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Diacylglycerol and lipid pathways link fragile X syndrome and SARS-CoV-2 infection: Role of FMRP binding RNA

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Abstract

SARS-CoV-2 interacts with ACE2 and infects ACE2-expressing cell leading to the down-regulation of ACE2 and angiotensin II (Ang II) accumulation. The interaction of angiotensin II with its G-protein coupled receptor results in the activation of phosphodiesterase phospholipase C that degrades membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol 1,4, 5-triphosphate (IP3) and diacylglycerol (DAG). This results in the release of cytokines and eicosanoids (leukotrienes, prostaglandin, and thromboxane A2). Inositol triphosphate (IP3)/DAG contribute to Ca2+ release from endoplasmic reticulum (ER) increasing intracellular Ca2+ and activating PKC and NF-kB, PI3K/AKT/mTOR and Ras/MAPK/ERK pathways releasing pro-inflammatory cytokines and regulating the transcription of viral and host proteins. Inflammasome NLRP3 is involved in the pathogenesis of diseases characterized by an excessive maladaptive inflammatory activation such as acute lung injury and recently described in COVID-19. We show how inflammasome function is regulated by DAG, as well as DAG increase results in the lack of B cell-T cell communication and abnormal antibodies function. This article collects for the first time the links betwenn lipids pathways, DAG and the pathophysiology of COVID-19. It described the potential role of mentioned pathways in potential drugs for SARS-CoV-2 infection treatment.

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Introduction

The recent and rapid worldwide spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus disease 19 (COVID-19) [1], led us to the urgent need for therapies against the virus. The knowledge of molecular mechanisms involved in the pathophysiology is crucial to investigate potential drugs to reduce SARS-CoV-2 infection or the severity of COVID-19. It is known that angiotensin-converting enzyme 2 (ACE2) provides the cell membrane receptor entry point for SARS-CoV-2 [2]. Grown factor receptor (GFR) has also been identified as necessary for the entry of some viruses, including coronaviruses, and it is known that GFR signalling is involved in viral replication in many instances [3].

Main

SARS-CoV-2 interacts with ACE2 and infects ACE2-expressing epithelial and endothelial cells in lung and other organs, leading to the down-regulation of ACE2 on endothelium of lung and presumably, other organs, such as brain. The downregulation of ACE2 leads to unopposed angiotensin II (Ang II) accumulation, which may accelerate the progress of COVID-19 via increased activity of renin-angiotensin-system (RAS) [4].

The interaction of Ang II with its G-protein coupled receptor results in the activation of phosphodiesterase phospholipase C (PLC). PLC degrades membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). Since, synthesis of DAG is crucial for activation of diverse downstream signalling cascades, including the Ras, NF-kappa B (NF-kB), and AKT pathways, DAG levels must therefore be finely tuned not only through controlled production but also by its metabolism [5].

On the other hand, Ang II and K+ constitute the main stimuli for the production of mineralocorticoids through the inositol triphosphate (IP3)/DAG pathway and protein kinase C (PKC) activation [6]. Then, a positive feedback loop is created, ensuring the increase of Ang II and DAG activity.

Ang II induces aldosterone raise and eicosanoids formation by phospholipase A2 from arachidonic acid. These eicosanoids include thromboxane A-2 (TXA2), prostaglandin-I2 (PGI2) and leukotrienes (LTB4) which facilitate thrombosis, capillary permeability, cytokines release and superoxide release from neutrophils, and they are involved in bronchoconstriction, anaphylaxis and atherosclerosis. Moreover, TXA2 induces intracellular Ca2+ increase and contributes to the deleterious effects of Ca2+ elevation. However, eicosanoids derived from eicosapentaenoic acid (EPA),

thromboxane-3, prostaglandin-3, and leukotriene-5 are less potent inducers of inflammation, blood vessel constriction, and thrombus formation than eicosanoids derived from arachidonic acid. In addition, it has been shown that EPA suppress arterial calcification *in vitro* and *in vivo* via suppression of inflammatory responses, oxidative stress, Wnt/β-catenin and phosphoinositide 3-kinase (PI3K)/AKT/mTOR signalling [7], and indirectly suppresses the SARS-CoV-mediated cleavage of polyADP-ribose polymerase (PARP) for its replication [8]. PI3K is needed for SARS-CoV-2 endocytosis, why its inhibition has been proposed as an antiviral agent [9][10].

