Mucormycosis and glucose-regulated protein 78 in COVID-19: amenable to statin treatment?

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Dear Editor,

Alarminglly, in SARS-CoV-2-infected patients, a growing number of cases of mucormycosis are being reported [1]. Mucormycosis is a deadly angioinvasive infection caused by the opportunistic fungi of the family Mucorales. After inhalation of the fungal spores, the infection affects the lungs, and typically also the nasal sinuses, from where the infection may
reach the eyes and the brain [2]. The estimated prevalence of mucormycosis in India was already before the pandemic much higher than elsewhere [3]. The high numbers of mucormycosis cases in India may be due to health care deficiencies and the high numbers of diabetics in India. Overall, there is a concern that, in the developing world, mucormycosis has become more prevalent among COVID-19 patients.

A retrospective multicenter analysis by Moorthy and coworkers revealed that corticosteroid treatment of diabetic SARS-CoV-2-infected patients significantly associates with mucormycosis [4]. In 2010 Liu et al. [5] identified an endothelial cell receptor, the glucose-regulated protein 78 (GRP78), as a host receptor mediating the invasion of the mucormycosis-causing fungi. They showed in diabetic mice that increased glucose and iron levels, typical of ketoacidosis, enhance the expression of the endothelial GRP78 receptors in the nasal sinuses, lungs, and brain and that the receptor overexpression also increased fungal invasion and ensuing damage of the endothelial cells. Of note, besides the angiotensin-converting enzyme (ACE2), also the GRP78 can act as a receptor for SARS-CoV-2 and mediate its translocation into endothelial cells [6]. Intriguingly, the plasma levels of GRP78 are upregulated in patients with diabetes mellitus (DM), obesity, and atherosclerosis [7].

SARS-CoV-2 entry into the host cells increases the amount of unfolded proteins and endoplasmic reticulum (ER) stress in the infected cells [8]. A recent report showed that air pollution, and especially iron-rich nanoparticles (15-40 nm in diameter) typical for an urban environment, cause endothelial dysfunction and cardiac mitochondrial dysfunction [9]. Additionally, up-regulation of GRP78 is one of the markers reflecting air pollution-related ER stress. The pathological activation of ER stress can initiate the re-localization of GRP78 to the cell surface, which is then called cell surface GRP78 (csGRP78) [10]. Air pollution may be an additional risk factor to consider when assessing the increase in mucormycosis, especially in India. Thus, in an unfortunate environment, three exogenous air-borne disease-causing agents may enter the respiratory system: (i) SARS-CoV-2-containing aerosols, (ii) iron-rich nanoparticles, and (iii) fungi of the family Mucorales.

Because GRP78 appears to play role in the pathogenesis of atherosclerotic cardiovascular disease (ASCVD), its role in the most prevalent single gene inherited metabolic disease, the heterozygous familial hypercholesterolemia (HeFH), needs attention. HeFH affects about 1 out of 250 individuals. In these patients, the concentration of serum LDL-cholesterol (LDL-C) is two-fold since birth due to defective hepatic removal of LDL-particles from the
circulation. In these patients, endothelial dysfunction develops already in childhood. If left untreated with a statin, often combined with ezetimibe and, if necessary, also with a PCSK9 inhibitor, endothelial dysfunction persists and premature atherosclerotic cardiovascular disease (ASCVD) inevitably develops [11].

A surprising molecular link between HeFH and the GRP78 exists. Thus, in HeFH, the GRP78 plays a critical role in regulating ER homeostasis via the quality control of LDL-receptors, as shown by Sørensen and coworkers [12]. In the study, the unfolded mutant LDL receptors increased the ER stress. In the other, so far available study involving HeFH patients, overexpression of GRP78 decreased the processing rate of wild type LDL receptors and contributed to worsening of ASCVD in the patients [13].

The above presented seemingly separate mechanisms and conditions allowed us to intertwine a scheme in which we assign the statin drugs a therapeutic role in COVID-19 and its post-acute sequelae. Statins can activate the unfolded protein response and induce a cytoprotective GRP78 expression [14]. Moreover, statins potentially reduce the risk of fungal infections, and under careful clinical monitoring, they can also be used to potentiate the plasma concentrations of antifungal medications [15]. The potential endothelium-damaging effects of mucormycosis and the GRP78 receptors, along with the SARS-CoV-2-induced endothelial infection, underline the importance of effective statin treatment among those COVID-19 patients with an increased risk of immunothrombosis in the micro- and macrocirculation due to pre-existing endothelial dysfunction. They include patients with hyperglycemia (diabetes) and those with hypercholesterolemia due to mutated LDL-receptors, i.e., the HeFH patients [11].

