiotensin-converting enzyme (ACE) to form angiotensin II (Ang II) that is metabolized by ACE2 to produce angiotensin (2−8) (Ang 1−7), a vasodilator. Though the focus has been on ACE and Ang II, recent studies showed that ACE2 is needed to maintain the balance of the RAS. Acquired or genetic deficiency of ACE2 leads to an increase in tissue and circulating levels of Ang II and reduced levels of Ang 1−7. Thus, ACE2 controls vasoconstriction and blood pressure. Alternatively, reducing ACE activity can lead to a reduction in the circulating levels of Ang II that suppresses the necessity of ACE2. SARS-CoV-2 (COVID-19) leads to downregulation of the ACE2 receptor, but not ACE, through binding of the spike protein with ACE2. It is noteworthy that bioactive lipids inhibit the activity of ACE (3) and thus, may indirectly suppress the expression of ACE2 leading to reduction in the availability of ACE receptors to SARS-CoV-2 (COVID-19) to bind to enter the target cell. The other possibility is that bioactive lipids can get incorporated into the cell membrane phospholipids and alter the membrane fluidity that, in turn, changes the expression of receptors both their number and affinity to the respective proteins (4−6). Thus, it is proposed that supplementation of bioactive lipids can possibly, suppress ACE2 expression and decrease the affinity of SARS-CoV-2 (COVID-19) to ACE2.

Bioactive Lipids and Imunocytes

Bioactive lipids can induce leakage and lysis of microbial cell membranes, disrupt viral protein envelopes, inhibit respiratory activity, interfere with transportation of amino acids, and uncouple oxidative phosphorylation (7−10). Alveolar macrophages, leukocytes, T and B cells, NK cells and other immunocytes can release AA and other unsaturated fatty acids to inactivate SARS-CoV-2 (COVID-19), SARS and MERS, which are all enveloped viruses. It is possible that the ability of immunocytes to release bioactive lipids could be one of the fundamental innate immune response mechanisms needed to protect from various infections. Thus, failure of these immunocytes to secrete adequate amounts of bioactive lipids to inactivate various microbes including Coronary virus (COVID-19) may render a person more susceptible to infection. It has been shown that alveolar macrophages and other immunocytes in the lungs release bioactive lipids into the alveolar fluid and surrounding tissues to bring about their antimicrobial action (11,12). In this context, the work of Juers JA, et al. (12) in noteworthy. It was reported that alveolar macrophages do not kill *in vitro* unless the microorganisms have been incubated with alveolar lining material before phagocytosis. The factor that enhanced the microbicidal capacity of alveolar macrophages was found to be present in the lipid fraction of the alveolar lining material, which could be one of the bioactive lipids. These results imply that there is a close interaction/crosstalk between alveolar lining material and alveolar macrophages. This is further supported by the observation that activated macrophages release bioactive lipid to kill tumor cells (13).
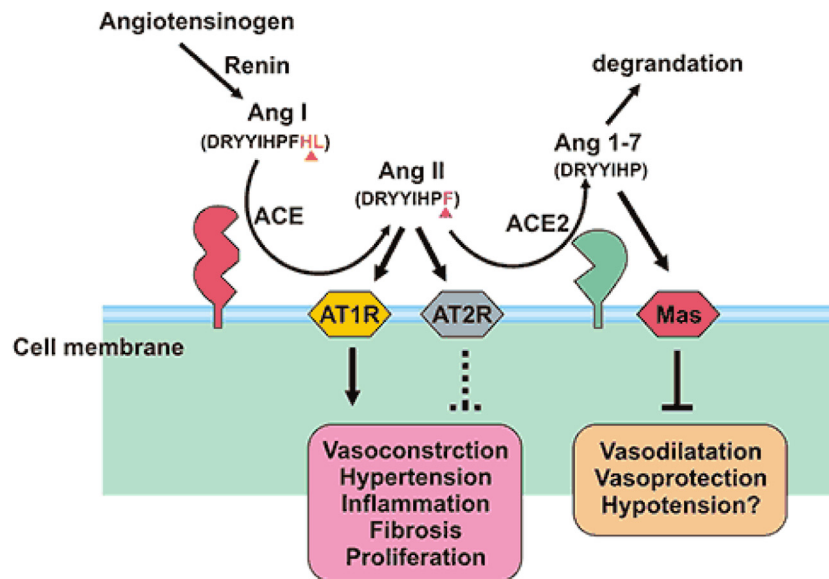
Figure 1. ACE2 has a strong affinity for type 1 and type 2 receptors of Ang II and regulates blood pressure, humoral balance, inflammation, cell proliferation, hypertrophy, and fibrosis. ACE2 may play a role in regulating cardiovascular and renal functions and fertility. ACE2 is a suppressor of renin-angiotensin system (RAS). ACE catalyzes angiotensin I (AngI) to convert to the potent vasoconstrictor angiotensin II (AngII), whereas ACE2 cleaves Ang I to produce inactive angiotensin 1-9 peptide (Ang 1-9). Ang 1-9 is converted to angiotensin 1-7 (Ang 1-7) by ACE. ACE2 hydrolyzes AngII to Ang (1-7), and the efficiency of hydrolyzing AngII is 400 times than that of AngI. It suggests that ACE2 mainly generates Ang 1-7 by hydrolyzing AngII. Furthermore, Ang 1-7 acts on the Mas receptor to exert cardiovascular protection of diastolic blood vessels, anti-inflammatory, anti-proliferation, anti-fibrosis, anti-alveolar epithelial cell apoptosis, and anti-oxidative stress, thereby antagonizing the biological effects of Ang II. The ACE/AngII/AT1R axis and the ACE2/Ang 1-7/MAS axis balance each other.

