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JIM Research Letter

doi: 10.1111/joim.13347

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

To the Editor:

Alarmingly, 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 amongst COVID-19 patients.

A retrospective multicentre 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, upregulation of GRP78 is one of the markers reflecting air pollution-related ER stress. The pathological activation of ER stress can initiate the relocalization 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 one out of 250 individuals. In these patients, the concentration of serum LDL-cholesterol (LDL-C) is two-fold since birth due to defective LDL receptor-mediated 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 ASCVD inevitably develops [11].

A 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 the LDL receptors [12,13]. As shown by Sørensen and coworkers [12], in Chinese hamster ovary cells, unfolded mutant LDL receptors are retained in the ER and increase the ER stress, which contributes to the ability of the cells to degrade the misfolded LDL receptors. In the other study, the mechanistic link between GRP78 and LDL receptor synthetic pathway was studied in detail in hepatic cells derived from two HeFH patients with an LDL receptor mutation (Type 2a) known to cause ER retention of the receptors [13].

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It was discovered that GRP78 strongly interacts with the mutated LDL receptors and thereby contributes to their complete retention in the ER. Interestingly, GRP78 also weakly interacted with the newly synthesized wild type LDL receptors and decreased their maturation rate. Accordingly, both studies show that GRP78 acts as a cytoprotective chaperone to ensure that misfolded LDL receptors are not leaving the ER and entering the path to cell surface. As any overexperession of GRP78 may also slightly slow the maturation of hepatic wild-type LDL receptors, it may result in reduced receptor expression on the hepatocyte surface and thereby lead to further elevation of serum LDL cholesterol concentration.

The various mechanisms and conditions presented in the above paragraphs allowed us to intertwine a scheme in which we assign the statin drugs a therapeutic role in COVID-19 and its post-acute sequelae at multiple levels. Statins can activate the unfolded protein response and induce a cytoprotective GRP78 expression [14], which is appropriate when the ER stress turns harmful to the cell. This may occur when the ER stress is excessive and/or prolonged, or when the cells are suffering from hypoxia, such as occurs in patients with severe COVID-19. As discussed above, hepatic regulation of GRP78 could slightly retard LDL receptor synthesis and the ensuing cell surface expression in hepatocytes. However, as evidenced by the significant serum LDL cholesterol-lowering effect of of statins in HeFH patients, their LDL receptor synthesis-inducing effect must override any such untoward effect. 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 amongst the COVID-19 patients with a particularly high risk of immunothrombosis in the micro- and macrocirculation due to an added pre-existing endothelial dysfunction. Such patients include those with hyperglycemia (diabetes) and those with hypercholesterolemia due to mutated LDL receptors, that is, the HeFH patients [11].

Conflict of interest

Petri T. Kovanen has received lecture honoraria and/or travel fees from Amgen, Novartis, Raisio Group and Sanofi.

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