Grown factor receptor (GFR) has been involved in SARS-CoV-2 entry to the host cell and replication through a tyrosine kinase (TK)-dependent process [3]. It has been seen that tyrosine kinase activity is increased during COVID-19[11]. Indeed, TK inhibitors possess inhibitory activities against coronaviruses [12].

Similarly, receptor tyrosine kinase (RTK) is involved in activating PLC-γ pathway. This enzyme has tyrosine residues that can become phosphorylated upon activation of RTK, and hence activating PLC-γ and allowing it to cleave PIP2 into DAG and IP3. This two molecules (IP3/DAG) contributes to increasing intracellular Ca2+ from the endoplasmic reticulum (ER) beside the activation of PKC and NF-kB, PI3K/AKT/mTOR and Ras/MAPK/ERK pathways [13] which results in pro-inflammatory cytokines release and regulating translation and transcription [14][15]. RTK activation also initiates PI3K/AKT/mTOR and Ras/MAPK/ERK pathways [15] directly. Likewise, PKC activation leads to reactive oxygen species (ROS) increase, ROS-mediated NF-kB activation and mTOR inhibition. These facts result in transcriptional activation of NF-κB target genes such as positive cell-cycle regulators, anti-apoptotic and survival factors, and pro-inflammatory genes, leading to cytokine production, increasing autophagy [16][17], and facilitates viral replication.

Besides, Ca2+ movement from the ER to mitochondria would be a key process in some apoptotic routes[18]. Analysis of macrophages from severe COVID-19 patients found higher levels of TK phosphorylation (active form) and higher IL-6 production [11].nGluR5 and Homer release calcium via DAG.

Then, TK activity would increase DAG levels in COVID-19, and activate PI3K/AKT/mTOR and Ras/MAPK/ERK pathways by both RTK-mediated DAG enhance and direct RTK activation. Therefore, TK inhibition could be useful against SARS-CoV-2 endocytosis, viral replication and elevated levels of Ca2+. Based on the role of TK in the production of inflammatory cytokines, treatment with these inhibitors have been proposed [11].

Surprisingly, DAG levels have been reduced in plasma of COVID-19 and other viral infections[19]. However, extracellular DAG is a product of triacylglycerol (TAG) hydrolysis during digestion and the catabolism of lipoprotein-associated TAG in the bloodstream. Since DAG generated in the digestive system or circulating is usually immediately hydrolysed to monoacylglycerol (MAG) and fatty acids, it is probably not involved in the regulation of signalling pathways. Nevertheless, intracellular changes in DAG levels are affecting various signalling pathways and processes [20]. Then, this different role of DAG in intra- and extracellular compartments could explain the low plasmatic levels of DAG observed in COVID-19. In addition, the reduced DAG levels were observed in mild and moderate COVID-19, but normal or slightly increased in severe cases [19]. Others studies found higher DAG levels in severe COVID-19 cases[21]. It should be noted here that DAG mediates fat-induced insulin resistance [22][23], which has been observed in COVID-19[24].

DGK is essential for the negative control of DAG function in T lymphocytes. In fact, DAG kinase (DGK) controls the switch between DAG and phosphatidic acid (PA) signalling pathways [25]. DGKs are members of a unique and conserved family of intracellular lipid kinases that phosphorylate DAG, catalysing its conversion into phosphatidic acid (PA). This reaction leads to attenuation of DAG levels in the cell membrane. DGKs provide a link between lipid metabolism and signaling (Mérida et al. 2008). Is an enzyme which converts DAG into phosphatidic acid, limiting inflammatory cytokine production [Diacylglycerol Kinase ζ Regulates Macrophage Responses in Juvenile Arthritis and Cytokine Storm Syndrome Mouse Models. Sahil Mahajan, Elizabeth D. Mellins, Roberta Faccio. The Journal of Immunology January 1, 2020, 204 (1) 137-146; DOI: 10.4049/jimmunol.1900721] DGK deficiency, as occurs in fragile X syndrome (FXS) results in sustained Ca2+ flux and increased MAPK/ERK activity [26]. Both facts are described in the pathophysiology of COVID-19, as mentioned. Loss of DGK limits inflammatory cytokine production in an arthritic mouse model. In vitro, DGK deficiency results in reduced production of TNF-α, IL-6, and IL-1β and in limited M1 macrophage polarization. Mechanistically, DGK deficiency decreases STAT1 and STAT3 phosphorylation [Mahajan, S., Mellins, E. D., & Faccio, R. (2020). Diacylglycerol Kinase ζ Regulates Macrophage Responses in Juvenile Arthritis and Cytokine Storm Syndrome Mouse Models. *Journal of immunology (Baltimore, Md.: 1950)*, *204*(1), 137-146. https://doi.org/10.4049/jimmunol.1900721]