The ability of various immunocytes (NK cells, cytotoxic tumor lymphocytes: CTL cells, lymphokine activated killer cells, dendritic cells, leukocytes, etc.,) to release cytotoxic molecules such as perforin and granzyme, cytokines IL-6, TNF-α, and IFN-γ is needed to kill tumor and infected cells. It is noteworthy that NK cells and CTLs induce apoptosis of tumor cells even when perforin, granzyme pathway is inactivated and is dependent on the expression of soluble phospholipase A2 (sPLA2) (14). This suggests that one additional mechanism by which NK cells and CTLs, even if do not secrete perforin and granzyme, induce apoptosis of tumor cells and those that harbor intracellular microbes is by activating sPLA2. It is likely that perforin and granzyme may have the ability to activate sPLA2 that needs to be established. But what is certain is the fact that PLD (phospholipase D) activation is necessary in the CD16-triggered signaling cascade that leads to NK cytotoxic granule exocytosis that, in turn, is associated with AA release (15−17). In this context, it is interesting to note that lipids are a constitutive component of cytolytic granules of CTL, NK and $\gamma\delta$T cells (18) and cytokine activated macrophages release bioactive lipids to induce apoptosis of tumor cells (13,19−21).

To exhibit their functions adequately, macrophages need cooperation of tissue-resident memory CD8+ T cells both for pathogen sensing and rapid protection of barrier tissues, a function that is reminiscent of what is described by Juers JA, et al. (12) on the close interaction/crosstalk between alveolar lining material and alveolar macrophages for the latter (macrophages) to bring about their ability to eliminate invading microbes and tumor cells. Thus, there is close cooperation not only between epithelial cells and macrophages but also between macrophages and other T cells. This close association among various tissue epithelial and other cells, macrophages and tissue resident T cells (that are needed for local immune response) seem to depend on their (mainly tissue resident memory T cells) ability to uptake fatty acids for their survival from the local tissues/cells that is regulated by the type of fatty acid-binding protein (FABP) expressed by the T cells. It was reported that tissue resident memory T cells show varying patterns of FABP isoform usage that are determined by tissue-derived factors. It appears that tissue resident memory T cells (and possibly other immunocytes including macrophages) modify their FABP expression depending on the tissue in which they are located or relocated. Thus, tissue resident memory T cells when relocated to different organs modify their FABP expression in line with their new location implying that each tissue resident memory T cells have or need a specific pattern of fatty acids both for their survival and action (22). This interesting observation also argues in favor of the suggestion that each tissue and their resident memory T cells (and macrophages and other immunocytes) need a specific type of bioactive lipid to bring about their action tailored to their location and hence, the necessity of different types of bioactive lipids. This

argument can be extended to suggest that, possibly, to inactivate a specific type of bacteria, fungi or virus a specific type or types of bioactive lipid(s) is needed depending on the tissue involved and microbe invading the tissues.

Macrophages are needed both for defense against infections and to clear debris and enhance tissue repair. Macrophages adopt initially an inflammatory phenotype (M1 type) to clear debris and bacteria and later change their phenotype to M2 type to produce anti-inflammatory cytokines and lipoxin A4 (LXA4) from AA, resolvins from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and protectins and maresins from DHA to dampen inflammation (7,23−34) restore homeostasis.

