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.

BBA - Molecular and Cell Biology of Lipids 1866 (2021) 158839

Contents lists available at ScienceDirect

BBA - Molecular and Cell Biology of Lipids

journal homepage: www.elsevier.com/locate/bbalip

BBA Research Letters

Cholesterol, inflammation, and phospholipids: COVID-19 share traits with cardiovascular disease

Lígia L. Pimentel*, Luis M. Rodríguez-Alcalá*

Universidade Católica Portuguesa, CBQF - Centro de Biotecnologia e Química Fina – Laboratório Associado, Escola Superior de Biotecnologia, Rua Diogo Botelho 1327, 4169-005 Porto, Portugal

ARTICLE INFO

Keywords:
Covid-19
Cholesterol
Lipid rafts
LDL
Omega 3 fatty acids
Phospholipids
S1P
Antiphospholipid syndrome

COVID-19, the severe acute respiratory syndrome produced by the coronavirus SARS-CoV-2, has resulted to date in more than 39 million infected cases and 1 million deaths worldwide since the first reported cases in December 2019 at the Chinese city of Wuhan (for updated information readers can consult https://covid19.who.int/). The disease can drastically evolve from fever, cough, breath shortness and alterations in smell and taste to acute respiratory distress, septic shock, multi-organ failure and blood clots [1] (Fig. 1). It is known that SARS-CoV and MERS-CoV can remodel the lipidome of the infected cells. Thus, this research letter aims to present and discuss the current information about observed changes in lipid metabolites in COVID-19 patients.

Indeed, different research works have started to report the metabolic hallmark of alterations associated to COVID-19. The characteristic features are i) the decrease in the levels of low-density (LDL-c) and high-density (HDL-c) cholesterol lipoproteins, this latter proportionally to the severity of symptoms, with ii) moderate increment in the population of T helpers cells ($CD3^+T$, $CD4^+T$) or lymphopenia of $CD8^+T$ (suggesting possible infection of such cells or exhaustion of immune system) and iii) hyperinflammation according to the levels of interleukins (IL-6, IL-7, TNF) and chemokines [1–3]. Moreover, total counts of white blood cells (WBC) were significantly higher in patients in critical condition [1] and those with severe respiratory failure showed macrophage activation syndrome [4], confirmed by the presence of monocyte recruiting chemokines in bronchoalveolar fluid [2].

The capability to affect at the same time to lipoproteins, WBC and trigger inflammation seems to suggest that the cardiovascular system is a main target of this virus. In fact, to infect cells (in first instance those in the respiratory system), SARS-Cov-2 uses its S spike glycoprotein to bind to the angiotensin-converting enzyme 2 (ACE2) receptor (Fig. 1), that is highly expressed in alveolar, epithelial, ileum, colon, myocardial, kidney and bladder urothelial cells [5]. It is part of the renin-angiotensin system that controls extracellular level, blood pressure and sodium/potassium balance, therefore is not surprising being expressed in many different cells types; this allows a systemic spread.

Such ACE2 receptor locates in lipid-rafts enriched in cholesterol and sphingomyelin [7]. Recently, works conducted by Toelzer et al. [6] https://doi.org/10.1101/2020.06.18.158584 found that the receptor binding domain specifically binds to linoeic acid, a fatty acid known by its pro-inflammatory activity. This is a feature shared by other SARS-CoV and MERS-CoV. The biological significance of this need to be further unravelled.

Interestingly, many research studies had reported that COVID-19 patients, previously presented comorbidities as type 2 diabetes mellitus, hypertension, and cardiovascular diseases (CVD) [2,4]. Furthermore, plasma lipidomic analyses have revealed a close relationship between the severity of COVID-19 and circulating lipids: a combination of larger levels of atherogenic diglycerides (DG 16:0/20:2/20:0) and triglycerides (TG 14:0/22:1/22:3), alterations of the phosphatidylinositol (PI) signalling system with decreased concentrations of phosphatidylcholine (PC) [8] and sphingosine-1-phosphate (S1P) [9]. It must be noted that,

* Corresponding authors.
E-mail addresses: lpimentel@porto.ucp.pt (L.L. Pimentel), lalcala@porto.ucp.pt (L.M. Rodríguez-Alcalá).