It should also be noted here that DGK is involved in immune system function since DGK deficiency leads to a lack of immune synapse. DGK regulates the balance in signalling between DAG and phosphatidic acid (PA) that is required for optimal B cell function and antibodies production. [26]. According to this, DAG increase, or DGK deficiency results in the lack of B cell-T cell communication (immune synapse) and an abnormal antibodies function. In COVID-19, DAG/PA activity balance is enhanced, as in DGK deficiency. This fact might be involved in impaired antibody developing.

B-cell depletion could compromise antiviral immunity, including development SARS-CoV-2 antibodies, increase the risk of reinfection, and impair vaccine efficacy (once a vaccine becomes available) [27]. Recently, Wurm et al. have reported that B cell suppression during COVID-19 results in lack of antibodies developing in a case of multiple sclerosis with immunotherapy [28].

The inflammasome NLRP3 [29] is involved in the pathogenesis [30] of diseases characterized by an excessive maladaptive inflammatory activation such as acute lung injury [31][32]. NLRP3 inflammasome is also involved in the pathophysiology of neuroinflammation by producing IL-1 family pro-inflammatory cytokines, such as IL-1β that induce IL-6 and TGF-β1 and promote Th17 cell differentiation (pivotal elements of cytokine storm), IL-18 with pro-fibrotic activity [33], and other damage-associated molecular patterns (DAMPs) [34]. It also drives caspase-1 cleavage and the secretion of other damage-associated molecular patterns (DAMPs) [34]. Caspase 3, among other caspases, and apoptosis are strongly increased in COVID-19 [35]. These caspases drive to the maturation and activation of pro-inflammatory cytokines[36] and gasdermins, a pore-forming protein. Then, formation of pores causes cell membrane rupture and release of cytokines, as well as various damage-associated molecular pattern (DAMP) [37] molecules, out of the cell. These molecules recruit more immune cells and further perpetuate the inflammatory cascade in the tissue [38][39].

DAG is also tangled in inflammasome function. Inflammasome activation is comprised of NF-κB activation and pro-interleukin-1β initiated by pro-inflammatory cytokines [40]. Besides, a variety of extracellular and intracellular stimuli

activate inflammasomes including pattern recognition receptor (PRR) [41] activation, phagocytosis [42], decrease in intracellular K+, Ca+2 increase, and ROS generated from ER stress and distressed mitochondria [43][44]. Sepsis induces intracellular Ca2+ increase and potassium efflux. Therefore, the rise of pro-inflammatory cytokines, the Ang II-mediated hypopotasemia, the Ca2+ increase, NF-kB activation, and the rise of ROS, all of them occur in COVID-19, as already discussed, and that would lead to inflammasome hyperactivation. On the other hand, calcium and DAG are known to activate the transient receptor potential melastatin type 2 (TRPM2). This receptor is reported activated by DNA damage in SARS-CoV-2 infection (Kouhpayeh S, Shariati L, Boshtam M, Rahimmanesh I, Mirian M, Esmaeili Y, Najaflu M, Khanahmad N, Zeinalian M, Trovato M, Tay FR, Khanahmad H, Makvandi P. The Molecular Basis of COVID-19 Pathogenesis, Conventional and Nanomedicine Therapy. Int J Mol Sci. 2021 May 21;22(11):5438. doi: 10.3390/ijms22115438. PMID: 34064039; PMCID: PMC8196740). Activation of TRPM2 increases NLR family pyrin domain containing 3 (NLRP3 inflammasome) activity and IL8 secretion, intensifying inflammation and cytokine storm [45]. Besides, the activation of TRPM2 in infected tissues, especially the lungs, causes the influx of extracellular calcium ions into the cytoplasm and promotes apoptosis. Temperature and calcium are TRPM2 stimulators.