Conflict of interest

PTK has received lecture honoraria and/or travel fees from Amgen, Novartis, Raisio Group, and Sanofi.
References

1. Erener S. Diabetes, infection risk and COVID-19. *Mol Metab* 2020; **39**:101044. doi:10.1016/j.molmet.2020.101044

2. Ibrahim AS, Spellberg B, Edwards J Jr. Iron acquisition: A novel perspective on mucormycosis pathogenesis and treatment. *Curr Opin Infect Dis* 2008; **21**: 620-25. doi:10.1097/QCO.0b013e3283165fd1

3. Prakash H, Chakrabarti A. Epidemiology of Mucormycosis in India. *Microorganisms* 2021; **9**: 523. doi:10.3390/microorganisms9030523

4. Moorthy A, Gaikwad R, Krishna S, et al. SARS-CoV-2, Uncontrolled diabetes and corticosteroids—an unholy trinity in invasive fungal infections of the maxillofacial region? a retrospective, multi-centric analysis. *J Maxillofac Oral Surg* 2021 Mar 6: 1-8. doi:10.1007/s12663-021-01532-1 [published online ahead of print, 2021 Mar 6].

5. Liu M, Spellberg B, Phan QT, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. *J Clin Invest* 2010; **120**: 1914-24. doi:10.1172/JCI42164

6. Allam L, Ghrifi F, Mohammed H, et al. Targeting the GRP78-dependant SARS-CoV-2 cell entry by peptides and small molecules. *Bioinform Biol Insights* 2020; **14**: 1177932220965505. doi:10.1177/1177932220965505

7. Girona J, Rodríguez-Borjabad C, Ibarretxe D, et al. The circulating GRP78/BiP is a marker of metabolic diseases and atherosclerosis: bringing endoplasmic reticulum stress into the clinical scenario. *J Clin Med* 2019; **8**: 1793. doi:10.3390/jcm8111793

8. Banerjee A, Czinn SJ, Reiter RJ, Blanchard TG. Crosstalk between endoplasmic reticulum stress and anti-viral activities: A novel therapeutic target for COVID-19. *Life Sci* 2020; **255**: 117842. doi:10.1016/j.lfs.2020.117842

9. Maher BA, González-Maciel A, Reynoso-Robles R, Torres-Jardón R, Calderón-Garcidueñas L. Iron-rich air pollution nanoparticles: An unrecognised environmental risk factor for myocardial mitochondrial dysfunction and cardiac oxidative stress. *Environ Res* 2020; **188**: 109816. doi:10.1016/j.envres.2020.109816

10. Crane ED, Al-Hashimi AA, Chen J, et al. Anti-GRP78 autoantibodies induce endothelial cell activation and accelerate the development of atherosclerotic lesions. *JCI Insight* 2018; **3**: e99363. doi:10.1172/jci.insight.99363

11. Vuorio, A., Raal, F., Kaste, M., Kovanen, P.T. Familial hypercholesterolaemia and COVID-19: A two-hit scenario for endothelial dysfunction amenable to treatment. *Atherosclerosis* 2021; **320**: 53-60. https://doi.org/10.1016/j.atherosclerosis.2021.01.021.

12. Sørensen S, Ranheim T, Bakken KS, Leren TP, Kulseth MA. Retention of mutant low density lipoprotein receptor in endoplasmic reticulum (ER) leads to ER stress. *J Biol Chem* 2006; **281**: 468-476. doi:10.1074/jbc.M507071200
13. Jørgensen MM, Jensen ON, Holst HU, et al. Grp78 is involved in retention of mutant low density lipoprotein receptor protein in the endoplasmic reticulum. *J Biol Chem* 2000; 275: 33861-33868. doi:10.1074/jbc.M004663200

14. Chen JC, Wu ML, Huang KC, Lin WW. HMG-CoA reductase inhibitors activate the unfolded protein response and induce cytoprotective GRP78 expression. *Cardiovase Res* 2008; 80: 138-150. doi:10.1093/cvr/cvn160

15. Tavakkoli A, Johnston TP, Sahebkar A. Antifungal effects of statins. *Pharmacol Ther* 2020; 208: 107483. doi:10.1016/j.pharmthera.2020.107483