Adipose GRP78, a significant host factor for COVID-19 and the association with older age, obesity, and diabetes

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Abstract

Aging, obesity, and diabetes are major risk factors for the severe progression and outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]), but the underlying mechanism has not been fully understood. In this study, we found that the SARS-CoV-2 spike protein physically interacts with cell surface GRP78, which promotes the binding to and accumulation in ACE2-expressing cells. GRP78 was highly expressed in adipose tissue and its expression increased in humans and mice with older age, obesity, and diabetes. The overexpression of GRP78 was attributed to hyperinsulinemia in adipocytes. Management of hyperinsulinemia by pharmacological approaches, including metformin, sodium–glucose cotransporter 2 inhibitor, or β3-adrenergic receptor agonist, decreased GRP78 gene expression in adipose tissue. Environmental interventions, including exercise, calorie restriction, fasting, or cold exposure, reduced the gene expression of GRP78 in adipose tissue.

Background & Results

Subjects with older age, obesity, and diabetes are vulnerable to COVID-19, but the molecular basis has yet been elucidated. ACE2 is known as a major viral receptor for SARS-CoV-2. This study provides scientific evidence for the role of GRP78 as a binding partner of the SARS-CoV-2 spike protein and ACE2, which promotes the cellular binding and accumulation. Cell surface and soluble forms of GRP78 significantly promotes the binding and accumulation of SARS-CoV-2 spike protein to ACE2-expressing cells. The expression of GRP78 is enriched in adipose tissues and increased by conditions of older age, obesity, and diabetes, which is attributed to the hyperinsulinemia-linked XBP-1 activity. Pharmacological or lifestyle interventions, such as anti-diabetic drugs, exercise, and calorie restriction, could reduce the expression of GRP78 in adipose tissues.

Significance of the research and Future perspective

This study would be helpful to understand the severe progression and outcome of COVID-19 in subjects with older age, obesity, and diabetes. The management of hyperinsulinemia and the related GRP78 expression could be a therapeutic or preventative target.

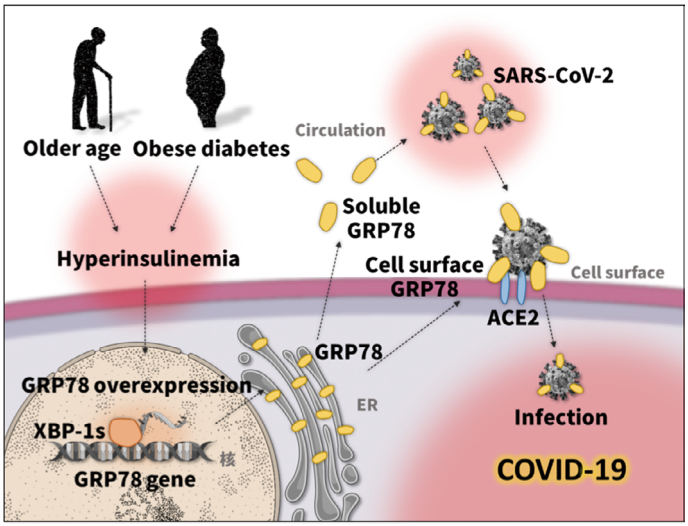

Fig. 1. GRP78 as a host factor for COVID-19

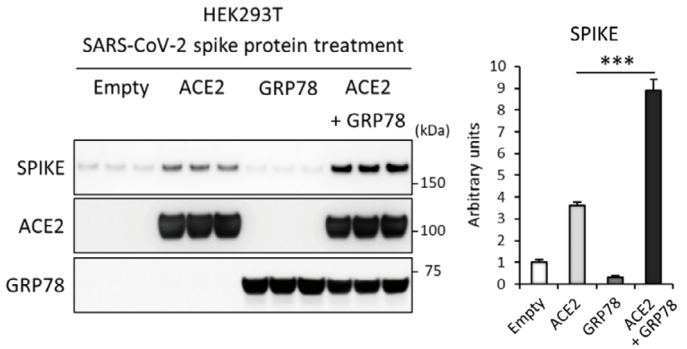

Fig. 2. GRP78 overexpression enhances spike protein binding to ACE2.

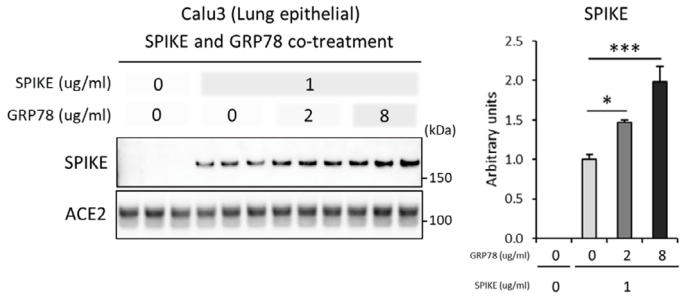

Fig. 3. Soluble GRP78 enhances spike protein binding to ACE2.

Patent

Treatise Shin, Jihoon; Shimomura, Iichiro et al. Possible Involvement of Adipose Tissue in Patients With Older Age, Obesity, and Diabetes With SARS-CoV-2 Infection (COVID-19) via GRP78 (BIP/HSPA5): Significance of Hyperinsulinemia Management in COVID-19. Diabetes 2021, 70(12): 2745–2755, doi: 10.2337/db20-1094

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Keyword SARS-CoV-2, COVID-19, GRP78, older age, obesity