Zhang et al. demonstrated that NLRP3 inflammasome stimuli promoted mitochondria-associated membranes (MAMs) localization to the adjacent Golgi membrane and DAG accumulation. DAG accumulation at Golgi activates protein kinase D (PKD), which subsequently phosphorylates NLRP3, resulting in assembly of the fully mature inflammasome [46]. On the other hand, DAG activates PKC leading to ROS increase, ROS-mediated NF-kB activation and mTOR inhibition, that results in transcriptional activation and increased autophagy [16] and NLRP3 inflammasome activation [46]. Thus, a positive feedback circuit is closed, facilitating the cytokine storm.

In T cell, statins are capable of inducing shifts from Th1 cytokine production to Th2 type cytokine secretion[47], (IL-4, IL-5, IL-9, IL-10, and IFN α/β instead IL-6 IL-1B, IL-8, and IFNγ), ameliorate cytokine storm and macrophage activation, and switch immune response in anti-inflammatory and pro-repair activity (M2). Therefore, statins not only block virus replication upon antiviral activity but also reduce the harmful effects of inflammation on the host [45]. Moreover, they reduce the synthesis of cholesterol, that is the main substrate for aldosterone synthesis in the Ang II function. Statins also inhibit NF-kB and Ras/MAPK/ERK pathways avoiding inflammation; endothelial dysfunction and increased vascular permeability that can lead to multi-organ failure; protein overexpression by increasing translation and transcription; and elevation of intracellular calcium. These phenomena may improve not only FXS symptoms but SARS-CoV-2 infectivity and COVID-19 severity. Thientriazolodiacepines (alprazolam, brotizolam, triazolam) play a similar role as bromodomain containing 4 (BRD4) inhibitors in nuclear compartment. Indeed, alprazolam has been shown inhibits main protease (Mpro) [48]. Besides, Gimeno et al. also showed several molecules that could interact with M-pro because their 3D structure and virtual teorical models. Then, seven potential M-pro inhibitors were identified: Perampanel, Carprofen, Celecoxib, Alprazolam, Trovafloxacin, Sarafloxacin and ethyl biscoumacetate [48]. Perampanel treatment downregulated the protein expression levels of receptor interacting serine/threonine kinase (RIP) 1, RIP3, and mixed lineage kinase domain like pseudokinase, and of the cytokines IL-1β, IL-6, TNF-α, and NF-κB [55A]. These results indicated that perampanel-mediated inhibition of necroptosis and neuroinflammation. The mentioned study demonstrated that perampanel improved neurological outcomes and reduced neuronal death by protecting against neural necroptosis and

neuroinflammation. Therefore, perampanel can be the best option along the putatives M-pro inhibitors since it seems to be neuroprotective and anti-inflammatory.

Thus, the combination of statins with thientriazolodiazepines (alprazolam) and perampanel could have therapheutics effects on COVID-19. Furthermore, the GABA function of thientriazolodiazepines ameliorates the GABA deficit observed in SARS-CoV and other viruses infections [49][50][51]. Furthermore, statins decrease the synthesis of DAG[52], which may ameliorate the intracellular Ca2+ increase and the activation of PKC, NF-kB, and Ras/MAPK/ERK.

Finally, as above indicated, EPA also can contribute to improving course of COVID-19 administering it with statins, thienotriazolodiazepines and perampanel.

Thus, targeting DGK activity emerges as a promising terapheutic strategy. Regarding this, ritaserin shows a possible option, since others DGK inhibitors present poor pharmacological properties.

Conclusion

Despite reviewing the different therapies that are currently being considered, the possibilities of the one presented in this article still need to be explored. The multiple points in these common pathways should be studied in order to find new therapeutic targets against COVID-19 pandemic.

We proposed the use of DGK inhibititors, statin, thienotriazolodiazepines, perampanel and EPA for COVID-19.

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