https://doi.org/10.1016/j.bbalip.2020.158839
Received 2 June 2020; Received in revised form 11 September 2020; Accepted 2 October 2020
Available online 17 October 2020
1388-1981/

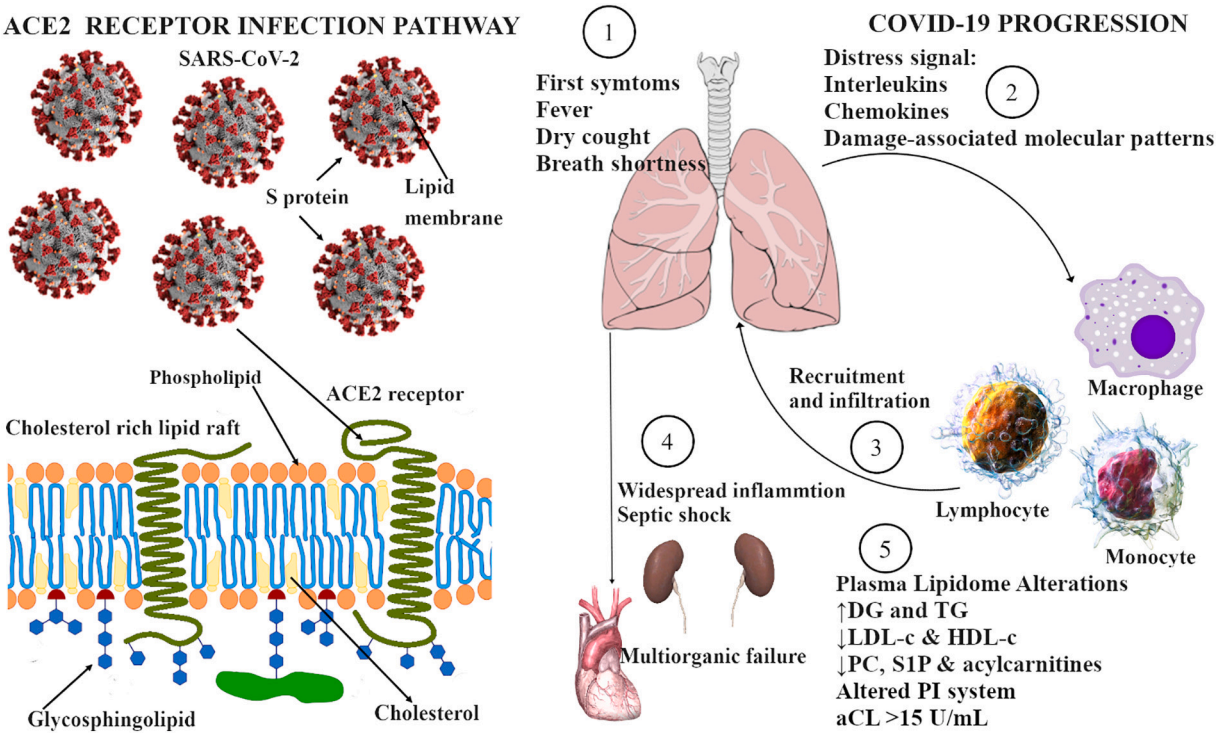

Fig. 1. SARS-CoV-2 infection pathway in humans and COVID-19 progression.

before the SARS-CoV-2 pandemic, patients after heart failure showed reduced concentrations of PI and PC in erythrocytes [10]. Besides, S1P is transported in plasma by HDL and may be involved therefore in the protective effects of this lipoprotein against CVD [11].

Moreover, antiphospholipid antibodies (aPL) are considered a cardiovascular risk factor. After being released by WBC (i.e. plasma B cells), aPL target platelet membrane phospholipids leading to abnormal clots formation in veins and/or arteries (thrombosis) that can occur also with inflammation (phlebitis). Thus, it was observed in SARS-CoV-2 positive subjects that anticardiolipin antibodies (aCL IgG) profile (> 15 U/mL) was associated to disease severity (i.e.respiratory distress) while those patients have not a previous record history of thrombosis [12]. Authors concluded that aCL IgG may be a risk marker in COVID-19 patients.