It is noteworthy that pro-inflammatory TNF-α and IL-6 inhibit the activities of desaturases that are essential for the generation of AA, EPA and DHA from their precursors LA and ALA respectively (35). Hence, in instances where there is substantial degree of inflammation due to high levels of IL-6 and TNF-α (as it may happen in COVID-19) it may lead to a deficiency of AA, EPA and DHA and decreased generation of LXA4, resolvins, protectins and maresins due to their precursor deficiency. AA, EPA, DHA, LXA4, resolvins, protectins and maresins are potent suppressors of IL-6 and TNF-α formation. Thus, there appears to be a delicate balance maintained between PUFAs and their metabolites and pro-inflammatory cytokines (7). This suggests that administration of PUFAs and their metabolites LXA4, resolvins, protectins and maresins suppress inappropriate production of IL-6 and TNF-α to resolve inflammation and enhance recovery and also prevent cytokine storm (17) that may occur in COVID-19.

Bioactive Lipids and Hematopoiesis

AA is the precursor of both prostaglandin E2 (PGE2) and LXA4. In general, it is believed that PGE2 is pro-inflammatory whereas LXA4 is an anti-inflammatory molecule. But, under some very specific conditions PGE2 shows anti-inflammatory actions and is highly beneficial (29,36,37). This anti-inflammatory action of PGE2 seems to depend on its ability to enhance LXA4 formation (29). This suggests that once the inflammation reaches a peak in which PGE2 plays a significant role, the metabolism of AA is redirected to form LXA4 instead of PGE2 indicating a crosstalk between PGE2 and LXA4. This switching of AA metabolism from PGE2 to LXA4 (and probably *vice versa*, if need be) appears to be a crucial event in the resolution of inflammation in which anti-inflammatory cytokines play a role (34). In this context, it is interesting to note that 15-PGDH−(15-prostaglandin dehydrogenase, a prostaglandin degrading enzyme) deficient mice showed a twofold increase in PGE2 levels in several tissues including bone marrow, colon, and liver, increased fitness of these tissues with enhanced hematopoietic capacity. These 15-PGDH deficient animals not only had rapid liver regeneration after partial hepatectomy but also showed accelerated recovery of neutrophils, platelets, and erythrocytes (38). These results are supported by other studies which showed that PGE2 regulates haematopoietic stem cell homeostasis, promotes wound healing and tissue regeneration and modulates stem cell trafficking, events that ultimately promote hematopoiesis (39−42). These evidences suggest that administration of AA and other bioactive lipids to those with SARS-CoV-2 (COVID-19) infection, who may develop fulminant activation of coagulation, resulting in widespread microvascular thrombosis and consumption of coagulation factors as evidenced by thrombocytopenia, prolongation of the PT/INR, PTT, elevation of D-dimer, and decreased fibrinogen levels, may show early recovery due to increased formation of PGE2 (from AA).

Bioactive Lipids and COVID-19 Associated Mortality

It has been reported that mortality due to SARS-CoV-2 (COVID-19) infection is higher in those with diabetes mellitus, hypertension and cardiovascular diseases and the elderly. Previously, we showed that plasma levels of AA and other bioactive lipid shave been shown to be low in diabetes mellitus, hypertension and coronary heart disease (43) and plasma LXA4 levels, a potent anti-inflammatory bioactive lipid, fall with age (44) that may explain adverse outcome in them. Furthermore, it has been shown that it is safe to administer GLA and AA intravenously (45) and oral supplementation of AA enhances LXA4 formation with little or no change in PGE2 formation (that shifts the balance more towards anti-inflammatory events) without increasing the severity of underlying condition with no adverse events (46−48). Previously, we showed that bioactive lipids (especially AA) have cytoprotective actions against many chemicals, prevents both alloxan and streptozotocin-induced apoptosis of pancreatic β cells and ameliorate development of both type 1 and type 2 diabetes mellitus that is associated with suppression of inflammation and increase in the formation of LXA4 (49−55).

Conclusions

It is evident from the preceding discussion that bioactive lipids especially AA have many beneficial actions that may be of benefit in the prevention and management of SARS-CoV-2 (COVID-19) infection and other enveloped viruses. Bioactive lipids are useful in view of their ability not only to inactivate enveloped viruses but also several other harmful microbes, enhance macrophage phagocytic capacity, augment wound healing and tissue regeneration, promote hematopoiesis and protect normal cells from both endogenous and exogenous cytotoxic agents with relatively few adverse actions. Hence, efforts need to be made to test

their efficacy in SARS-CoV-2 (COVID-19) infection. It is possible to deliver bioactive lipids orally, parenterally and as nasal drops.

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