It is remarkable that from the study of metabolic diseases (i.e. CVD, obesity, diabetes) we have understood how cholesterol has a close relationship with the immune system and inflammation. In CVD, LDL-c accumulates, aggregates and oxidizes (OX-LDL) in the artery walls, producing lesions and further recruitment of macrophages, probably from blood-borne monocytes [13]. Thus, in both macrophages and endothelial cells, OX-LDL activates Toll-like receptors (i.e. TLR2 and 4) and its inflammatory pathway: transcription factors promote interleukins production, inflammasome is assembled and finally result in pyroptosis, an inflammatory and lytic cell-death. Then, damage-associated molecular patterns (DAMOs) are released, recognised by neighbour cells that afterwards produce cytokines and chemokines to recruit monocytes, macrophages, and lymphocytes T.

All the above exposed about macrophages recruitment in CVD is related to mechanisms intended to respond in situations of tissue damage. The fact that oxidized phospholipids have been also detected in COVID-19 patients and that concentration of type I interferon (INF-I) remains low, even in the most severe situations [2], suggest that during COVID-19, macrophages activation is performed through the inflammasome pathway. Moreover, the decrease in LDL-c levels may indicate clearance of pathogenic lipids by the expression of PCSK9 in liver as response to septic shock [14]. However, it has been reported that reactive oxygen species are present in COVID-19 patients [9], therefore, formation of OX-LDL cannot be excluded as a way for the activation of macrophage during progression of the disease. On the other hand, circulating acylcarnitines as palmitoylcarnitine, stearoylcarnitine or oleoylcarnitine, were negatively affected in COVID-19 plasma samples, suggesting impairment of β-oxidation as fatty acids are not entering into the mitochondria [9]. As metabolites from tricarboxylic acid cycle are also reduced, SARS-CoV-2 hijacks the energy metabolism of the host not only by limiting blood oxygen through declining of lung functions but also by interfering in the oxidation pathways.

At this point, it can be hypothesized that metabolic state of the subject, before infection by SARS-CoV-2, plays a crucial role in the development of COVID-19 and the survival of the individual. According to the current available data, subjects with high cholesterol levels could be more prone to be infected when exposed to this virus. Usually, those individuals are under medical supervision and treatment to block intestinal cholesterol absorption (i.e. ezetimibe) or inhibiting its synthesis (i.e. statins). Although these latter can increase ACE2 expression, a recent cohort study evaluating 13,981 cases concluded that COVID19 patients treated with statins showed lower risk of death and lower inflammatory response [15]. On the other hand, since 2008 it is known that ezetimibe combined with simvastatin may increase upper respiratory infections [16]. Therefore, how these drugs are used to fight against SARS-CoV-2 need to be carefully addressed.

Nevertheless, if the key-feature of the disease is the macrophage activation involving TLR2 and/or 4, it is worthy to note that G protein-coupling receptors (GPR), namely GPR120, are expressed in such cells, and counter-balance TLR-inflammation but more importantly: GPR120 can be activated by omega 3 fatty acids (ω3-FA) [17]. These FA have been proven to be effective against CVD and they are included in the list of functional ingredients approved by EFSA about health claims for nutrient, substance, food, or food category. Aligned to this, it has been recently suggested, as a complementary treatment, to provide fish oil lipid emulsions to hospitalized COVID-19 patients, as eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids attenuate cytokine storm by peroxisome proliferator activated receptor, they are precursors of maresins, resolvins and protectins (i.e. inflammatory resolution mediators) and can disrupt lipid rafts [18]. Therefore, diet may also

integrate the set of strategies to fight back against COVID-19.

According to the above-discussed information, SARS-CoV-2 first target cells of the respiratory system of the host. In the following stages the biomarkers associated to the alteration of the lipidome point out that inflammatory and immune response are resulting from extensive damage of tissues of the cardiovascular system as well as sepsis. This may suggest that in a strategy to avoid being neutralized, the disease engage the immune system aiming to induce an impaired and sustained response that finally lead to exhaustion of lymphocytes (i.e. $CD8^+T$) and, unfortunately for some patients, in dead.

However, all these above-commented research results bring new questions and opportunities to deepen our understanding about disease and biochemistry: are alterations of cholesterol or other lipid biomarkers actually a feature solely of this condition or it is shared by other diseases?; does it provide us with information relatively to biochemical/metabolic unbalance or about the activation of mechanisms to restore body homeostasis?. The number of spotted lipid biomarkers associated to disease are incredibly low when compared with the number of total compounds belonging to this family. Moreover, the fact that human genome encodes TLR, GPR, transcription factors (i.e. SREBP) and other proteins that can interact with specific lipids suggest that the role of this family of compounds is far more important and complex than what we already know. Further investigations, where differences between normal condition and disease can be observed, measured and studied to *i*) identify involved lipid biomarkers (i.e. lipobonomics) and *ii*) afterwards understand their interaction with different cell/metabolic pathways, are therefore needed. In this context the sentence from Hypocrates, “let be thy food be your medicine and thy medicine be your food”, seems to be more accurate than ever.

CRediT authorship contribution statement

Lígia L. Pimentel: Investigation, Writing - original draft, Writing - review & editing. **Luis M. Rodríguez-Alcalá:** Investigation, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] X. Wei, W. Zeng, J. Su, H. Wan, X. Yu, X. Cao, W. Tan, H. Wang, Hypolipidemia is associated with the severity of COVID-19, J. Clin. Lipidol. 14 (2020) 297–304, https://doi.org/10.1016/j.jacl.2020.04.008.

[2] M. Merad, J.C. Martin, Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages, Nat. Rev. Immunol. (2020) 1–8, https://doi.org/10.1038/s41577-020-0331-4.

[3] X. Wang, W. Xu, G. Hu, S. Xia, Z. Sun, Z. Liu, Y. Xie, R. Zhang, S. Jiang, L. Lu, SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion, Cell. Mol. Immunol. (2020) 1–3, https://doi.org/10.1038/s41423-020-0424-9.

[4] E.J. Giamarellos-Bourboulis, M.G. Netea, N. Rovina, K. Akinosoglou, A. Antoniadou, N. Antonakos, G. Damoraki, T. Gkavogianni, M.E. Adami, P. Katsaounou, M. Ntaganou, M. Kyriakopoulou, G. Dimopoulos, I. Koutsodimitropoulos, D. Velissaris, P. Koufargyris, A. Karageorgos, K. Katrini, V. Lekakis, M. Lupse, A. Kotsaki, G. Renieris, D. Theodoulou, V. Panou, E. Koukaki, N. Koulouris, C. Gogos, A. Koutsoukou, Complex immune dysregulation in COVID-19 patients with severe respiratory failure, Cell Host Microbe. 27 (2020) 992–1000.e3, https://doi.org/10.1016/j.chom.2020.04.009.

[5] I. Astuti, Ysrafil, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response, Diabetes Metab. Syndr. Clin. Res. Rev. 14 (2020) 407–412, https://doi.org/10.1016/j.dsx.2020.04.020.

[6] C. Toelzer, K. Gupta, S.K.N. Yadav, U. Borucu, A.D. Davidson, M. Kavanagh Williamson, D.K. Shoemark, F. Garzoni, O. Staufer, R. Milligan, J. Capin, A.J. Mulholland, J. Spatz, D. Fitzgerald, I. Berger, C. Schaffitzel, Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein, Science (80-.) (2020) eabd3255, https://doi.org/10.1126/science.abd3255.

[7] Y. Lu, D.X. Liu, J.P. Tam, Lipid rafts are involved in SARS-CoV entry into Vero E6 cells, Biochem. Biophys. Res. Commun. 369 (2008) 344–349, https://doi.org/10.1016/j.bbrc.2008.02.023.

[8] D. Wu, T. Shu, X. Yang, J.-X. Song, M. Zhang, C. Yao, W. Liu, M. Huang, Y. Yu, Q. Yang, T. Zhu, J. Xu, J. Mu, Y. Wang, H. Wang, T. Tang, Y. Ren, Y. Wu, S.-H. Lin, Y. Qiu, D.-Y. Zhang, Y. Shang, X. Zhou, Plasma metabolomic and lipidomic alterations associated with COVID-19, Natl. Sci, Rev, 2020, https://doi.org/10.1093/nsr/nwaa086.

[9] J.W. Song, S.M. Lam, X. Fan, W.J. Cao, S.Y. Wang, H. Tian, G.H. Chua, C. Zhang, F.P. Meng, Z. Xu, J.L. Fu, L. Huang, P. Xia, T. Yang, S. Zhang, B. Li, T.J. Jiang, R. Wang, Z. Wang, M. Shi, J.Y. Zhang, F.S. Wang, G. Shui, Omics-driven systems interrogation of metabolic dysregulation in COVID-19 pathogenesis, Cell Metab. 32 (2020) 188–202.e5, https://doi.org/10.1016/j.cmet.2020.06.016.

[10] H.Y. Tang, C.H. Wang, H.Y. Ho, P.T. Wu, C.L. Hung, C.Y. Huang, P.R. Wu, Y.H. Yeh, M.L. Cheng, Lipidomics reveals accumulation of the oxidized cholesterol in erythrocytes of heart failure patients, Redox Biol. 14 (2018) 499–508, https://doi.org/10.1016/j.redox.2017.10.020.

[11] E. Jozefczuk, T.J. Guzik, M. Siedlinski, Significance of sphingosine-1-phosphate in cardiovascular physiology and pathology, Pharmacol. Res. 156 (2020) 104793, https://doi.org/10.1016/j.phrs.2020.104793.

[12] D. Bertin, A. Brodovitch, A. Beziane, S. Hug, A. Bouamri, J.L. Mege, N. Bardin, Anti-cardiolipin IgG autoantibodies are an independent risk factor of COVID-19 severity, Arthritis Rheumatol. (2020), https://doi.org/10.1002/art.41409 art.41409.

[13] A.R. Tall, L. Yvan-Charvet, Cholesterol, inflammation and innate immunity, Nat. Rev. Immunol. 15 (2015) 104–116, https://doi.org/10.1038/nri3793.

[14] K.R. Walley, K.R. Thain, J.A. Russell, M.P. Reilly, N.J. Meyer, J.F. Ferguson, J.D. Christie, T.A. Nakada, C.D. Fjell, S.A. Thair, M.S. Cirstea, J.H. Boyd, PCSK9 is a critical regulator of the innate immune response and septic shock outcome, Sci. Transl. Med. 6 (2014) 258ra143, , https://doi.org/10.1126/scitranslmed.3008782.

[15] X.J. Zhang, J.J. Qin, X. Cheng, L. Shen, Y.C. Zhao, Y. Yuan, F. Lei, M.M. Chen, H. Yang, L. Bai, X. Song, L. Lin, M. Xia, F. Zhou, J. Zhou, Z.G. She, L. Zhu, X. Ma, Q. Xu, P. Ye, G. Chen, L. Liu, W. Mao, Y. Yan, B. Xiao, Z. Lu, G. Peng, M. Liu, J. Yang, L. Yang, C. Zhang, H. Lu, X. Xia, D. Wang, X. Liao, X. Wei, B.H. Zhang, X. Zhang, J. Yang, G.N. Zhao, P. Zhang, P.P. Liu, R. Loomba, Y.X. Ji, J. Xia, Y. Wang, J. Cai, J. Guo, H. Li, In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19, Cell Metab. 32 (2020) 176–187.e4, https://doi.org/10.1016/j.cmet.2020.06.015.

[16] J. Strony, R. Hoffman, M. Hanson, E. Veltri, Tolerability and effects on lipids of ezetimibe coadministered with pravastatin or simvastatin for twelve months: results from two open-label extension studies in hypercholesterolemic patients, Clin. Ther. 30 (2008) 2280–2297, https://doi.org/10.1016/j.clinthera.2008.12.008.

[17] D.Y. Oh, S. Talukdar, E.J. Bae, T. Imamura, H. Morinaga, W.Q. Fan, P. Li, W.J. Lu, S.M. Watkins, J.M. Olefsky, GPR120 is an Omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects, Cell. 142 (2010) 687–698, https://doi.org/10.1016/j.cell.2010.07.041.

[18] R.S. Torrinhas, P.C. Calder, D.L. Waitzberg, Response to Bistrian BR. Parenteral fish-oil emulsions in critically Ill COVID-19 emulsions, J. Parenter. Enter. Nutr. (2020), https://doi.org/10.1002/jpen.1933 jpen.1933.